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Approved by:

A. Sakr, Ph.D., Chair
R. Dansereau, Ph.D.
R. Wickett, Ph.D.

A STUDY OF VARIOUS PROCESS FACTORS IN THE SCALE UP OF A HIGH SHEAR GRANULATED PRODUCT

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David M. Pappa

B.S., Chemical Engineering, 1992

The Ohio State University, USA

Committee Chair: A. Sakr Ph.D.

ABSTRACT

The effects of water level, granulation endpoint, atomization spray, and drug bulk density on granulation / tablet characteristics were studied in a 25L Gral, a 600L Diosna, and 1250L Diosna mixer using a poorly compressible drug substance.

For the 25L lots, increases in granulation water level resulted in a decreased granulation blend bulk density, increased tablet hardness, and slightly decreased tablet dissolution. Increases in granulation endpoint (measured by mixer torque) resulted in increases in granulation blend bulk density and particle size, but did not significantly impact tablet properties. Use of atomization spray at 25L had a small effect on tablet friability weight loss.

For the 1250L lots, increases in water levels resulted in decreased granulation blend bulk density, decreased mean particle size for higher torque levels, higher tablet friability, and lower tablet dissolution. Increases in granulation endpoint (Diosna probe %K) led to increases in granulation blend particle size, increased tablet hardness, and reduced friability Variation of drug bulk density at 1250L only affected granulation blend bulk density.

In comparison to the 600L and 1250L Diosna scales, similar granulation particle size and density as well as tablet hardness and dissolution could be achieved at 25L for similar water levels (21.5-23%) and proper choice of granulation endpoint

(140-160 in lbs of torque). Tablet friability for 600L and 1250L scales was not well predicted at 25L.

In comparison to the 600L scale, slightly larger and denser granulation blends were observed at 1250L with lower hardness tablets. While tablet dissolution was equivalent to 600L, tablet friability, particularly capping during friability, was worse in the 1250L system. Increases in granulation endpoint and decreases in water level were necessary to provide similar tablet friability while maximizing dissolution rate.

Despite the differences in scale and equipment (Diosna vs. Gral), water level scaled directly with scale of the mixer. It was possible to empirically determine suitable granulation endpoints to achieve similar product characteristics for all characteristics except tablet friability at 25L.

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CHAPTER 1 INTRODUCTION

1.1 Importance of Scale Up

An important rule of efficient process development work in the pharmaceutical industry or any industry for that matter is to "Commit your blunders on a small scale and make your profits on a large scale" (Baekeland 1916). This is true whether one is developing a process for a new compound or attempting to trouble shoot or increase capacity of an existing process. In accordance with this rule, one must not only understand differences in the equipment/systems in question for both scales but how these manifest themselves in the behavior for a given process as well as resulting product attributes. The operating principles in system A may not be true or even entirely different in system/scale B. These issues may be especially complex in pharmaceutical scale up, where it is difficult to control key attributes in scaling processes, i.e. similarity of equipment, materials, personnel and methods across different scales. The pharmaceutical scientist usually does not have the luxury of a geometrically similar pilot size mixer in which to test a granulation process for a larger plant scale mixer. To be cost efficient and successful, the scientist must still find a way to identify key trends and results in pilot system/scale A and efficiently reapply these to plant system/scale B. This work will provide such a real life comparison for high shear granulation systems.

By its very design of high speed interactions, particle and fluid dynamics in a high shear granulator are not simple. A variety of critical system transformations or events can simultaneously overlap with each other (e.g. wetting, nucleation, coalescence, consolidation (Ennis and Litster 1999)), making modeling of such systems extremely complex. Other significant parameters such as differences within a given feed material (Chowhan, 1988) or differences in processing behavior across different materials (Holm, *et al* 1985a,b) contribute to the complexity of modeling these systems. Currently, there are three strategies for scaling granulation systems: 1) system based approaches focusing on the relationship of macro based dimensionless quantities and their relationship to some product quality, i.e. a top-down approach, 2) material based approaches based on study of changes in material/product characteristics with key process factors at different scales and an attempt to correlate these to some system attribute like power, i.e. more of a bottom-up approach or 3) a combination of the two involving correlation of macro dimensionless quantities directly to a specific product attribute.

1.2 System Based Approach

This approach is widely based on similar engineering approaches to scaling liquid mixers and makes assumption of similarities of liquids and solids. Leuenberger (1983) describes three principles for successful scale up which provide a basis for this approach. These include geometric similarity (requiring the ratio of linear dimensions to be equivalent across two scales), kinematic similarity requiring the ratio of velocities between corresponding points in two systems to be similar in addition to their geometric similarity, and dynamic similarity requiring ratio of forces between corresponding points in two systems to be equal in addition to their geometric and kinematic similarity.

This type of approach commonly uses the Buckingham Pi method for comparing and determining similarities of dimensionless quantities based on macro measurements (power draw, mixer dimensions, material pseudo viscosity). These are used to calculate macro based dimensionless numbers such as power, Froude, and pseudo Reynolds numbers, which are ideally correlated to some product attribute. Leunberger describes an example dimensionless model based on Buckingham Pi as follows:

$\pi_1 = a\pi_2^b\pi_3^c\pi_4^d\pi_5^e$

where

$\pi_1 = \dfrac{P}{r^5\omega^3\rho}$ Power Number (drag force on impeller/inertial stress))

$\pi_2 = \dfrac{q't}{V\rho}$ Specific amount of granulation liquid

$\pi_3 = \dfrac{V}{V^*}$ Fraction of volume loaded with particles

$\pi_4 = \dfrac{r\omega^2}{g}$ Froude Number (Centrifugal/gravitational energy)

$\pi_5 = \dfrac{r}{d}$ Geometric number (ratio of characteristics lengths)

Symbols:

P = Power consumption
r = Radius of rotating blade
ω = Angular velocity
ρ = Specific density of particles
q' = Amount of granulating liquid per unit time
t = Process time
V = Volume loaded with particles
V* = Capacity of mixer
g = Gravitational acceleration
d = Second characteristic length of mixer

The author cites a previous study which used a similar model to scale critical variables while showing that the amount of granulating fluid per amount of granulation was scale independent. The macro based dimensionless quantities were also used to compare granulation qualities. Another study using a Lodige 125 l mixer showed similar power number readings provided similar granulation consistency, though the difference was not in scale but in feed material particle size. The author suggests when feed material were different, the dimensionless model developed could be modified to not only include the dimensionless numbers described earlier, but also an additional dimensionless number comparing direct material attributes (e.g. (d_i/d_f) or the ratio of feed particle size to final particle size). However, this full model was not confirmed empirically.

A more classic Buckingham Pi application was conducted by Landin, *et al* (1996) in a study of 25, 100, and 600 l Fielder mixers. A dimensionless model from Buckingham Pi relating power number as a function of the Froude, fill height, and pseudo Reynolds numbers was developed. The assumption made is that the power number provides an indication of granulation properties. The pseudo Reynolds number was calculated as [(diameter^2 x rotational speed x density of the material) / pseudo viscosity (Landin, *et al* 1995 ; *Parker, et al* 1990)]. When using the full model, the data across all 3 scales collapsed on to a single line suggesting independence of scale on these numbers. They then verified importance of each dimensionless factor by testing reduced models and observing whether the data collapses to a single line. The underlying assumption in this approach that there is a correlation between power number and granulation quality, i.e. similar power numbers provide similar quality of granulation, although this was not confirmed.

Although this approach is technically sound when properly applied, a key requirement is verification that the macro based quantities really do correlate with more “micro” based product attributes, i.e. does a similar power number really provide similar granulation qualities (particle size, density, etc.). Additionally, this approach relies heavily on the principles of system similarity described earlier, especially similarity of geometric similarity in equipment, which is not always the case. This approach may also have difficulty dealing with contributions from other system components, (e.g. contribution of the chopper) which may be difficult to model. Finally, it may rely on measurement of difficult, unavailable macro based quantities (e.g. pseudo viscosity).

1.3 Material Based Approach

Another approach to high shear granulation scale up is the product/material based strategy which studies material transformations and product attributes changes across scales. It is highly empirical in nature and can be used to overcome at least some of the disadvantages of a pure system approach. This approach involves less rigorous macro system modeling and simply studies product changes/properties as a function of key process variables. Observed trends are used to predict appropriate process conditions in different systems/scales. A disadvantage to this approach can be that it typically requires more data and may not consider the effects or interaction of all relevant system attributes.

Schaefer, *et al* (1986) studied granulation of dicalcium phosphate in 25,65, and 150 l Fielder mixers, 25, 50, and 250 Diosna mixers a 300 l Gral, and 5 and 50 l Lodige mixers. The effect of different granulating times, impeller and chopper speeds on granule size distribution, porosity, and liquid distribution were studied for each type of mixer. Faster speeds resulted in larger granules. Additionally, it was suggested that atomization of binder becomes more important in production size mixers to improve liquid distribution. In general, it was concluded that scale up results in less intimate contact of powder with the mixing tools, thus reducing shear and compaction. Therefore, poorer liquid distribution, wider particle size variation, and higher porosity resulted in larger mixers (Schaefer, *et al* 1987).

Published data also offers the opportunity to compare differences across mixers (Schaefer, *et al*, 1986, 1987). Some notable differences for similar size mixers included:

- Fielder mixers provided less energy input and less densification relative to the Diosna at pilot and lab scales, especially early in the process. Fielder mixers also showed a smaller increase in product temperature, assumed to result from a lower power input, which coincided with smaller relative swept volumes and mixing blade inclinations at these scales.
- Comparison across production size mixers for the Fielder, Diosna, and Gral mixers showed limited differences in the change in granule size, porosity and temperature rise. The Gral mixer showed a larger impact from its chopper speed since its chopper was relatively larger compared to the other two mixers.
- Scale up in the Diosna mixer was concluded to be complex since the relative swept volume (the volume actually swept out by the geometry of the mixing blade as a ratio of total mixer volume) is related to the energy input to the system and decreases with size. It was also reported that the angle of blade inclination also changed for the Diosna bowl sizes studied.

Despite these differences, an important observation was that the same relative amount of binder solution could be utilized in all machines from 5 to 300 liters, because similar levels of liquid saturation provide similar granule growth.

1.4 Combined Approach

The combined approach mixes aspects of the first two strategies. A full dimensionless Buckingham Pi model is not utilized. Rather, specific dimensionless macro quantities are correlated to selected product attributes. Horsthuis, *et al* (1993) used separate comparisons of relative swept volume, mixer tip speed, and Froude number to compare lactose granulation endpoints in 10, 75, and 300 l Gral mixers. Interestingly, although the relative swept volume and tip speed related very well to the specific energy input to the system (i.e. area under the power consumption curve divided by the batch load), it was the Froude number which provided the best correlation to the endpoint (defined as the point at which no further changes in particle size were seen).

The authors reported that the Froude number is most descriptive of shearing and compaction of the granules at the edge of the blades and wall of the mixer, which is a key factor which controls the overall process. This study illustrates the importance of relating macro based quantities (such as power input) to micro based product attributes. It also shows that maintaining similar power input to a system may not necessarily guarantee equivalent product attributes. The authors suggest that the poorer descriptive capability of the power related parameters may be due to unknown power contributions from the chopper, different mixing efficiencies in the mixers, and effect of heavier loads in larger mixers.

Rekhi, *et al* (1996) used a similar approach where granulation and tablet characteristics were compared with scales for certain macro quantities (tip speed and dimensionless mix number). Granulations of metroprolol tartrate, lactose and microcrystalline cellulose were prepared in 10, 65, 150,and 300 L Niro Fielder PMA mixers. Mixers were scaled such that the tip speed of the impeller was constant across all scales. The authors found that the amount of granulating liquid could be scaled linearly with batch size to provide similar granule characteristics. Generally within a given scale, lower amounts of liquid result in finer granule sizes and lower density granulations. Lower liquid volumes also resulted in lower tablet hardness and faster dissolution. The authors found that the granulating time could be scaled to provide granulations of similar size and density by multiplication by the ratio of the speeds. Tablets properties (hardness, thickness, disintegration, and dissolution) were similar using this approach.

1.5 Key Variables In High Shear Granulation

As described in the earlier examples, depending on the scale up strategy, there are multiple factors which can be chosen for a scaling study. For the purposes of this study, more of a material based approach will be used, prompting the question of which processing factors may be most impactful in a scaling study. Previous studies have shown that amount of granulating fluid, wet mixing time, and mixing speeds are among the most impactful on granule and tablet characteristics (Kornchankul, 2000). With relation to this study, two of these factors will be used with addition of two others selected at certain scales.

1.5.1 Amount of Granulating Solution

Granule growth and consolidation (densification) occur at the same time in the high shear system with deformation having a large impact on growth. (Ennis & Litster, 1999) The importance of liquid level in high shear granulation is well documented for this system (e.g. Kristensen and Schaefer, 1987), particularly when it is expressed as a liquid saturation level and related to the ability of the material to deform under stress (Holm, *et al* 1985a,b). Larger amounts of liquid in relation to relative porosity of the granule, reduce the yield stress necessary to deform the particles in collision, thus allowing growth by coalescence with other granules. This deformation also makes it possible to consolidate the granules, further feeding the process by increasing the % liquid saturation and also squeezing additional fluid to the granule surface for continued growth. This behavior makes the amount of granulating liquid one of the most impactful variables on granulation changes during processing as suggested by Rekhi, *et al* (1996).

The liquid level is not only important because of its control of kinetics and dynamics of the granulation process, but also because these effects impact performance of the granules and tablets. Vojnovic, *et al (*1992) showed that moisture level in the granulation had a major effect on the particle size and flow rate of granules. Unvala, *et al* (1988) showed that increases in the amount of granulating solution decreased dissolution up to a certain liquid level.

1.5.2 Granulation Endpoint

Another highly impactful process variable is the total extent of granulation, typically gauged by granulation time. If the amount of liquid provides the fuel for the granulation “reaction”, the amount of time determines its extent, i.e. the level of granulation as determined by the final size, density, porosity of the granules. One example by Ertel, *et al* (1990) illustrates the effect of kneading time on granulation and tabletting properties of dyphylline granules. Kneading time was found to move density and porosity of the granulation through mid range extremes which impacted granule dissolution and, to a lesser extent, dissolution of the tablets. Granulation providing optimum tablet weight and hardness variation did not coincide with optimum dissolution suggesting a trade off of these properties could be necessary. Zoglio, *et al* (1976) also suggested this type of trade off in knead time in balancing optimum processing performance with optimum product performance (dissolution).

1.5.2.1 Torque Endpoint

A wide variety of granulation endpoint determinations have been well documented throughout literature (Ennis & Litster 1999; Holm, *et al* 1985b, 1997; Kopcha 1992; Kornchankul, 2000). Mixer torque measurements, a method which will be utilized at small scale in this study is among these.

For the purposes of this study torque (measured in inch-lb_f), is measured directly on the shaft of the main impeller through strain gauge transducers. The signal generated can be viewed as an integration of all the forces and moment arms generated along each of the mixing blade arms. (A moment arm is the distance from the center point around which the force is acting.) As the granulation grows in size and density, the forces exerted against the blades in moving the granulation become greater, thereby increasing the torque. By integrating the individual torques along each point of the mixing blades, irregularities at individual points in the mixer can be "smoothed" (Bubb, 2000).

1.5.2.2 Diosna %K Endpoint

Also among the possible methods of endpoint determination is the probe endpoint parameter, developed by the Boots Company for Diosna mixer. The main Diosna probe endpoint parameter is a quantity known as "Consistency", or "Konsistenz", in German. The Konsistenz (abbreviated as "K") parameter is designed to detect changes in momentum of granules in a constant velocity region of the mass with use of strain gauges instrumented on the probe. (Holm , 1997) It measures the pressure exerted by the probe head, which is converted to a force using the probe area. To avoid bias due to random events (e.g. large lumps due to inhomogeneous solution distribution), signal pulse heights, sampling times, and pulse density are all manipulated mathematically to attain the final signal. (Holm, 1997) This is normalized over a calibrated range of forces 0 to 100%. The signal is dependent on the size of the probe head (i.e. its area) and how far the probe is inserted into the moving granulation. The changes in force, which the probe measures, should correlate to changes in the size and density of the granulation. Higher percent K values signify larger forces being exerted by the granulation, which signify larger and denser granules.

When properly developed and calibrated for a given system, the percent K parameter can successfully be used to determine a repeatable granulation endpoint (similar particle size and density). However, it is system and material specific, and similar % K values may not necessarily lead to the same endpoint for different systems or materials. This limitation can also apply to mixers of the same design but different scales as will be utilized in this study. An endpoint of X % in a Diosna P600 may not necessarily provide the same granulation qualities in a Diosna P1250. (Diosna, 2000) Differences in the parameters (e.g. Froude No. and energy input), which will be described in section 1.6, as well as differences in the flow dynamics (flow patterns, positioning of the probe) may explain the difference.

1.5.2.3 %K / Torque Comparison

Although both parameters can be used to judge granulation endpoint, they do not mathematically correlate to each other directly. Each measures different attributes of the granulation system, and they have different sensitivities to these systems.

The %K parameter can be viewed as a normalized amount of force exerted by the granulation at the point of insertion of the probe. As noted previously, its displayed value is dependent on various signal characteristics of the measured force such as amplitude, density, and sampling times as well as the spatial positioning of the probe. The latter point is particularly critical since it means the probe is more sensitive to localized disturbances which may result from the action of the chopper or random events such a large ball of granules (Bubb, 2000).

Torque, on the other hand, is a mechanical work term equal to the force acting over a distance. It is an integration of the individual torque products over the lengths of the mixing blades, which makes it less sensitive to localized disturbances.

While it may be theoretically possible to multiply the force readings from the probe by an equivalent moment arm, the differences in location of the measurement and their respective sensitivities make it unlikely they would mathematically correlate with each other. Additionally, there are complexities due to differences in scale and/or design of the mixers, which are likely to result in different flow dynamics within each mixer. Since the flow dynamics are likely to influence measurement and changes in the probe force and torque, this factor makes it even less probable to find direct correlation between the two methods.

Although each measures different properties in different positions, both measure properties which correlate to changes in granulation properties (particle size, density, consistency). Therefore, in theory it should be possible to empirically determine a range for each which corresponds to similar granulation properties for a given formulation. This approach will be challenged in this work.

1.5.3 Binder Dispersion & Feed Material Density

<u>Binder Dispersion</u>

The degree of binder dispersion is a topic of high interest in fluid bed granulating (Ennis and Litster, 1999) but seems to have received less attention in high shear applications. This may be due to the relatively higher material flow and mass transfer within the high shear mixer, which make this parameter less critical. Another reason may be that its importance is very case and system specific. The dispersion is a function of binder and solution properties, the interaction of binder solution with the drug substance, and intensity of the agitation, all of which are system specific.

Binder solution is generally sprayed in atomized form into the granulation rather than dumped in order to avoid lumps (Ennis and Litster 1999; Holm, 1997). Distribution of the binder can influence the granulation particle size distribution and homogeneity (Holm 1997; Chalmers and Elworthy 1976).   Additionally, Schaefer, *et al* (1986) suggested that the degree of atomization of the binder solution was important to achieving controlled granule growth, particularly when slower mixing speeds were used.

The 25L Gral system in this work has the option to use spray atomization or direct liquid addition. Therefore, the effect of the use of atomization spray will be studied.

Feed Density

Also of practical interest is the effect of bulk feed physical attributes, especially bulk density on granulation and tablet properties. Although there is a large literature data base which examines differences in granulation/ tablet properties for different raw materials (e.g. *Holm, et al* 1985a,b; Remon and Schwartz 1987), there is a smaller data base exploring more subtle variation of properties within a given feed material. Tapper and Lindberg (1986) provide one such example in studying effect of different mesh sizes of lactose in a granulation process. Chowhan (1988) also discussed the importance of feed material attributes in studying granulation processes and scale up. Holm (1997) reported that there can be a variety of critical physical parameters for the feed material which are impactful to the granulation process such as particle size, surface area, particle shape/morphology, etc. Bulk density, which is a result of several of these (particle size, shape, surface area, etc.) is known to vary within an acceptable but impactful range for the drug substance used in this study. Therefore, effects of varying bulk density will be studied at the 1250L scale.

1.6 Mixer Background And Comparisons

Since the mixer granulators of interest in this study are quite different in design and operation (Schaefer *et al* 1986, '87), some comparison of differences is justified to predict expected performance. The key parameter for mixer comparison used in this work was relative swept volume since this variable appeared to correlate with temperature increase in the bed and assumed power input. For this work, schematics of each mixer are shown in Figures 1 and 2 on pages 18-19, and a comparison of key quantitative parameters, listed in Table 1 on page 20, will be used for a more comprehensive comparison.

A significant difference among the mixers is the obvious difference in <u>shape</u> of the bowl and blades. The Gral mixer utilizes a curved blade design allowing the tips of the mixing blade to reach up the sides wall of the mixing bowl which is curved in a similar shape. The Diosna mixers by contrast have a flat blade design, parallel to the lid and bowl bottom. Only a small portion of the blade directly sweeps off the wall, relying on the wall design, which bends back towards the center, to fold material back into the mixing blade. These differences in blade and bowl design are expected to result in different flow patterns and dynamics.

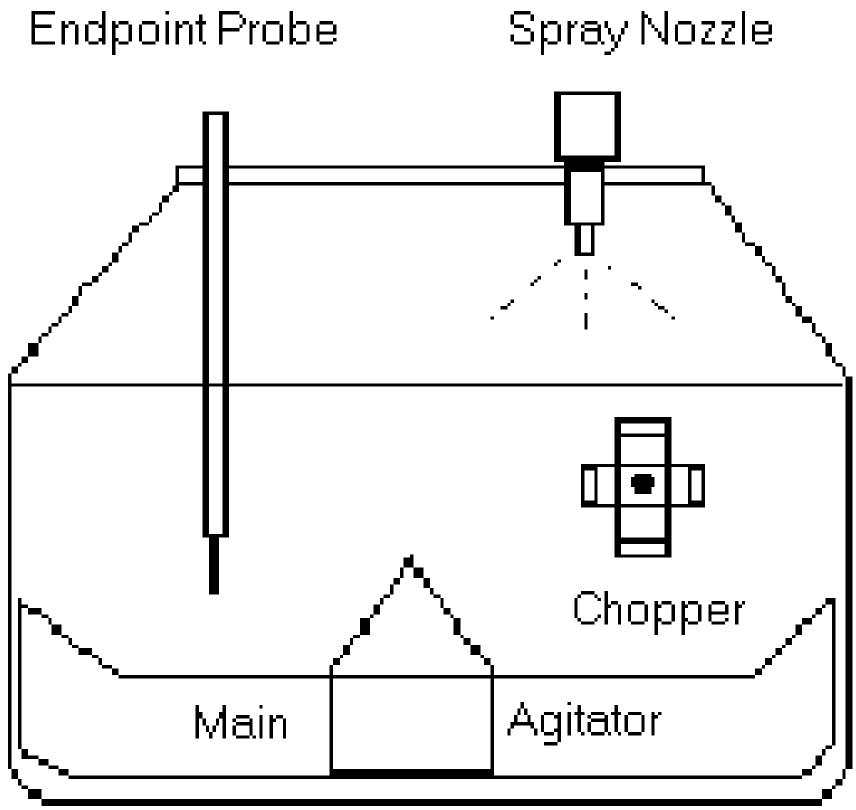


Figure 1: Schematic Diagram of Diosna Mixer

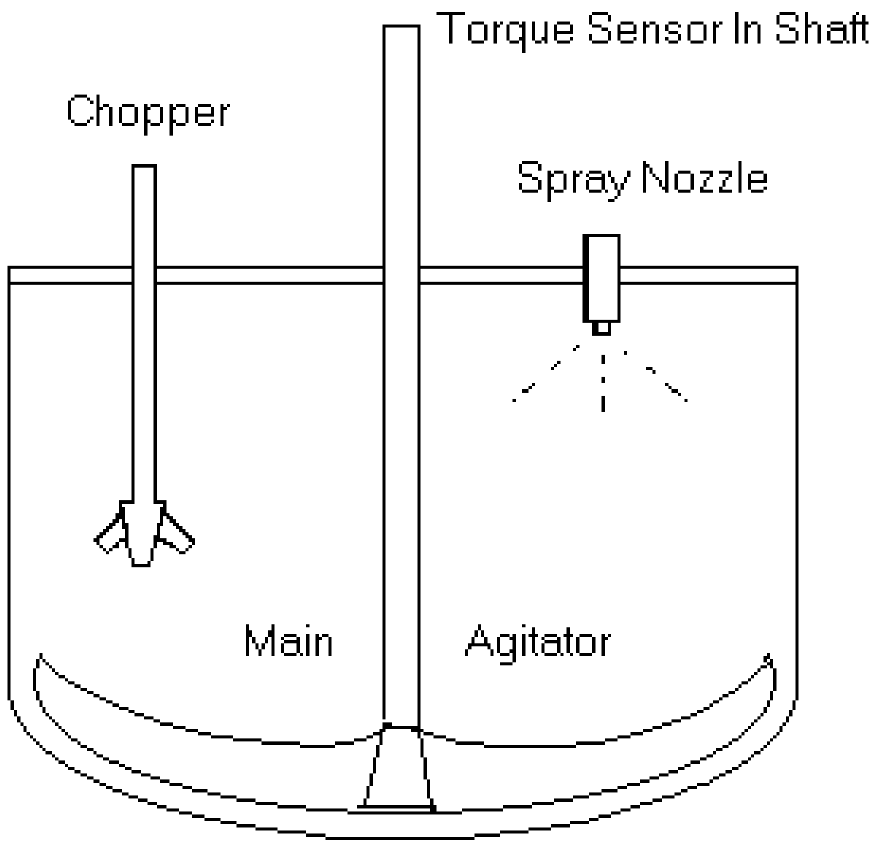


Figure 2: Schematic Diagram of Gral Mixer

Table 1: Comparison of Mixer Parameters

Mixer	Diosna P600		Diosna P1250		Gral 25L	
Blade/Bowl Shape	Relatively Flat		Relatively Flat		Curved	
Blade Diameter (m)	1.23		1.58		0.36	
Speed Setting	Low	High	Low	High	Low	High
Mixer Speed (rpm)	57	114	45	90	295	440
Tip Speed (m/s)	3.7	7.3	3.7	7.4	5.6	8.3
Froude No.	3.6	14.5	2.3	9.1	97.4	216.6
Specific Kinetic Energy ($J/kg*m^3$)	11.2	44.9	5.5	22.2	618.4	1375.7
Mix Time (min)	---	9.00	---	11.4	---	2.33
Dimensionless Mix Time	---	1026	---	1026	---	1025

The next key difference in the mixers, besides the blade diameter, which is a function of scale, is the difference in speeds. Both the 25L Gral and 600L have only high or low speed settings. A variable speed drive on the 1250L Diosna permits use of any speed below maximum. The Gral mixer has very fast speeds relative to the Diosna mixers. This translates into large differences between the Gral and Diosna mixers in the other parameters.

The tip speeds (mixing blade circumference x speed) in the two Diosna mixers are similar by design. Tip speed is considered by the Diosna manufacturer to be a key process parameter in their machines and is used to scale mixer speeds. The tip speed represents the amount of shear rate provided to the granules (Ennis and Litster, 1999). This is important to the granulation process, especially during coalescence and consolidation of the granules, where shear results in granule changes. Although the diameter of the mixing blade is much smaller in the Gral mixer than the Diosna mixers, the high speeds of its main mixing blade still result in higher tip speeds (higher shear rates) than the Diosna's.

The Froude Number, proportional to the centrifugal force divided by the gravitational force, is commonly used to compare liquid mixing systems and has found application in comparing solids mixing and granulating (Ennis & Litster, 1999). The Froude number can be viewed as a measure of the "fluidization" of the materials or how much is being pushed out versus pulled down in the bowl (Mort, 1999). Table 1 shows the Gral mixer has significantly higher Froude numbers than the Diosna mixers, again a result of its relatively high mixing blade speeds. Thus, there is a much higher force of the granulation being pushed out against the walls of the bowl, which might be expected to lead to greater consolidation and densification of the granulation. The Froude numbers for the 1250L Diosna mixer are lower than those for the 600 L Diosna, indicating a relatively higher ratio of gravitational force to that of the centrifugal force and a less "fluidized" state. This factor deserves careful consideration, particularly for the scale up from the 600L to the 1250L process in the Diosna mixers. It means that while the current practice of scaling by tip speed should keep the shear rate the same for the process it does result in a higher proportion of vertical (gravitational) force in the P1250.

Consideration of both the Froude number and tip speed as key scale up parameters results in an interesting paradox. To maintain similar granule densification and growth due to shear upon scale up, constant tip speeds are necessary. Thus, relatively slower mixing speeds are needed, and this always results in a lower Froude number, signifying greater gravitational component of the total system forces. Thus, it is expected that there will be more granule densification or altered granule growth due to greater vertical forces in the mixer, even though the shear rate was held constant by the tip speed. A possible solution to the paradox may be splitting use of the criteria (Mort, 1999). One such split may be to use faster speeds necessary for a constant Froude number in the early portion of the process, since “fluidization” may be more critical to nucleation and early granule growth during this stage. The speed is then lowered to achieve constant tip speed for latter portions of the process, since constant shear rate may be more critical for the coalescence and consolidation which takes place during these stages. This thesis will assess the validity of this approach.

Another calculation in Table 1 is one not typically found in literature, but may be useful in understanding system differences. Since granule growth and densification is largely impacted by physical stress imparted upon the granules, some assessment of the energy added to the system allows a quantitative comparison of granulating systems. This may be estimated by monitoring the power consumption or temperature rise of the system directly (Holm, *et al* 1985 a,b; Schaefer, *et al* 1986,1987), through experimentation. Another way to estimate it without any experimentation is to simply calculate the nominal specific kinetic energy per unit mass (0.5 x velocity^2) per unit volume of the mixing chamber. Tip speed is used as the velocity term, and 25, 600, and 1250 liters are used as the volumes of each respective mixer. Although this term uses the entire bowl volume and does not consider how well the energy is transferred across this volume or into the product (efficiency), it provides a simplistic estimate of system behaviors by describing maximum available energy for the main mixer. Values in Table 2 show that this normalized kinetic energy input is much higher for the Gral mixer than either Diosna mixer, suggesting shorter granulating times or altered processes may be necessary to get the same product. The table also shows that the energy input for the Diosna P1250 is lower than that for the P600, indicating more granulating time or other adjustments may be necessary for similarity.

As a final check of system differences among the three listed in Table 1, dimensionless mix times have been compared for each. The dimensionless mix time, (mixer speed x actual mix time, really represents the number of revolutions of the mixing blade and can be used to scale granulators (Rekhi, *et al* 1996) or liquid mixers. The analysis shows longer granulation times are needed in the 1250L Diosna mixer and much shorter granulation times are needed in the Gral 25L mixer to achieve the same dimensionless mix number.

1.7 Material Characteristics

The material granulated in this study is a low density, poor flowing, poorly compressible crystal. These properties require that the material be granulated. Other relevant physical properties follow:

Table 2: Drug Substance Properties

Property	Description
Bulk Density	< 250 g/l
Median Particle Size	< 30 um on Average
Solubility	Very Slightly Soluble (H_2O)
Hygroscopicity	Low

1.8 Significance of the Proposed Research

Scale-up or scale-down of a granulation processes is a common need in pharmaceutical process development. There are a variety of approaches for scaling discussed previously. However, it's quite common in industry to be faced with the need to cross over granulation equipment as well as scale, and there are no previous literature studies on this subject. This work studies such a case by comparing a 25L Gral process to Diosna processes at 600L and 1250L. Additionally, in order to optimize processes at any scale it's critical to know key process levers and how they affect intermediate and final product attributes. This knowledge can be used in scaling a process to make necessary modifications to the process. This work studies key process levers at the 25L and 1250L scales and will be used to determine best levels of these factors in order to maintain similarity of key intermediate or process parameters.

Finally, while use of Diosna mixers in common in the Pharmaceutical industry, the use of a unit as large as 1250L is quite limited. The manufacturer of the Diosna unit utilizes a simple “constant tip speed” approach to design its mixers. While this approach may work for smaller mixers, it’s not certain if this approach works when scaling to larger volumes, where several hundred kilograms of material are used and mass effects may become more significant. Additionally, if this approach doesn’t maintain desired similarity of product attributes, it’s not always clear what process modifications can be made to address this. This study will address these questions.

Chapter 2. OBJECTIVES

2.1 Hypothesis

For granulations made with similar starting materials, key granule attributes of particle size distribution, density, and overall morphology(structure) as well as resulting tablet properties (weight variation, hardness, friability, and dissolution) are primarily governed by the liquid level in the material and the rate and extent of shear input to the process. The scale up can achieve similar granulations and tablet characteristics by maintaining similarity of these factors. Additionally, the granulation quality can be optimized by adjusting the same factors. Primary levers to control these factors are 1) varying the amount of water used to granulate the system and 2) varying the degree of granulation / granulation endpoint for a given shear rate (mixing speed).

2.2 Objective

The primary objective of this research is to determine the effect of key processing parameters on the granulation process as well as resulting intermediate product attributes at different scales and in different granulating equipment. A secondary objective is to determine whether a particular approach to scale up (i.e. maintaining constant Froude number early in the process followed by constant tip speed later in the process) result in a similar process and product for Diosna mixers at the 600 and 1250 l scales.

2.3 Specific Aims

1. To determine and compare the effects of water level and granulation endpoint on granulation blend (particle size, density) and tablet characteristics (weight, hardness, friability, dissolution) across the 25L Gral and 1250 L Diosna mixers. Additionally, the effects of 1) changing the drug substance bulk density (Diosna 1250L unit only) and 2) using binder solution atomization (25L Gral only) on these same parameters will be assessed. These effects will be compared to those determined in the previous literature.
2. To determine levels of water, granulation endpoint torque, and atomization spray in the 25L Gral which best correlate to the 600L Diosna baseline as

well as the 1250L final centerline condition in providing similar granulation blend and core tablet properties.

3. To determine whether the following approach to scaling a granulation from a 600 L to a 1250 L Diosna granulator provides similar granulation blend and tablets:
   - Mixing speed is scaled by maintaining constant Froude number for the early portion of the binder addition (first 2 minutes of the process) , followed by maintaining constant tip speed for the remainder of the process.
   - Binder solution addition is scaled by maintaining a constant binder addition time, i.e. increasing the rate of binder addition upon scale up. A change in the method of adding binder solution (gravity flow through an orifice in the P600 versus pumping through a spray nozzle in the P1250) is allowed.
   - The amount of granulation liquid will be scaled by linearly increasing the amount of water with batch size. (Alternate water levels will also be evaluated for process/product effects.)
   - The granulation time/endpoint will be scaled by empirically evaluating a range of endpoints on a larger Diosna probe which provide similar granulation blend (particle size, density) and tablets (weight, hardness, friability, and dissolution).

Chapter 3. EXPERIMENTAL

3.1 Materials

Table 3: Experimental Materials

Name	Manufacturer/Supplier	Location of Manufacturer/Supplier
Drug Substance 690215	---	---
Lactose	Meggle	Germany
Povidone (K 25)	BASF	Germany
Silicon Dioxide	Degussa	Germany
Talc	Whitaker, Clark & Daniels	New York, USA
Sodium Starch Glycolate	Penwest	Germany
Magnesium Stearate	Merck	Germany
Purified Water	Procter & Gamble Pharmaceuticals	Norwich, NY
Sodium Hydroxide*	J.T. Baker of Mallinckrodt-Baker Inc.	Phillipsburg, NJ
Potassium Phosphate Monobasic*	J.T. Baker of Mallinckrodt-Baker Inc.	Phillipsburg, NJ

* Analytical reagents

3.2 Equipment

3.2.1 Pilot Scale

Table 4: Pilot Scale Equipment

Equipment	Model	Manufacturer/Supplier	Location of Manufacturer/ Supplier
High Shear Mixer/Granulator	Colette Gral 25	GEI Processing	Towaco, NJ
Glatt Fluid Bed Dryer	GPC-G1	Glatt Air Techniques	Ramsey, NJ
Glatt Quicksieve	TR 80	Glatt Air Techniques	Ramsey, NJ
PK V- Blenders	1 & 16 Qt. Blendmaster	Patterson Kelley Corp.	East Stroudsburg, PA
Tablet Press	Manesty Beta * Press 16 Station	Thomas Engineering	Hoffman Estates, IL
Tap Density Tester	Stampf Volumeter STAV 2003	J. Engelsmann	Ludwigschafen, Germany
Digital Micrometers	CD-4"P	Mitutoyo Corp.	Japan
Friabulator	TAD	Erweka GmbH	Heusenstamm, Germany
Automated weight, gauge, hardness tester	Elizatest 3+	Elizabeth Hata International	North Huntingdon, PA
Moisture Balance	IR100	Denver Instruments Inc.	Arvada, CO
Dissolution Bath	Vanderkamp 600	Vankel Industries	Cary,NC
UV Spectrometer with pump for continuous monitoring	DU-62	Beckman Instruments	Fullerton,CA

* Tablet press instrumented with strain gauge sensors on main and pre-compression rolls to measure compression and pre-compression forces during compression.

3.2.2 Plant Scale

Table 5: Plant Scale Equipment

Equipment	Model	Manufacturer/ Supplier	Location of Manufacturer/Supplier
High Shear Mixer/Granulator	P600 & P1250	Diosna Dierks & Sohne GmbH	Osnabrueck, Germany
Fluid Bed Dryer	WST 200	Glatt Process Technology GmbH	Binzen, Germany
Vortex Sieve	E 650 E	Azo GmbH & Co.	Osterburken, Germany
Oscillating Granulator	OR5030	Glatt GmbH	Dresden, Germany
Tablet Press	GRP 42*	Horn	Germany
Hardness Tester	H	Kraemer Elektronik GmbH	Darmstadt, Germany
Digital Micrometers	PK-1012E	Mitutoyo	Japan
Friabulator	TAD	Erweka Apparatebau	Heusenstam, Germany
Moisture Balance	L420D	Sartorius AG	Goettingen, Germany
Tap Density Tester	Stampf Volumeter STAV 2003	J. Engelsmann	Ludwigschafen, Germany

* Tablet press instrumented with strain gauge sensors on main and pre-compression rolls to measure compression and pre-compression forces during compression.

3.3 Software

Table 6: Software Used

Name	Version/Registration	Manufacturer
Microsoft Excel For Windows 95	Version 7.0a on Procter & Gamble Pharmaceuticals's Shared Server	Microsoft Corporation, Redmond, VA
IDISCOM	Version 1.36 Procter & Gamble Pharmaceuticals's Process Development Software	Icalis Data Inc.
Design Expert	Version 5.0.3 on Procter & Gamble Pharmaceuticals's Shared Server	Stat-Ease Corporation, Minneapolis, MN
LabVIEW Program For Gral 25L Torque Record	LabView Version 5.1; Data Acquisition Program Version 1 Within Procter & Gamble Pharmaceuticals's Internally Developed Software Programs	National Instruments, Austin, TX
LabVIEW Program For Log Normal Particle Size Analysis	LabView Version 5.1; Data Acquisition Program Version 1 Within Procter & Gamble Pharmaceuticals's Internally Developed Software Programs	National Instruments, Austin, TX

3.4 Experimental Design & Justification For Variables

3.4.1.1 25 L Gral Pilot Scale

Two different sets of experimental runs were made. The main set (Set A) used lots designed in a full factorial design, and the second set (Set B) included lots made to stress extremes of process factors. It also included intermediate points within the factorial study to allow more continuous mapping of trends within a region of interest.

For set A, a 2-level, 3 factor full factorial study with two centerpoints was completed using amount of granulating water, granulation endpoint (mixer torque), and use of atomizing spray as factors. The importance of the amount of granulating liquid and extent of granulation has been discussed in section 1.4. Overall, water levels as wide as 18% to 25% were challenged with a range of 20% - 23% for the set A factorial lots. The range of water levels was chosen based on previous pilot trial which showed this range provided the extremes of granulation quality from very fine and powder like to very large and dough like. Torque level ranges of 110-170 in-lbs were also challenged with 130 – 170 in lbs as the bracket range for the set A factorial lots.

All lots utilized lots of drug substance within a similar bulk density range (within 15 g/l).

To simulate the range of binder dispersion available in the larger scale units, the spray variable will be on or off for the 8 lots. An atomizing air pressure of 40 psig was used when the spray was on. For the mid-points lots 9 and 10, a lower amount of atomizing air pressure (10 psig) was used. This was determined experimentally as the pressure needed to produce a narrower spray cone with larger droplets versus the broader cone with very fine droplets for 40 psig or the direct fluid stream for 0 psig. Tables 7 and 8 summarize the granulation conditions for the all lots made.

Table 7: Factorial Design for 25L Gral Scale Lots - Set A

Lot No.	Water Level (%w/w)	Endpoint Torque Value (in-lbs)	Spray
1	23%	170	On
2	20%	130	On
3	23%	130	On
4	20%	170	On
5	23%	170	Off
6	20%	130	Off
7	23%	130	Off
8	20%	170	Off
9	21.5	150	On (~10 psig)
10	21.5	150	On (~10 psig)

Table 8: Additional Lots for 25L Gral Scale – Set B

Lot No.	Water Level (%w/w)	Endpoint Torque Value (in-lbs)	Purpose
11	20%	110	Challenge lower torque level at low water.
12	23%	110	Challenge lower torque level at high water
13	19%	150	Challenge lower water level at intermediate torque
14	25%	150	Challenge lower water level at intermediate torque
15	20%	140	Test intermediate torque #1 at low water
16	20%	160	Test intermediate torque #2 at low water
17	23%	140	Test intermediate torque #1 at high water
18	20%	160	Test intermediate torque #2 at high water
19	21.5	140-150	Test middle range of water & torque with spray on

All “additional” lots made in Table 8 used the atomization spray “on”, since this was the primary condition of interest and matched the Diosna P1250 spray conditions.

3.4.1.2 Diosna P1250 Pilot Scale

For the P1250, a 2 level, 3 factor, full factorial study was completed using amount of granulating water, granulation endpoint, and bulk density of the drug substance as the three variables. Levels of granulating water were chosen based on pilot work in the 25L Gral, as described earlier for the 25L Gral experiments. The granulation endpoint is measured by a %K, representing % consistency on the Diosna probe. The levels were chosen based on a test lot at this scale which indicated this range resulted in a broad range of granulation particle size and density but was capable of being processed into tablets. Drug substance bulk density was chosen as the third variable for this study, since it is known as an important raw material attribute known to vary over the course of normal production and can impact the granulation process and resulting product. The density range chosen covered a 45 g/l range.

Table 9: Granulation Conditions for the 1250 Diosna Factorial Lots

Lot No.	Water Level (%w/w)	Probe Endpoint (%K)	Drug Substance Bulk Density
1	23%	48%	High
2	20%	33%	High
3	23%	33%	High
4	20%	48%	High
5	23%	48%	Low
6	20%	33%	Low
7	23%	33%	Low
8	20%	48%	Low
9	21.5%	41%	Middle (50:50 mix of high & low lots)

In addition to these lots, three additional lots were made to confirm potential centerline settings at 1250L as shown in Table 10.

Table 10: Granulation Conditions for the 1250 Diosna Confirmation Lots

Lot No.	Water Level (%w/w)	Probe Endpoint (%K)	Drug Substance Bulk Density
10	23%	33%	Intermediate
11	23%	33%	Intermediate
12	21.5%	38%	Intermediate

Product data for the P600 and P1250 processes was compared to evaluate similarity of its ranges. This includes granulation blend particle size and density as well as core tablet weight, hardness, friability, and dissolution (at intermediate compression forces). For dissolution, this includes comparison with the SUPAC f_2 similarity test.

3.4.1.3 Diosna P600 Pilot Scale

For the P600 Diosna, no factorial studies were possible due to additional cost of drug substance for such work. Thus, data was collected for multiple lots to represent typical ranges for each attribute (for example blend density or tablet hardness). A standard granulation process at a constant granulation endpoint (35 %K value) was used. A water level of approximately 23% was used.

3.5 Methodology

3.5.1 Formulation

Table 11: Tablet Formulation For All

Material	% weight/tablet
Drug PGP690215	76
Lactose, Povidone, Sodium Starch Glycolate, Talc, Silicon Dioxide, and Magnesium Stearate	24
Total	100

3.5.2 Granulation Manufacture

Processing was done on 3 scales (pilot scale and 2 plant scales) as described in the following sections. Due to differences in available equipment between pilot and plant scales, there are several differences in various process parameters and type of equipment between these scales, e.g. type of tablet press and press speed, use of a V-blender for 25L blending versus the Diosna's for 600L and 1250L final blending, and differences in some screen sizes and type of sizing equipment. Only the differences in tablet press type and press speeds are believed to have affected the results of these experiments. These may have led to differences in certain tablet characteristics as described in the Chapter 4 Results section.

3.5.2.1 25 L Gral Pilot scale:

1. Povidone was dispersed into the desired amount of water using a magnetic mixer and stir bar. Mixing continued until the solution was dissolved.
2. Granulation was completed in a 25L Coullete Gral unit equipped with a torque measure measurement device on the main agitator shaft as described in section 6.0.1. Mixer and chopper speed were set at setting 1.
3. The Wet granulation was passed through a Comil at low speed with a large screen (4.5 mm).
4. Granulation was dried in a Glatt GPC G-1 fluid bed dryer with 100C inlet air to a moisture content of 1.5% or less. Because of the size of the batch, two drying sub-batches were produced for each batch.
5. Granulation was passed through a 1.25 mm screen by hand. Overs were sized through a Glatt Quicksieve with a 1.5 mm screen at low to medium speed.
6. Two separate premixes of 1) sodium starch glycolate and talc and 2) magnesium stearate and silicon dioxide were made by mixing each in a 1 qt. V-Blender for 5 minutes.

7. Sized granulation was blended with premix #1 in a Patterson Kelly V-blender for 5 minutes. The premix was passed through a 0.6 mm screen as it was added to the blender.
8. Premix #2 was added to the blend from No. 5 by passing it through a 0.6 mm screen. The mix was blended for 5 more minutes.

3.5.2.2 600 and 1250 L Diosna Plant Scale:

1. Povidone was dispersed into the desired amount of water using a propeller mixer. Mixing will be continued until the solution was dissolved.
2. Granulation was made in the appropriate Diosna unit, each equipped with a Diosna probe for endpoint measurement. Mixer and chopper speed will be varied throughout in the same way at both scales. The chopper was not turned on until later in the process (approximately 8 minutes).
3. Granulation for the 1250 L unit was passed through a Quadro Comil at low speed with a 16 mm screen to disperse agglomerates in the larger batch size. This de-agglomeration step was not available or used for the 600 L batch.
4. Granulation was dried in a in a fluid bed dryer at 100C air to a moisture content of 1.5% or less.
5. Granulation was passed through a Vortex sieve with 1.5 mm screen. Overs will be sized through an oscillating granulator with a 1.5 mm.
6. Two separate premixes of 1) sodium starch glycolate and talc and 2) magnesium stearate and silicon dioxide will be made by mixing each in

double cone mixer for 5 minutes for each premix. Each premix was passed through a 0.6 mm vibrating sieve.

7. Sized granulation was blended with premix #1 in the appropriate Diosna for 5 minutes.
8. Premix #2 will be added to the blend from No. 5. The mix was blended for 5 more minutes.

3.5.3 Granulation Blend Characterization

3.5.3.1. Bulk and Tap Density:

Bulk density was measured by adding 50 -100 g +/- 1 g of granulation blend into a 250 ml graduated cylinder. The apparent volume read was used to calculate the bulk density by dividing the weight by the volume.

3.5.3.2 Particle size

Sieve analysis was used to determine mean particle size and particle size distribution. A sample of 50-100 g +/- 1 g was added to a standard set of US size sieves. The sieve stack will be added to the CSC sieve shaker and agitated for 10 minutes before weighing each sieve. The weight fraction retained on each sieve size was determined. Graphical representations of the fraction retained on each sieve were compared graphically. Additionally, a P&G developed Lab View software was used to calculate the geometric mean particle size equal to the x-intercept of a sigma versus particle size graph on a log probability plot, with sigma being the number of standard deviations is point is away from the mean.

This weighted regression method reduces sensitivity to sieve selection and small variation in weights at the extremes of the sieve stack.

3.5.4 Tablet Manufacture

3.5.4.1 25 L Gral Pilot Scale

Blends were compressed on an instrumented Manesty Beta press using capsule shaped tooling and the following settings:

- 4 stations
- 2 kN precompression force
- Main compression forces at 4-5 different points within a 7-14 kN range (~at least 50 tablets each force)
- 100 tablets per minute press speed

3.5.4.2 600 and 1250 L Diosna Plant Scale

Tablets blends will be compressed on a production size tablet press at standard speeds using the similar tooling as in 6.4.1. The following conditions will be used:

- 4 stations
- 2 kN precompression force
- Main compression forces at 4-5 different points within a 7-14 kN range (~at least 50 tablets at each force). Once the compression study was finished, the lot was compressed out at an intermediate force (~9-12 kN)
- 60 rpm press speed

3.5.5 Tablet Characterization

3.5.5.1 Tablet Hardness

Diametrical compression strength was measured for at least 10 tablets at each compression force using an appropriate testing machine (the Elizatest 3+ automated tester or the Schleuniger tester). In some cases, 1-2 additional tablets were added to verify low results. Crushing strength for each tablet was recorded in Newtons (N) and averaged. Graphical comparisons of hardness versus compression force were used to compare compressibility of the blends.

3.5.5.2 Tablet Weight

Tablets made at each compression force were weighed individually for at least 10 tablets using a suitable apparatus (an Elizatest 3+ or and a suitably accurate balance for plant scale). The mean, standard deviation and relative standard deviation were measured for each force.

3.5.5.3 Tablet Friability

Tablet friability was measured using for tablets made at an intermediate compression force (10-12 kN) A sample of 100 g +/- 1 g was weighed and added to the friability wheel and spun at 25 revolutions per minute. The tablets were weighed at 10, 20, and 30 minute time points after rotation. The percent weight loss, number of capped or laminated tablets, and number of chipped tablets were measured at each time point and compared for each batch. USP friability testing only requires rotation for 100 revolutions or 4 minutes. Longer time periods were used for this work since they are believed to better simulate stress experienced by the tablets during subsequent unit operations such as coating and packaging.

3.5.5.4 Tablet Dissolution

Tablet dissolution was measured using for tablets made at an intermediate compression force (10-11 kN). The amount of drug substance released from each tablet was determined using a variation of an internally developed dissolution method for Procter & Gamble Pharmaceuticals (previously validated for drug development use). A paddle assembly (apparatus 2 was rotated at 50 rpm) in 900 mL of pH 7.2 buffered media at 37 +/- 0.5 C. Six tablets were selected from each batch and put into separate vessels. A peristaltic pump and poly tubing (with 0.45 um filters) were used to continuously circulate media through a Beckman UV spectrophotometer. Absorbance values were read every 5 minutes and compared to absorbance of a standard solution to compute the % of label of drug substance dissolved from 0 to 90 minutes. For the 1250L factorial lots, values were read every 2 minutes. Data points at 5, 15, 25, … minutes were calculated by determining the average of the points on either side of the time point of interest (e.g. 5, 15, 25,… minutes).

3.5.5 Statistical Data Analysis

Data for both the 25L and 1250L scales were analyzed to determine statistical effects of the process parameters on the granulation blend mean particle size and bulk density as well as tablet friability (weight loss and number of chipped or capped tablets at 30 minutes) and dissolution at 20,30, or 45 minute time points. Only lots which were part of the factorial design were used in the analysis.

Chapter 4. RESULTS AND DISCUSSION

4.1 Effects of Granulation Factors On Granulation Blend and Tablets

4.1.1 Effects of Water

4.1.1.1 25L Gral

Overall, water appears to accelerate the granulation process. Granulation times for the 19 lots made at 25L have been summarized in Table A1 on page 100. These times indicate that the granulation reached its desired torque endpoint faster as the water level increased. Differences in these granulation times may explain some of the differences noted in the granulation blend and tablet parameters:

Granulation Blend Particle Size: As shown in the Table 12 on page 45, mean particle sizes ranged from 180 to 501 microns. While there is some increase in particle size with water for some 140 150 in lbs lots, the trend is not consistent. In fact, statistical analysis of factorial points (130, 150, and 170 in lb lots) does not indicate a significant water effect initially. However, this may be due to missing data points for over granulated lots at 20% water and 170 in lbs. If mean particle sizes of 1000 microns are assumed to represent the over granulated lots, there is a significant water effect indicating decreasing particle size with increasing water. A torque*water interaction indicates this decrease is present for the high torque lots (170 in lbs) but there little to no change on average for low torque levels (130 in lbs). Review of data in Figure 3 on page 46 indicates an interesting trend for 150 in lb lots which is related to water level. There is shift towards coarser particles for the increase in water from 18 to 21.5%. However, from 21.5 to 25%, there is a substantial decrease in particle size. The reason for the shift to smaller particles is again due to the high water level for the 25% water lot which greatly accelerates its granulation time (< 4 minutes). This unusually short time stops granulation before sufficient energy has been added to really build the granules, despite the fact that the 150 in lbs torque level was reached. This example illustrates the problem of considering granulation endpoint alone without consideration of water levels or granulation time. The difference in this lot is also reflected in the density and later in the hardness profiles.

Bulk Density: Blend bulk densities are presented in Table 13 on page 47. As with particle size, a statistical effect of water on granulation blend bulk density was not detected initially. However, the reason for this may be missing data points for the 2 lots which over granulated (lots made at 20% water and 170 in

Table 12: Effect of Water and Torque on Mean Granulation Blend Particle Size at 25L

25L Blend Mean Particle Size (microns)						
		Water (%)				
		18%	**20%**	**21.50%**	**23%**	**25%**
Torque (in lbs)	**110**		218		218	
	130		180/261*		260/237*	
	140		211		270	
	145			430		
	150 – lot a	263		366		206
	150 – lot b			298		
	160		317		319	
	170		>1000**		399/501	

* First number shown is for atomization spray on. Second number is for atomization spray off.

** Not measure-able but very large due to over granulation at this condition.

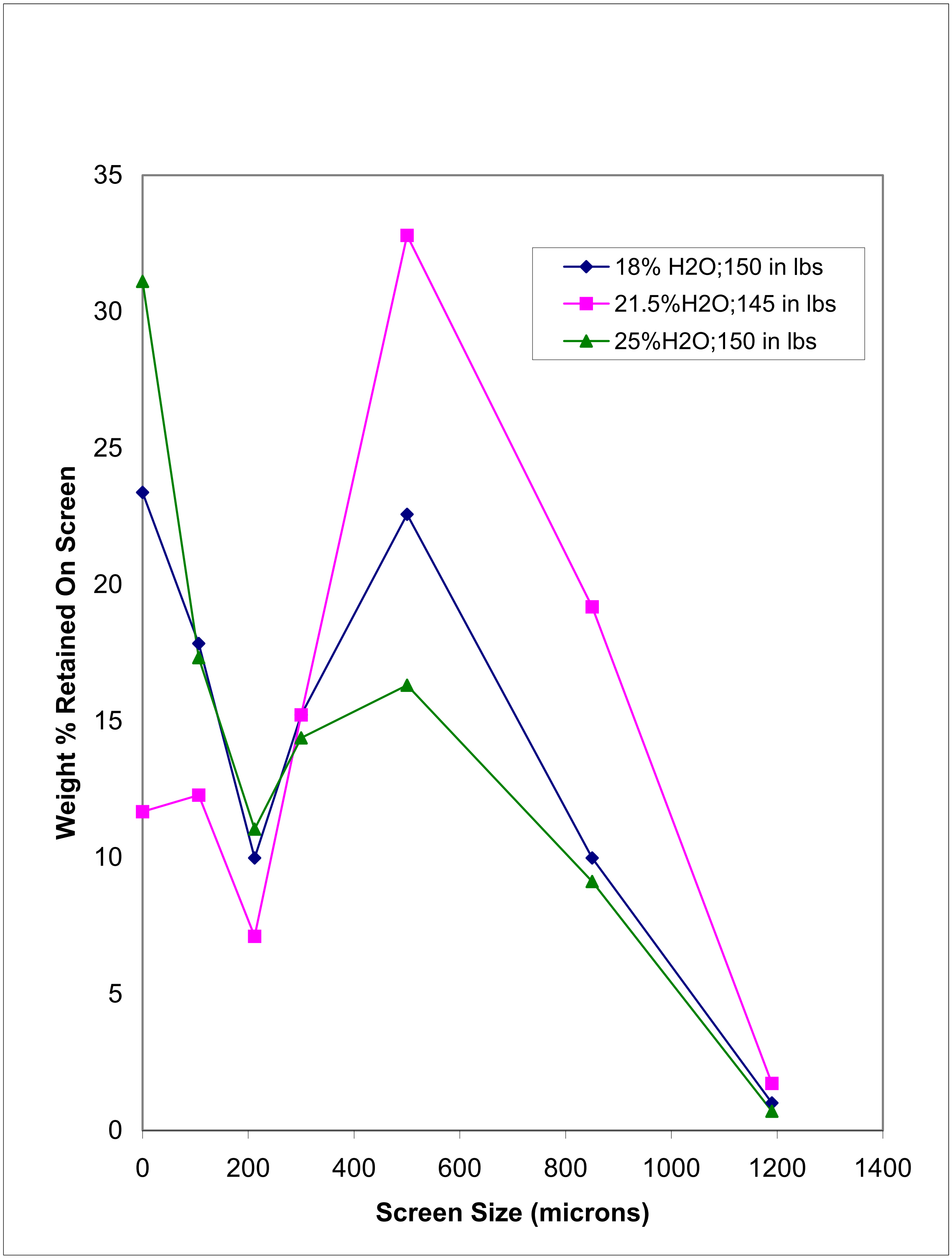


Figure 3: Effect of Water Level On Blend Particle Size For 145-150 In-Lbs Torque (25L)

Table 13: Effect of Water and Torque Endpoint on Granulation Blend Densities at 25L

25L Blend Bulk Densities (g/ml)						
		Water				
		18%	20%	21.50%	23%	25%
Torque (in lbs)	110		0.62		0.56	
	130		0.62/0.66		0.67/0.60	
	140		0.64		0.64	
	145			0.72		
	150 - lot a	0.71		0.71		0.53
	150 - lot b			0.68		
	160		0.70		0.68	
	170		Assume 1.0		0.68/0.69	

NOTE: First number listed is for lot utilizing atomization spray.

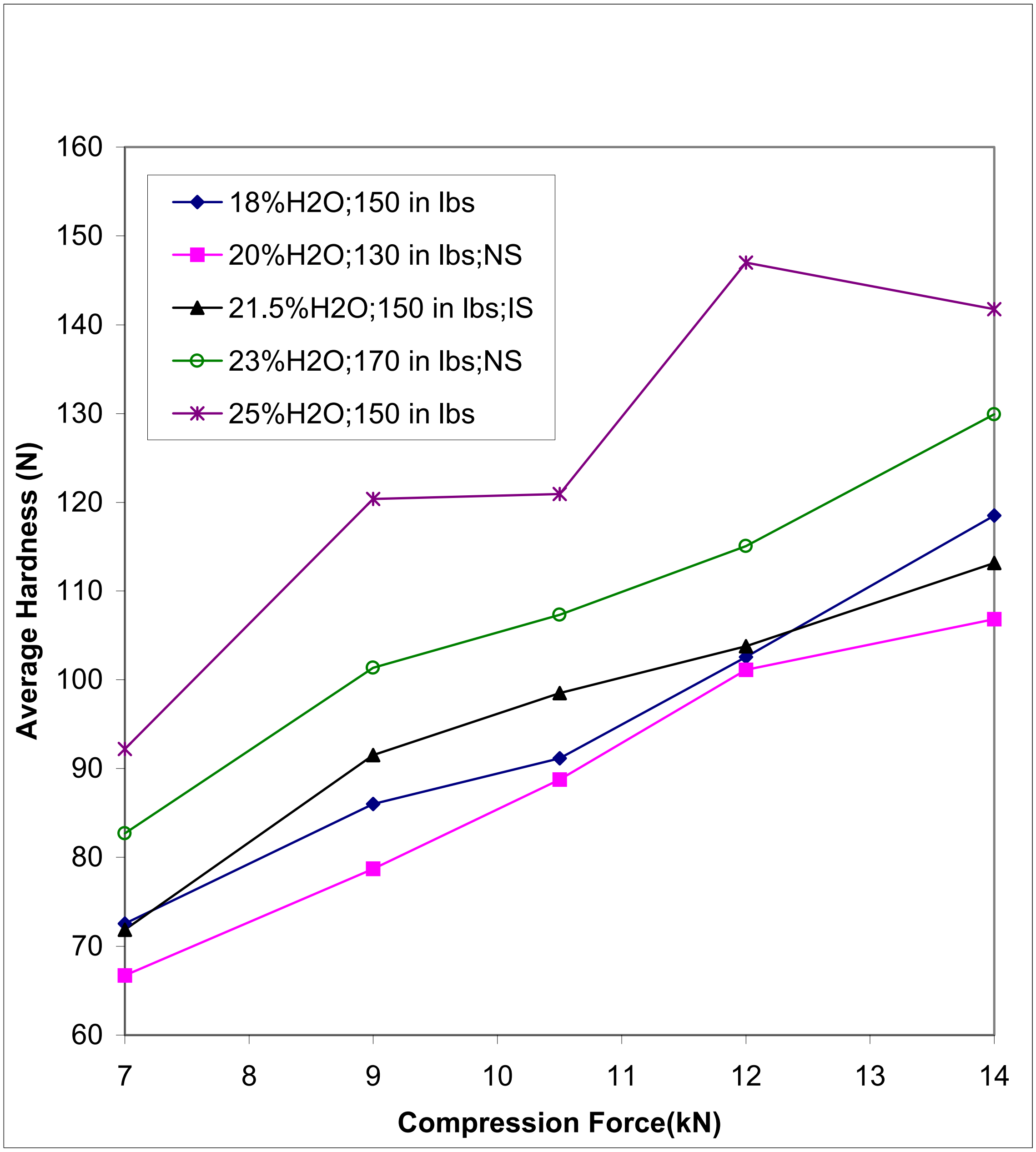
Second number listed is for lot using no spray.

lbs). If large densities values (~1.0 g/ml) are assumed to represent the over granulated condition, then a statistical effect of decreasing average bulk density on for increasing water level is present. Additionally, a torque*water interaction was significant which showed the decrease was much more substantial for high torque lots (170 in lbs) than low torque lots(130 in lbs). The trend of lower densities for higher water levels is especially apparent for the increase from 21.5% to 25% water for the 150 in lbs torque endpoints. There is a decrease from 0.68-0.71 g/ml to 0.53 g/ml for this case, which correlates with a decrease in granulation time from approximately 10 minutes for 21.5% water to under 4 minutes for 25% water. This matches a similar decrease in particle size as explained previously.

Tablet Weight and Hardness: Compression curves collected for 25L lots were generally linear across the range of compression forces tested (7-14 kN) As shown in Table A7 on pages 105-112, tablet weight data collected together with the hardness testing shows that average tablet weight was maintained within 98% of the theoretical target weight of 522.6 mg. With the exception of the lot made at 25% water and 150 in lbs of torque, all individual weights were within 5% of target. The 25% water lot showed wider variation with an individual tablet weight which was only to 88% of target weight. This lot also had the highest % relative standard deviation (RSD) of combined tablet weights from all compression forces (4.3%). This is not unexpected given the fine particle size distribution seen for this lot previously. The lot made with 23% water and a torque endpoint of 110 in lbs had the second highest %RSD at 2.5%. This lot also was fine in particle size. The remaining 15 lots had even better weight constant with 11 lots at 1% RSD and 4 lots between 1-2 % RSD. This indicates excellent weight control for the majority of the lots. Thus, the tablet weights may be considered essentially equivalent across all lots for hardness evaluation.

Examination of the hardness data indicates that water does affect average tablet hardness for the 25L lots. Tablet hardness decreases with increasing water level as demonstrated in the curves in Figure 4 on page 50. Lots made with 18-20% water are near the bottom of the curves. The lot utilizing a 25% water level exhibited the highest hardness values.

Although higher water levels also appeared to result in lower blend densities, a significant correlation between blend density and average tablet hardness could not be found, when analyzing average tablet hardness values at 10.5 kN. (Since hardness profiles were relatively linear, trends in hardness values at 10.5kN would be hold for other compression forces as well.) However, the water effect was statistically significant.



NOTE: IS = Intermediate Spray Level; NS = No Spray
All other conditions utilized atomization spray

Figure 4: Effect of Water Level On Average Tablet Hardness (25L)

Tablet Friability: Tablet friability results for 25L lost are summarized in Table A12 on page 130-131. Percent weight loss numbers varied from 0.3% for 10 minutes to 1.2% seen after 30 minutes of test time. No capped tablets were observed for any time point, and the number of chipped tablets varied from 0 to 60, seen in a sample tested for 30 minutes. Despite the wide range of results, no correlation of friability results with water level was observed.

Tablet Dissolution:

Tablet dissolution values reached 100% by the 60 minute time point. Dissolution variation is widest within the 15 to 45 minutes window. Data in Table A15 on pages 135-147 shows variation in 20 minutes average dissolution values ranged from 66 to 94%.

Statistical analysis conducted on factorial points (20, 21.5 and 23% water) indicates a significant water effect for 20 minutes profiles. The 20 minute time point was chosen for analysis since this was one of the times showing the widest variation in dissolution. Average dissolution appears to decrease slightly (~10% or less) with increasing water level within the range of 20-23%. However, as dissolution profiles in Figure 5 on page 60 indicate, the trend does not hold when adding in the non-factorial lots, thereby expanding the water level range to 18-25%. The dissolution profile for the 18% water level is virtually the same as

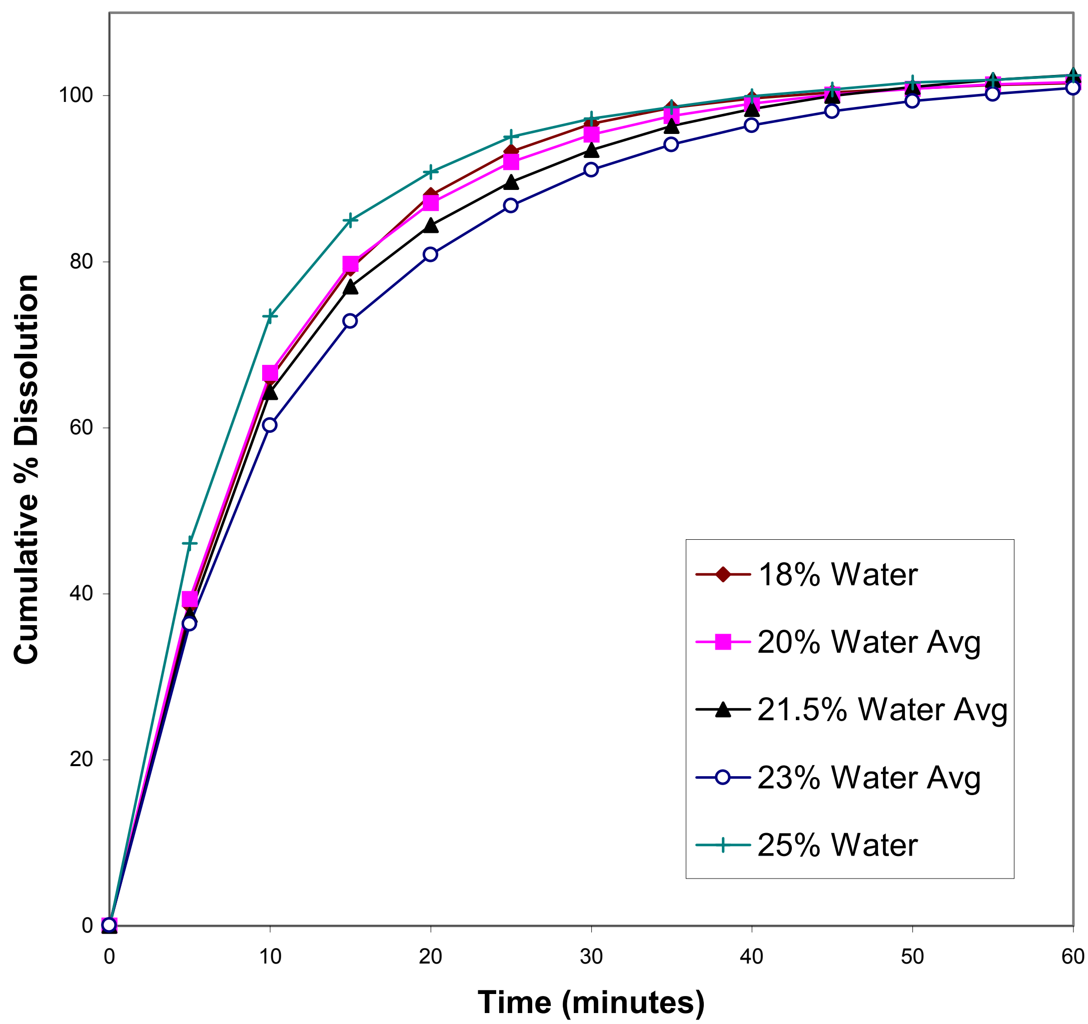


Figure 5: Effect of Water on Average Tablet Dissolution (25L)

the 20% level, and the dissolution for the 25% water level is faster than predicted. Individual profiles for the 20% water level are presented in Figure 6 on page 55 as an example of the relatively wide variation in rates at a given water level. The departure of the 25% water lot from the trends within the 20-23% water level is not surprising given similar departures in granulation blend and particle size for similar water levels.

4.1.1.2 1250L Diosna

Granulation Blend Particle Size: Comparison of particle size profiles at 1250L shows that water does influence particle size, as seen in the mean particle sizes calculated in Tables 14 and 15 on pages 55-56. The effect of water on particle size depends on the torque level. Statistical analysis indicates that water and a torque*water interaction are significant at the $p=0.05$ level. Particle size increases with increasing water level for the low %K endpoint lots, but decreases with increasing water for the high %K endpoint lots. The reason for this behavior is not clear, but a similar interaction was seen for 25L lots.

Granulation Blend Density: Granulation blend densities are listed in Tables 16-17 on pages 59-60. Density values were narrow, within the range of 0.70 – 0.76 g/ml. However, there is a consistent decrease in bulk density with increasing water. Statistical analysis shows this effect is statistically significant at the $p=0.05$ level. As with the 25L lots, this effect may be due to the shorter granulation times for higher water lots than low water lots. Granulation times for 1250L are

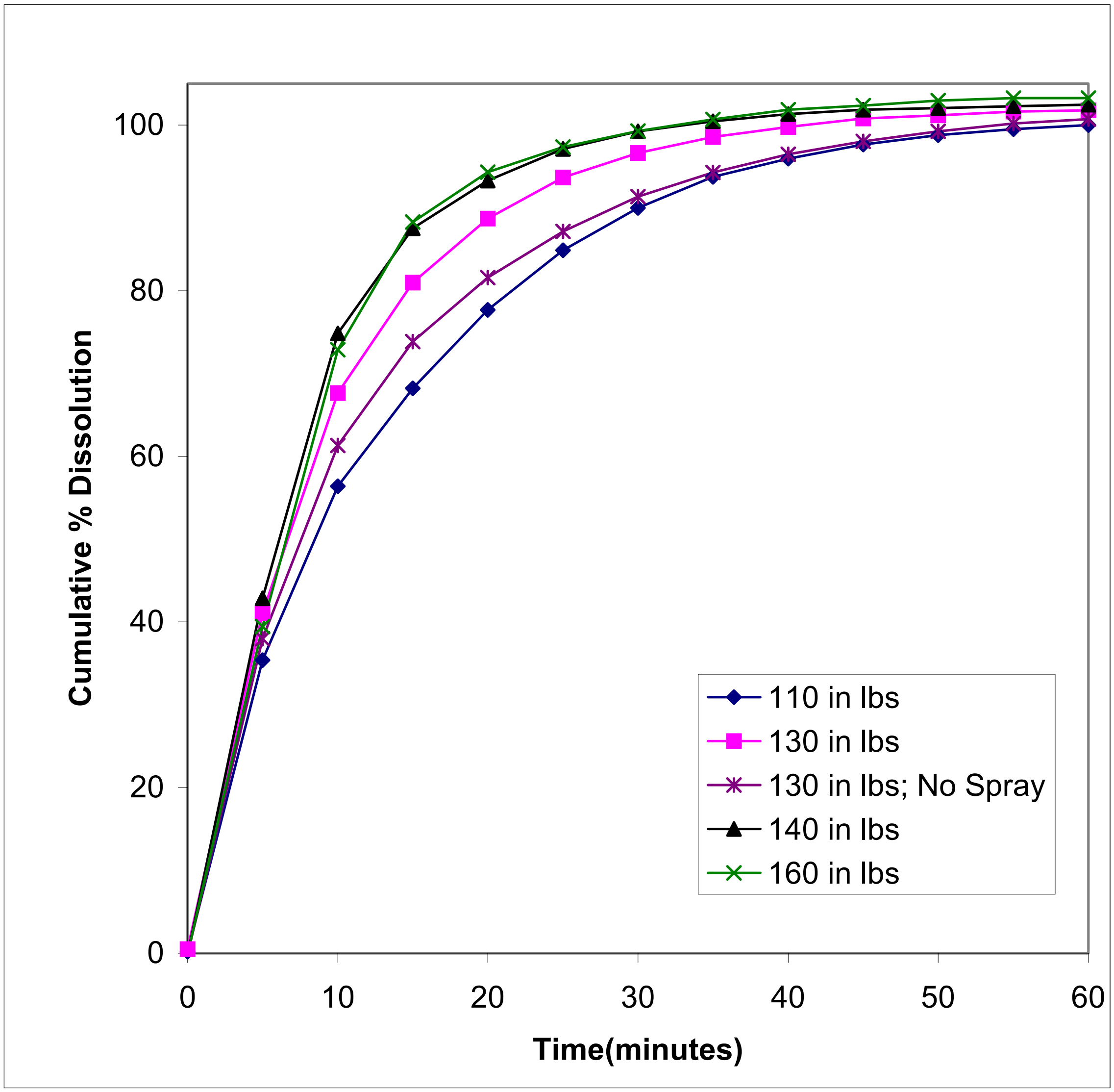


Figure 6: Average Dissolution For 20% Water Level Lots (25L)

Table 14: Effect of Water and Torque on Granulation Blend Mean Particle Size (1250L) For Lots Using Low Drug Density

1250L Mean Particle Size (microns)				
Low Drug Bulk Density Lots				
		Water		
		20%	21.5%	23%
% K	33	314		330
	41		402*	
	48	646		513
* Lot used middle drug bulk density lots.				

Table 15: Effect of Water and Torque on Granulation Blend Mean Particle Size (1250L) For Lots Using High Drug Density

1250L Mean Particle Size (microns)				
High Drug Bulk Density Lots				
		Water		
		20%	21.5%	23%
% K	33	301		354
	41		402*	
	48	607		491
* Lot used middle bulk density drug lots.				

Table 16: Effect of Water and Torque on Granulation Blend Bulk Density (1250L) For Lots Using Low Drug Density

1250L Blend Bulk Densities (g/ml)				
Low Drug Bulk Density Lots				
		Water		
		20%	21.5%	23%
% K	33	0.76		0.71
	41		0.73*	
	48	0.75		0.71
* Lot used middle bulk density drug lots.				

Table 17: Effect of Water and Torque on Granulation Blend Bulk Density (1250L) For Lots Using Low Drug Density

1250L Blend Bulk Densities (g/ml)				
High Drug Bulk Density Lots				
		Water		
		20%	21.5%	23%
% K	33	0.73		0.70
	41		0.73*	
	48	0.74		0.70
* Lot used middle bulk density drug lots.				

listed in Table A2 of page 99. Shorter granulation times limit total energy input in to the system, thereby limiting densification of the granulation.

Tablet Weight and Hardness: Tablet weight data presented in Table A8 on pages 113-116 indicates had tablet average weights were within 98% of target (522.6 mg). Weight variation within each lot was held to 2.7% or less. Thus, tablet weights may be considered equivalent across all lots for purposes of comparing tablet hardness data.

Evaluation of tablet hardness data does not show a significant impact of water level on tablet hardness.

Tablet Friability: There was no effect of water apparent for the friability weight loss during friability testing. This includes test results for 10, 20, and 30 minutes of testing time. However, there was a water effect observed for the number of capped tablets after 30 minutes as well as the number of chipped tablets obtained after friability testing for 20 and 30 minutes as shown in Table 18 on page 60. Statistical analysis for both parameters verifies a significant water and water * %K interaction at a $p=0.05$ level, indicating the water effect varies with level of %K. The number of capped tablets decreased with increasing water for low %K lots but was unchanged for high %K. A different trend was seen for chipped tablets. The number of chipped tablets increased with increasing water for low %K but decreased with water for high %K. The reason for the difference

Table 18: Effect of Water And Torque On The Number of Chipped Tablets After Friability Testing For 10, 20 or 30 Minutes

%K	33 %K				48 % K			
% Water	20% Water		23% Water		20% Water		23% Water	
Drug Bulk Density	Low	High	Low	High	Low	High	Low	High
10 minutes	1	2	0	0	0	0	0	0
20 minutes	23	40	94	56	10	0	3	1
30 minutes	95	102	175	146	48	37	25	25

in trends and effect of water is not clear, especially since water level did not affect hardness, which could impact friability performance, but the effect on chipped tablets is statistically significant.

Tablet Dissolution: Dissolution profiles flattened at 100% after 60 minutes of test time. Comparison of profiles prior to 60 minutes shows a water effect on dissolution. Dissolution is slightly higher for lower water lots. The effect is small (less than 10%) but statistically significant at the p=0.05 level for 30 minute data. To further verify this effect, dissolution data for three additional 1250L confirmation lots (two at 23% water and one at 21.5% water) was assessed as shown in Figure 7 on page 62. The trend was consistent. The 20 and 21.5% water lots were slightly faster on average (10% or less) than those at 23%.
Dissolution profiles data for individual lots are provided for reference in Tables A16-A17 on pages 149-154.

4.1.2. Effects of Granulation Endpoint

4.1.2.1 25L Gral Torque Endpoint

Particle Size: As expected, granulation endpoint had a significant impact on the particle size of granulation blend. Higher torque endpoints correspond to greater amounts of energy added to the granulation, which results in larger particle size.
This increase is seen an increase in mean particle size presented in Table 12 on

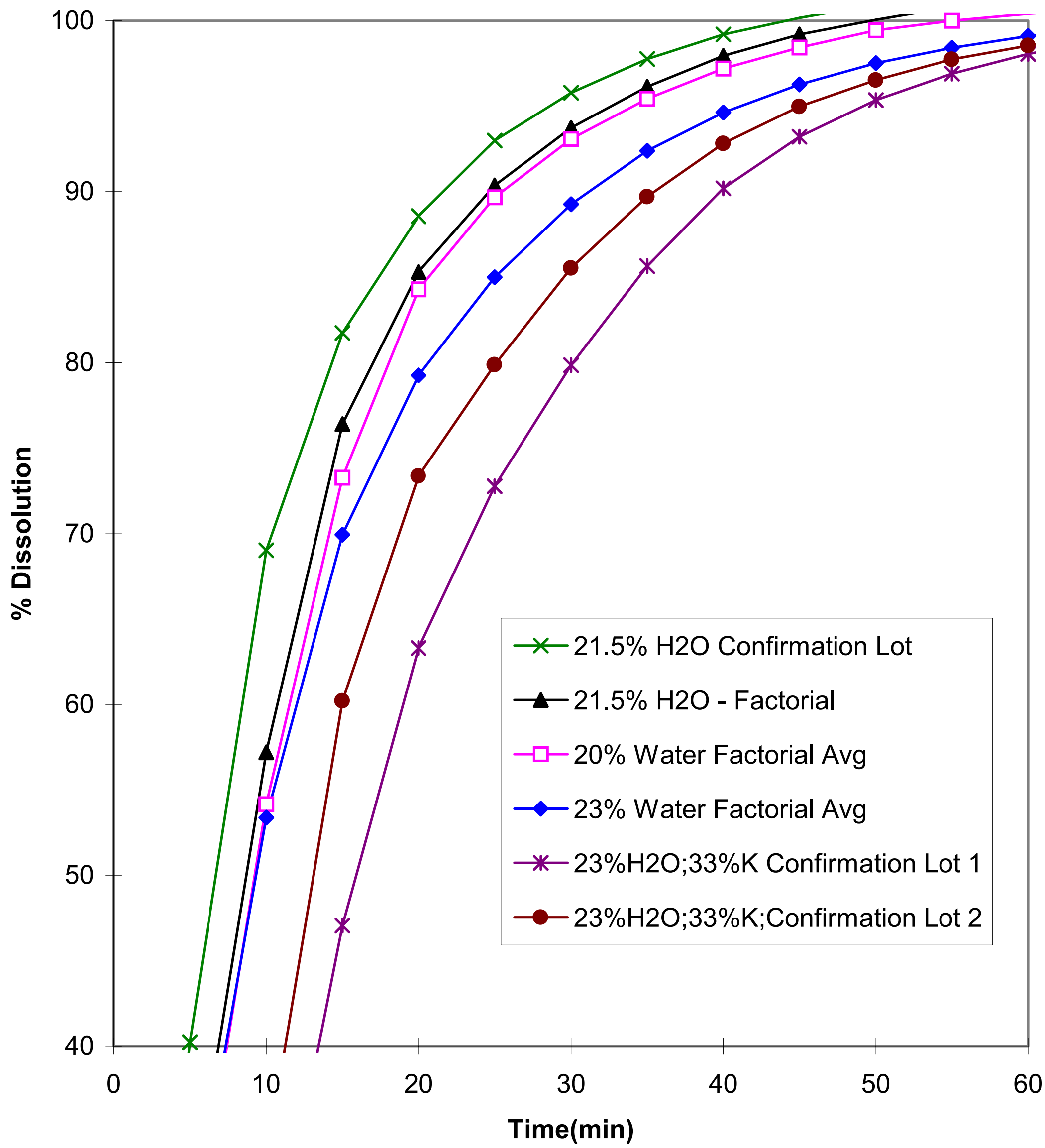


Figure 7: Effect of Water Level On Tablet Dissolution (1250L)

page 45. The effect is further illustrated for 23% water level lots in Figure 8 on page 64. The torque effect was most obvious for the two lots made at 20% water with granulation endpoints at 170 in lbs which over-granulated. Statistical analysis for factorial points (130 – 170 in lbs) indicates the granulation endpoint effect is statistically significant at the p=0.05 level, when assuming mean particle size of 1000 microns to represent the over granulated lots at 170 in lbs.

Density: Granulation endpoint also influenced granulation blend densities, as seen in Table 13 on page 47. In general, higher torque endpoints result in higher blend densities, again due to the higher amounts of energy added into the granulation, which results in more densification. Although statistical analysis does not support significance of torque (p=0.06) with data missing for the 2 over granulated lots 170 in lbs, the torque effect becomes significant if densities of 1.0 g/ml are assumed to represent these lots.

Tablet Weight, Hardness, and Friability: Trends in tablet weight, hardness, or friability (weight loss and number of chipped tablets) due to torque level endpoint were not detected.

Tablet Dissolution: Statistical analysis and comparison of profiles does show a significant effect increase of 20 and 30 minutes average dissolution with increasing torque for factorial lots. However, this correlation is lost when results for non-factorial lots are included.

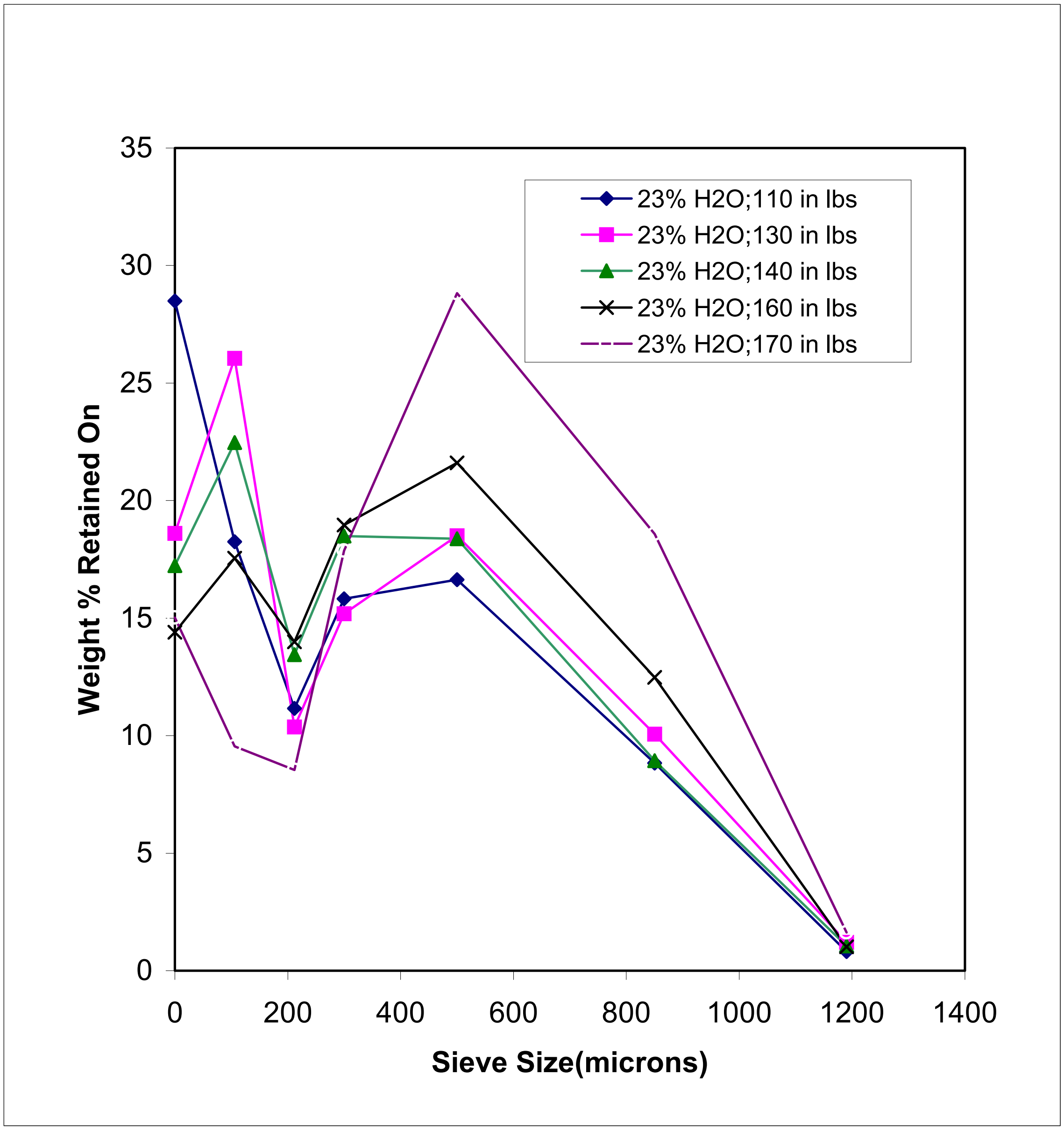


Figure 8: Effect of Torque Granulation Endpoint on Blend Particle Size Distribution (25L)

4.1.2.2 1250L Diosna %K Endpoint

Granulation Blend Particle Size: Mean particle sizes for 33%K lots ranged from 301 to 354 microns as shown in Tables 14 and 15 on page 55-56. This is within the target range of 200-400 microns. Mean particle size results for 48%K lots ranged from 491 to 646 microns. Higher %K's result in higher energy input into the granulation which results in larger particle size granulations. The %K effect was statistically significant at the $p=0.05$ level. As described in section 4.1.1.1, water and %K were involved in an interaction, where the effect of water varied with %K.

Granulation Blend Density: Blend densities are summarized in Tables 16 to 17 on pages 57-58 and ranged from 0.70 to 0.76 g/ml. Higher %K should result in more energy input to the system, which should increase densification as well as particle size. However, a correlation of %K and blend density was not observed. The reason for this is not clear.

Tablet Weight and Hardness: As described in section 4.1.1.2, average tablet weights were controlled within 98% of target (522.6 mg) and considered equivalent across lots for hardness testing.

Tablet hardness profiles (hardness vs. compression force) do show an effect of %K on tablet hardness. As shown in Figure 9 on page 66, higher average tablet

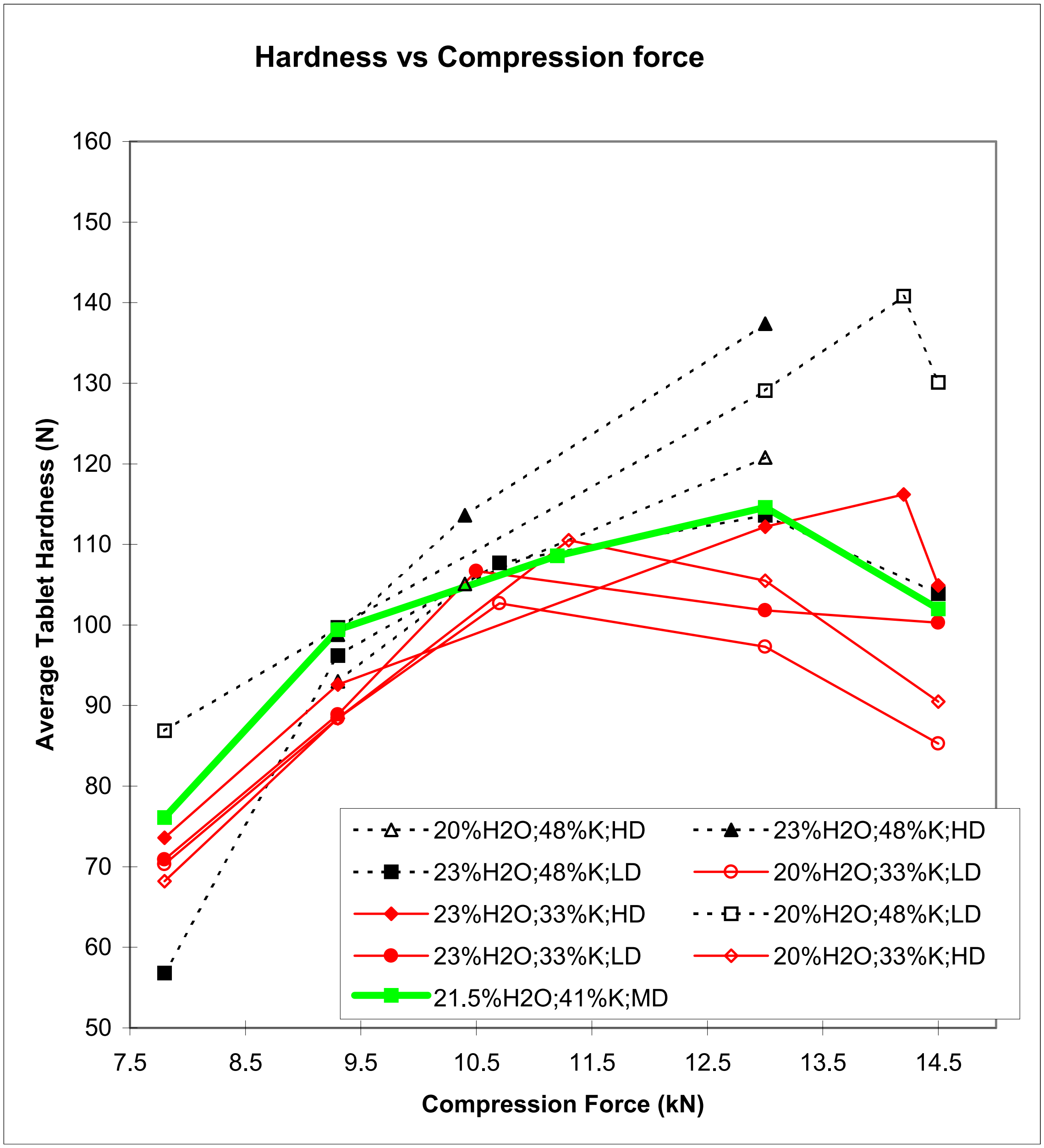


Figure 9: Effect Of %K Endpoint On Average Tablet Hardness Profiles (1250L)

NOTE: HD = High drug density lots; LD = Low drug density lots; MD= Middle drug density lots.

hardness is observed for higher %K lots than lower %K lots at a given compression force. Said another way, lower %K lots generally have to be compressed at higher forces to achieve the same tablet hardness. Unlike the 25L lots, the increase in hardness is not linear across the entire range of compression forces (7.5-14.5kN). Tablet hardness averages peak and slightly decline at compression forces >10.5 kN. Peak hardness values for 33%K lots range from 102 to 116N, while those for 48%K lots range from 114 to ~140N.

Tablet Friability: Results for post friability weight loss and number of capped tablets listed in Table A13 on page 132 are affected by the %K endpoint. The ability to see the impact increases with the test time, i.e. differences between %K lots are easier to detect for 30 minutes versus 10 or 20 minutes of test time. Statistical analysis of factorial lots shows significant decrease in weight loss for increasing %K at the p=0.05 level. Results ranged from 0.70% to 1.04% for 33%K lots and 0.12 to 0.23 for 48%K lots. The results for capped tablets do also show a statistical correlation for the factorial lots. Addition of confirmation lots made at 33%K to the data set indicates a clear trend towards less capping for higher %K endpoints (>33%) as shown in Figure 10 on page 68. This effect may be related to tablet hardness which was higher for higher % K (>33%) lots.

Tablet Dissolution: No significant affect of %K on tablet dissolution was observed.

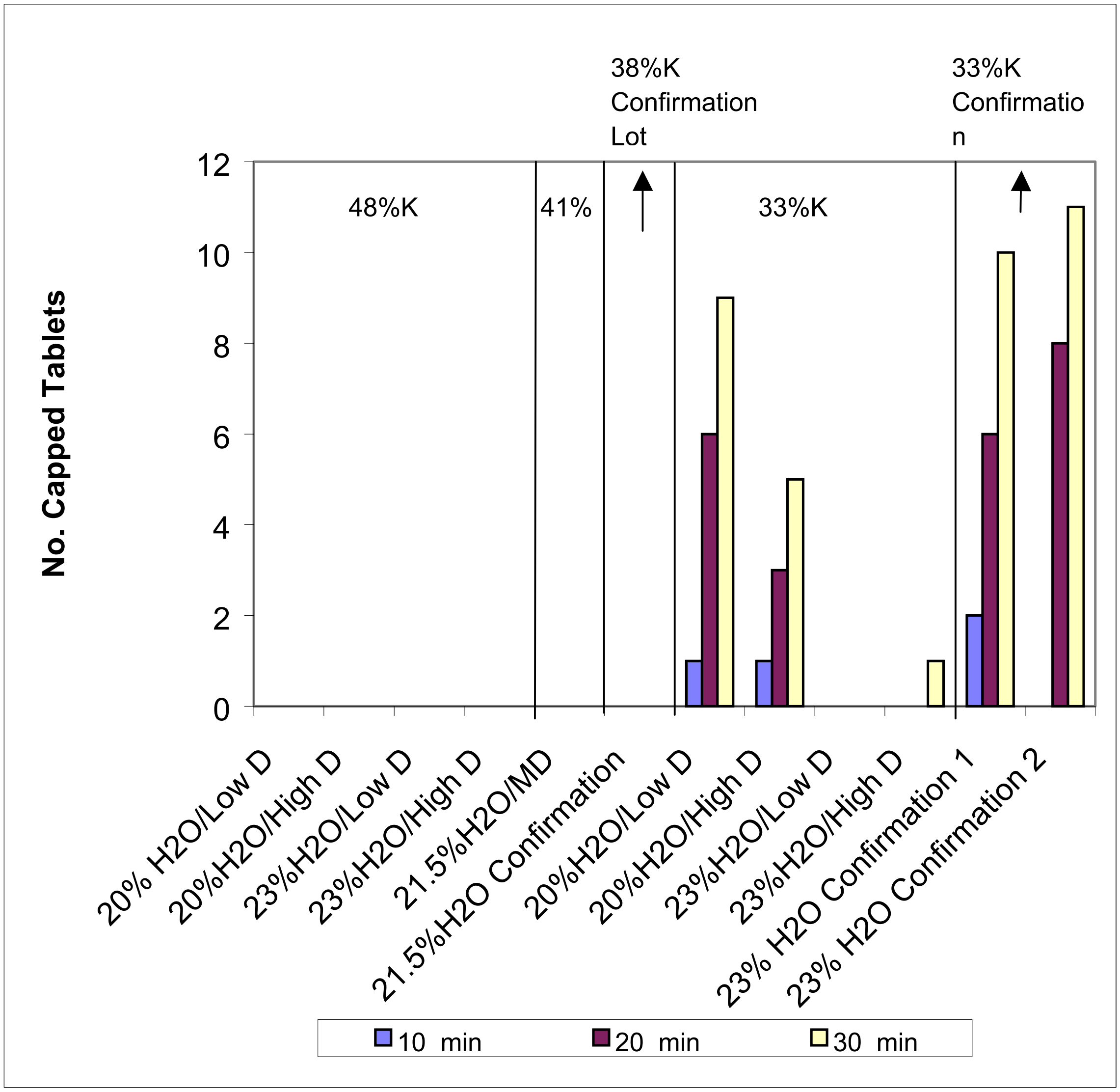


Figure 10: Effect Of %K On Post Friability Number of Capped Tablets (1250L)

4.1.3 Effect of Atomization Spray in the 25L Gral

There was only one apparent correlation of atomization spray use with granulation blend tablet characteristics. Tablet friability weight loss decreased with increasing amount of atomization spray. Friability weight losses listed in Table A12 on page 130-131 show the widest ranges in weight loss for 30 minute test results. Results varied from 0.47% to 1.13% for lots utilizing atomization spray but were higher (0.78% – 1.17%) for lots without atomization spray. Statistical analysis shows the decrease in 30 minute weight loss for increasing atomization spray was statistically significant at $p= 0.05$.

4.1.4 Effect of Drug Bulk Density in the 1250L Diosna

Drug bulk density only affected one granulation blend or tablet characteristic. A decrease in granulation blend bulk density is observed for increasing drug bulk density as shown in Tables 16 -17 on pages 57-58. Blend densities for low drug density lots range from 0.71-0.76 g/ml while those for high drug density lots varied from 0.70-0.74 g/ml. While the differences are not large, they were statistically significant at the $p=0.05$ level. This trend is unexpected as the granulation bulk density moves in the opposite direction of the drug bulk density. The reason for this trend may be linked to the granulation times. Data in Table A2 on page 99 indicates that the granulation times for the high drug density lots are roughly 0.5 to 7 minutes longer than low drug density lots, which would result in less energy input into the system and less densification.

4.2 Determination of Factor Levels to Provide Similar Granulation Blend and Tablets for 25L Gral

4.2.1 25L Compared to 600L Diosna

Granulation Blend Particle Size: Comparison of 25L data to baseline data for 600L lots indicates that torque levels of approximately 140 in lbs most closely follow the particle size distribution of the 600L lots as shown in Figure 11 on page 71.

Granulation Blend Bulk Density: Bulk densities for 600L baseline lots range from 0.63 to 0.70 as shown in Table A6 on page 104. Review of density results for 25L lots indicate that this range is achieved for lots made with 140 in lbs of torque and 20-23% water. Density values for lots made with these conditions were both 0.64 g/ml.

Tablet Hardness: Tablet hardness profiles between 25L lots and 1250L lots are compared in Figure 12 on page 72. Tablet hardness for the 600L lots is higher than most of the 25L lot conditions. Only the 25% water level lot showed comparable hardness values to the 600L scale. Lots made at the 23% water level were next closest to the 600L scale, and the differences from the 600L scale increase as the 25L water level decreases.

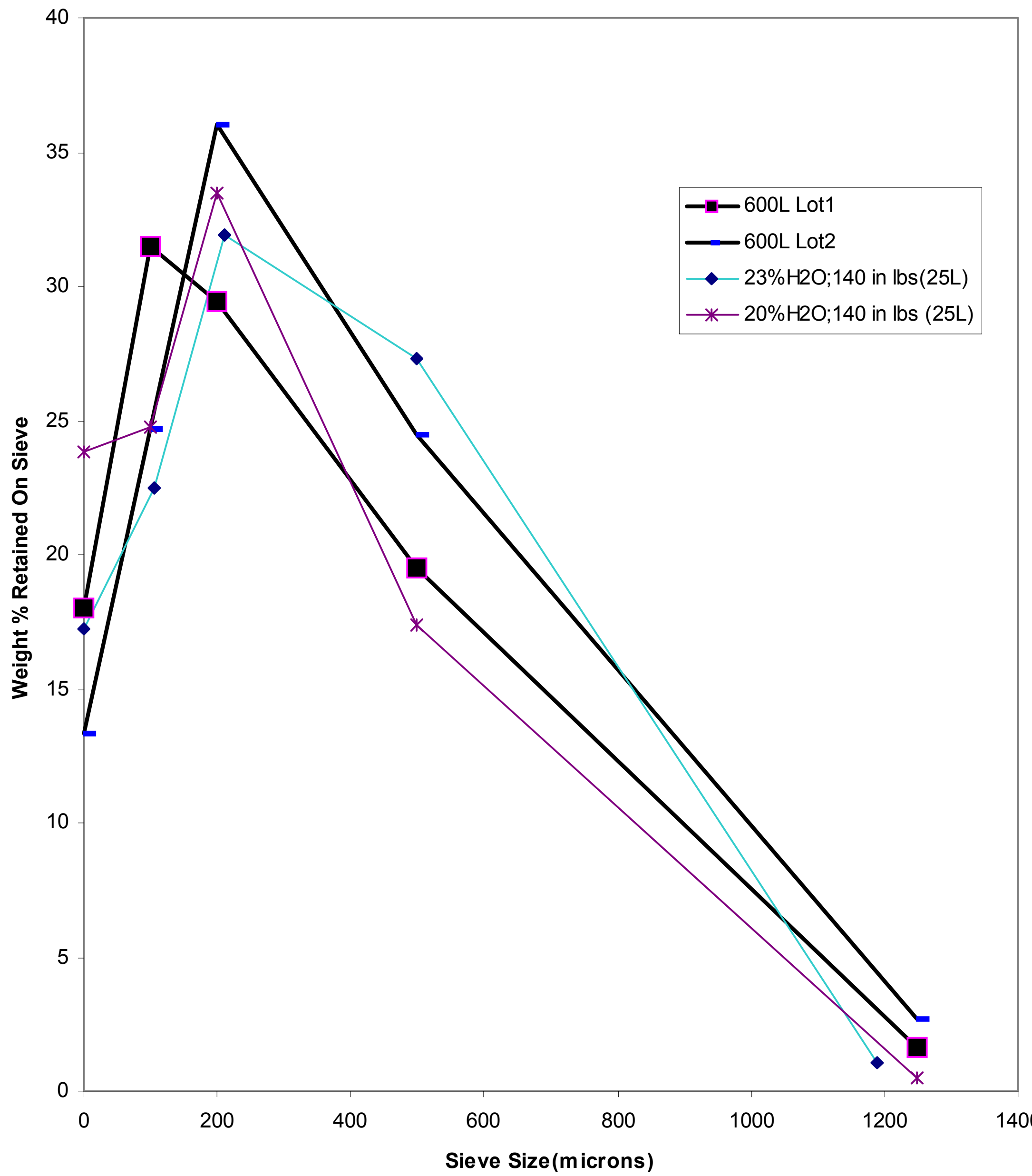


Figure 11: Comparison of Particle Size Distribution: 25L Lots Vs. 600L Lots

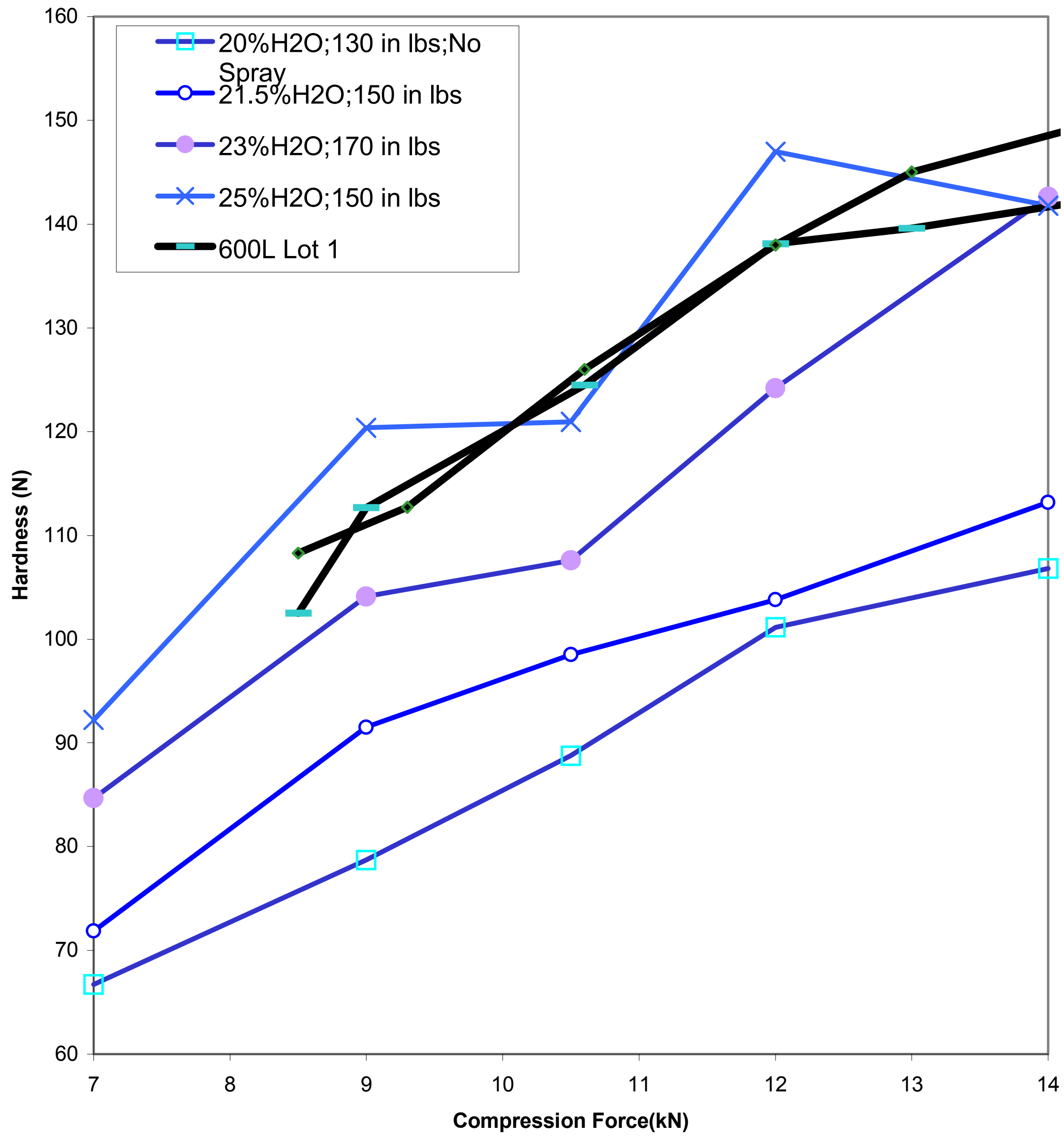


Figure 12: Comparison of Tablet Hardness Profiles For 25L and 600L Lots

Tablet Friability: Tablet friability weight loss for 25L lots varied from 0.47 to 1.17% after 30 minutes of testing. Thirty minute results for 600L varied from 0.24 to 1.32%. No tablet capping was observed for either the 600L or the 25L lots. The number of chipped tablets for 30 minute results varied from 1 to 60 tablets for the 25L lots, while this number ranged from 126-139. Thus, while weight loss ranges were similar across the entire range of lots produced, chipping results were much lower for the 25L lots and not at all predictive of the 600L results. Therefore, it is not possible to specify 25L granulation conditions which are predictive of 600L friability performance. This may be due to differences in the tablet press equipment and compression conditions (e.g. dwell time) which could not be scaled. Friability data is presented in Tables A12 on pages 130-131 and Table A14 on page 134.

Tablet Dissolution: Comparison of dissolution profiles via the SUPAC f2 analysis indicates that all 25L lots met the similarity criteria (50< f2 value <100) as shown in Table 19 on page 74. In general, f2 values were consistently higher for 21.5 and 23% water lots. Comparison of dissolution profiles indicates that these lots were generally closer to the 600L lot profiles.

Table 19: SUPAC f2 Comparison of 25L to 600L Lots

SUPAC f2* Values 25L Vs. 600L Average						
		Water				
		18%	**20%**	**21.50%**	**23%**	**25%**
Torque (in lbs)	**110**		58		60	
	130		60/85		52/79	
	140		51		79	
	145			76		
	150 - lot a	54		65		62
	150 - lot b			70		
	160		51		62	
	170		NA		67/80	
NOTES: 2nd number is without atomizing spray.						

* f2 values of 50 to 100 indicate equivalent dissolution.

4.2.2 25L Gral Compared to 1250L Diosna

Granulation Blend Particle Size: Particle size distribution for both 25L and 1250L lots was highly dependent on choice of endpoint (torque &K). Overall, some overlap of particle size distributions could be achieved by varying endpoints. In order to focus on one specific comparison, particle size profiles at 25L were compared to one specific baseline at 1250L. The confirmation lot made with 21.5% water and 38%K was chosen as the baseline since this appears to be optimized condition for tablet friability and dissolution at 1250L. Figure 13 on page 76 shows that 25L lots made at 140-150 in lbs are closest in shape and magnitude compared to the 1250L baseline. There still were some minor differences in particle size distribution shape, i.e. the lots made at 25L tend to have higher % of material on the pan (fines) and higher percentages retained on the 200 microns sieve. However, these differences are minor and do not appear to prevent achieving similar tablet hardness or dissolution at 25L.

Granulation Blend Density: Granulation blend density values for 1250L lots ranged from 0.70 – 0.76 g/ml as seen in Tables 16 and 17 on pages 57-58. For 25L lots, bulk densities above 0.70 g/ml were generally achieved for lots made with 145-150 in lbs and 18% - 21.5% water as shown in Table 13 on page 46.

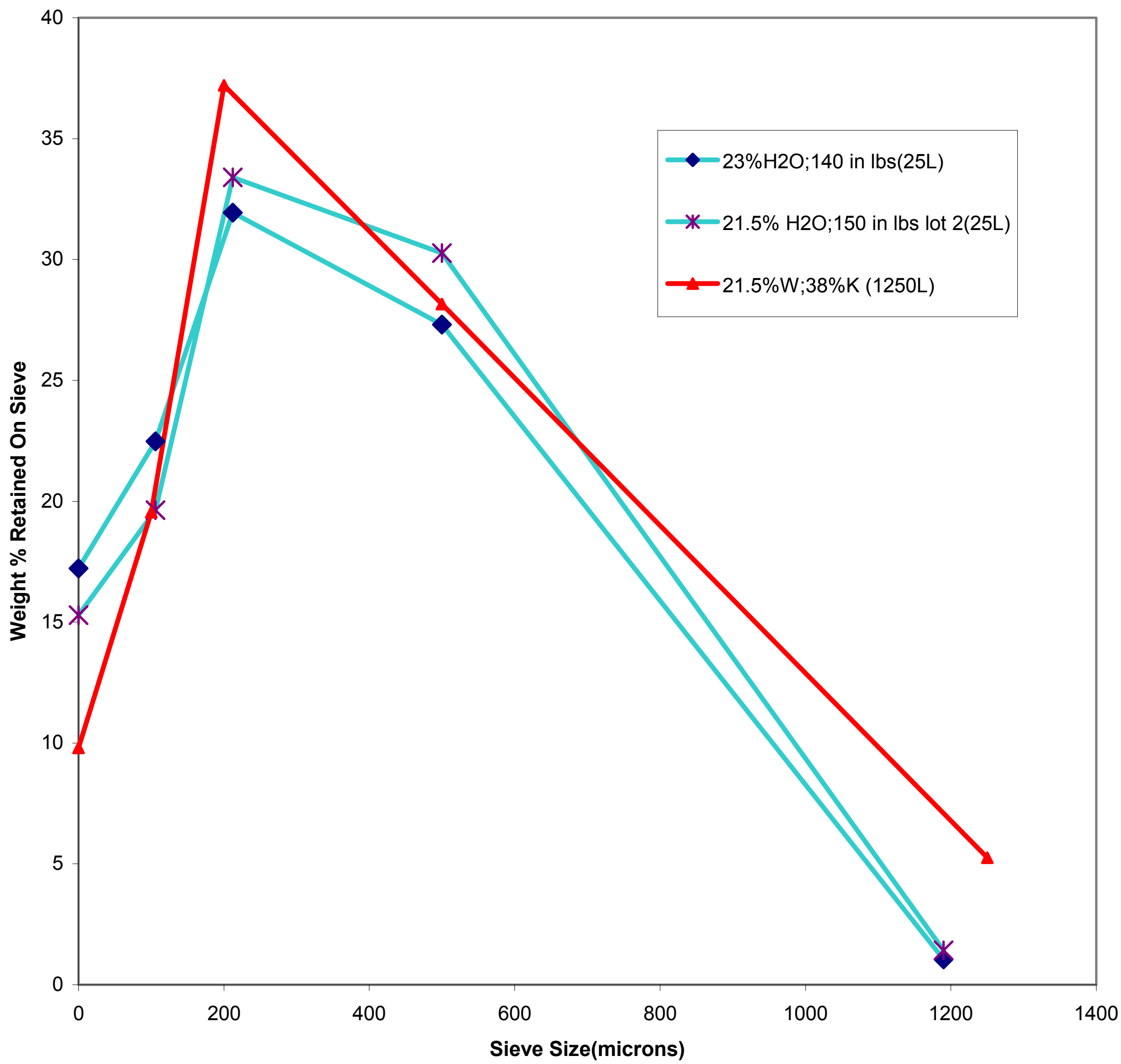


Figure 13: Comparison Of Particle Size Distribution 25L Vs. 1250L Lots

Tablet Hardness: Tablet hardness profiles for 25L lots were more linear than those at 1250L as seen in Figure 14 on page 78. Profiles for 1250L lots had a peak hardness seen for compression forces greater than 10 kN while those at 25L kept increasing with force. Given the similarities in granulation blend particle size, density and appearance, it's believed that these differences are mostly related to the differences in tablet press and run conditions. The slower press speed for the 25L lots would increase the dwell time for compression which could eliminate or move the peak hardness values seen at 1250L. Overall, similar tablet hardness can be achieved at 25L for 20-23% water and 150 – 170 in lbs of torque.

Tablet Friability: Differences in tablet friability results for 25L and 1250L are most easily seen in the 30 minute test results, particularly for the number of capped an chipped tablets as listed in Tables A12 and A13 on pages 130-133. The number of capped tablets varied from 0 to 11 tablets for 1250L but was 0 for all 25L lots. The number of chipped tablets varied from 25 to 175 for 1250L and from 3 to 60 tablets for 25L. Thus, friability problems seen at 1250L were not well predicted at 25L.

This may be due to the differences previously described in the tablet press equipment and run conditions between the two scales.

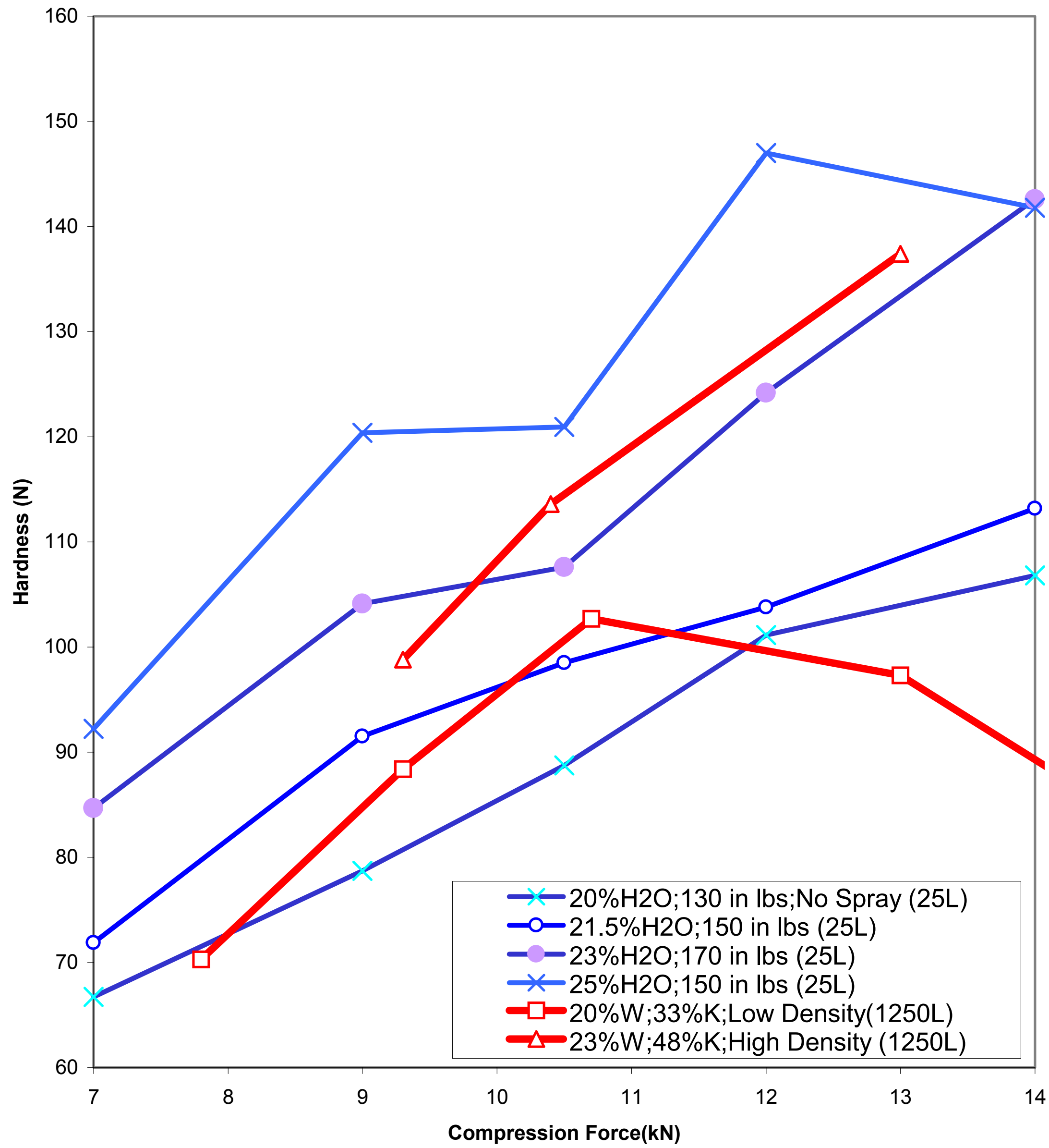


Figure 14: Comparison of Hardness Profiles: 25L to 1250L Lots

Tablet Dissolution: Tablet dissolution profiles at 25L and 1250L were compared with the SUPAC f2 comparison as shown in Table 20 on page 80.

The 1250L confirmation lot made with 21.5% water and 38% K was again used as the 1250L baseline. All 25L lots met the 50 to 100 f2 similarity criteria with exception of 1 lot made with 23% water and 130 in lbs of torque. Thus all 25L lots may be considered equivalent to 1250L in dissolution. The reason for the single lot failing to meet the similarity criteria is not clear, and couldn't be correlated with any other granulation blend or tablet parameters for this lot.

4.3 Evaluation of Diosna 600L to 1250L Scale Up

Granulation Blend Particle Size: Particle size could be increased or decreased with choice of granulation endpoint. The 1250L lots made with 33% K were closest in particle size distribution to the 600L baseline but were slightly coarser as shown in Figure 15 on page 81.

Granulation Blend Bulk Density: Granulation blend bulk densities for the 600 L lots range from 0.63 to 0.70 g/ml while those for 1250L ranged from 0.70 to 0.76 g/ml as shown in Tables A6 on page 104 and 16 to 17 on pages 57 -58. Thus 1250L densities are slightly larger than those at 600L. This difference is

Table 20: SUPAC f2 Values 25L Vs. 1250L Lots

SUPAC f2* Values 25L Vs. 1250L Average						
		Water				
		18%	20%	21.50%	23%	25%
Torque (in lbs)	110		88		86	
	130		96/67		41/54	
	140		73		60	
	145			70		
	150 - lot a	79		82		90
	150 - lot b			79		
	160		72		97	
	170		NA		65/68	
NOTES: 2nd number is without atomizing spray.						

* An f2 value of 50 to 100 indicates equivalent dissolution.

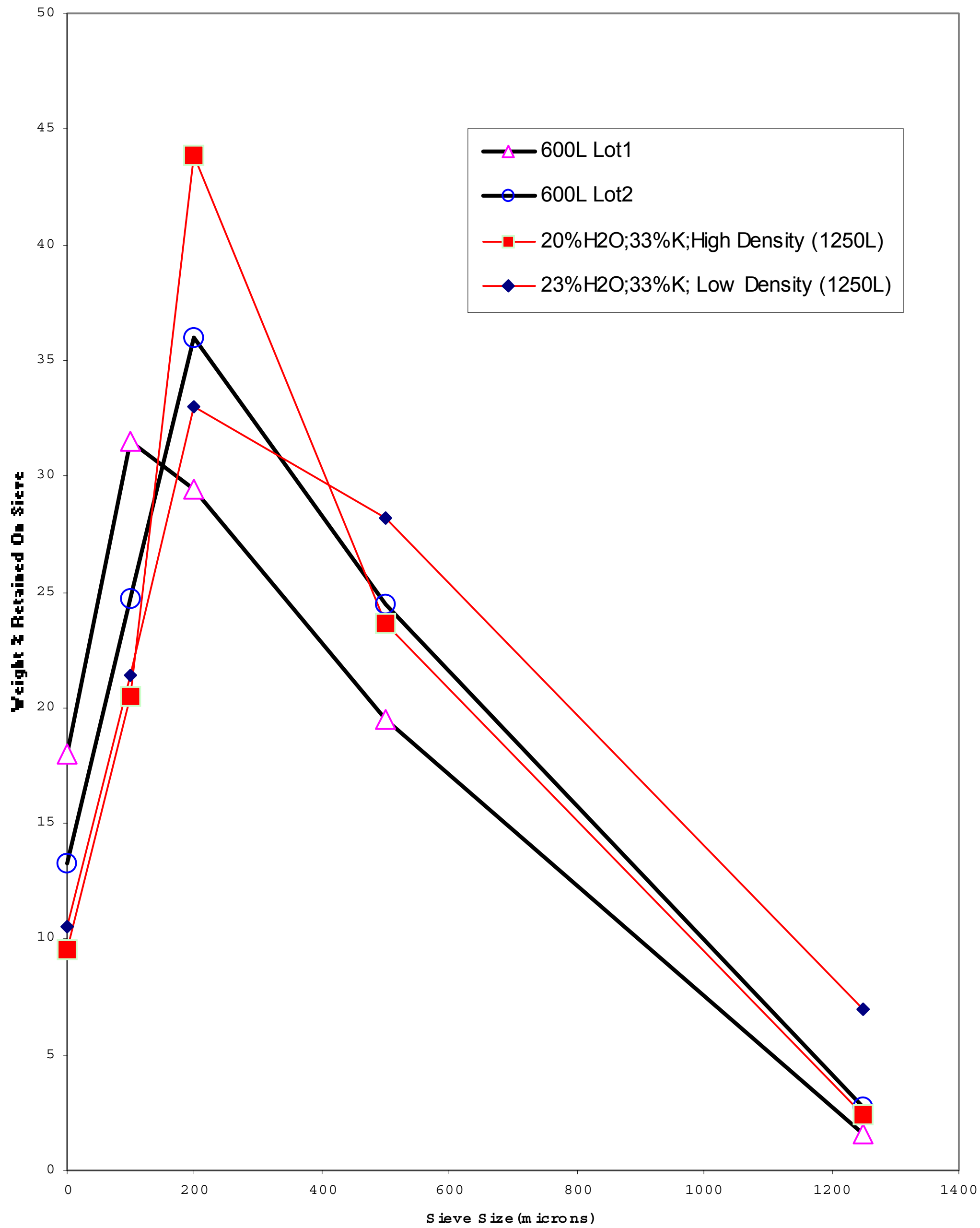


Figure 15: Comparison of Particle Size Distribution 1250L Vs. 25L

minimized for 23% water lots which were on the low side of the 1250L range (0.70 – 0.71 g/ml).

Tablet Hardness: Tablet hardness values for 600L lots were significantly higher than those at 1250L for a given force as shown in Figure 16 on page 83 . Higher %K (48%) lots were closest to the 600L baseline lots but still were approximately 10N lower in tablet hardness for a given compression force.

Tablet Friability: Tablet friability results for 1250L lost were not equivalent to 600L results for all lots as listed in Table 21 on page 84. The 1250L lots which used a 33%K endpoint showed more friability problems than those at higher %K endpoints, despite the similarity of particle size and density of these granulation blends. This trend coincides with much lower hardness values seen for the 33%K lots relative to the 600L lots.

As with previous friability assessments, differences are most easily seen with the 30 minute test data. For 33%K lots, the number of capped tablets ranged from 0 to 11. This number was consistently 0 at 600L. The number of chipped tablets after friability testing ranged from 95 to 175 for the 33%K lots, while this number varied from 126 to 139 for the 600L lots. Since tablet friability improved with increasing %K at 1250L, this difference could be eliminated by increasing the %K endpoint at 1250L. A confirmation lot made at 38%K confirms this (0 capped tablets and 137 chipped tablets at 30 minutes of testing).

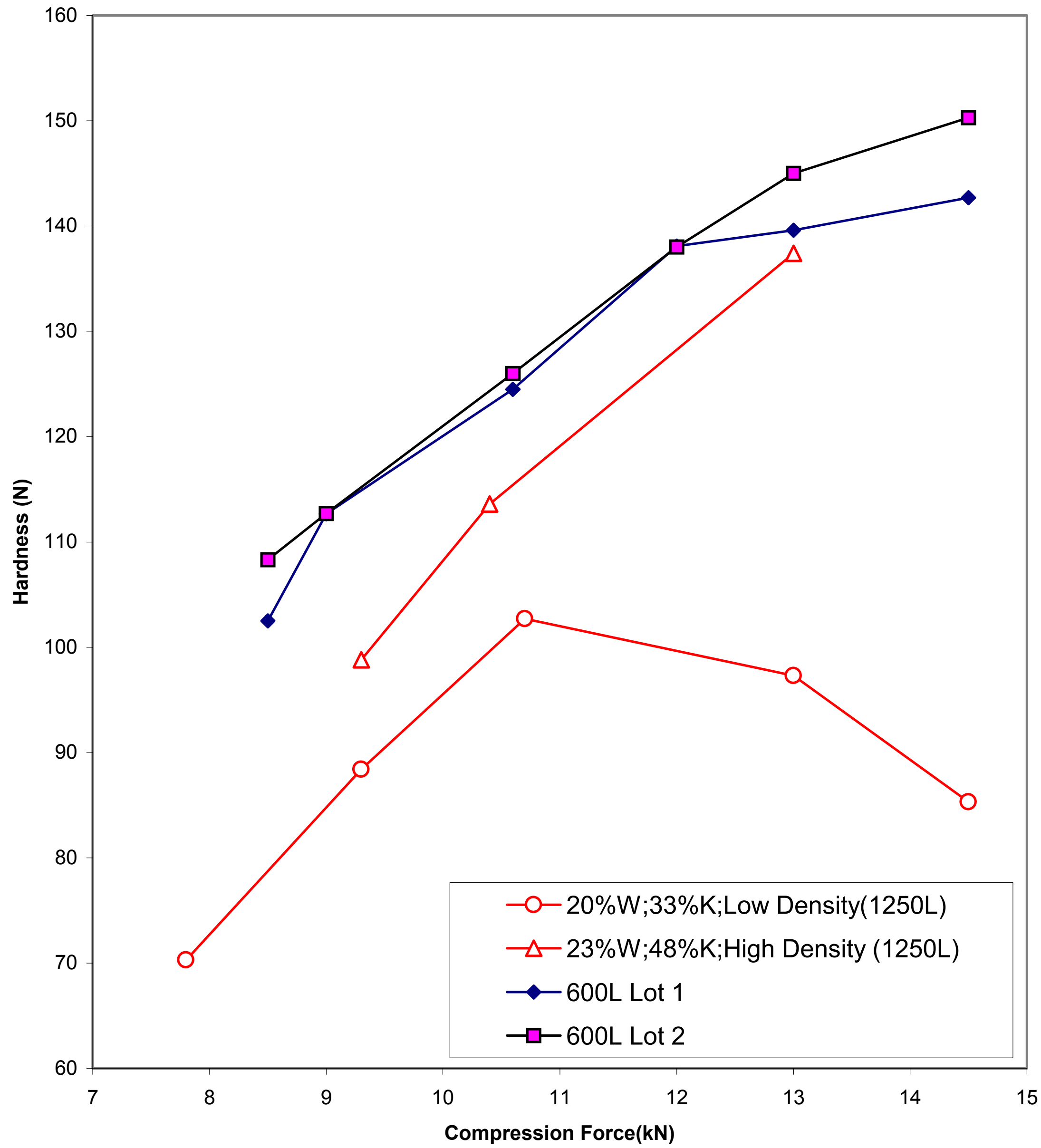


Figure 16: Comparison of Tablet Hardness Profiles: 1250L Vs. 600L Lots

Table 21: Comparison of Table Friability Results After 30 Minutes: 1250L Vs. 600L

	600L Lots	33% K Lots at 1250L	38% K Lot at 1250L
No. Capped Tablets	0	0 - 11	0
No. Chipped Tablets	95-175	126 - 139	137

Tablet Dissolution: Dissolution profiles for 1250L lots were compared to the 600L baseline using the SUPAC f2 test as shown in Table 22 on page 86. All values met the 50 to 100 criteria for similarity. This includes the confirmation lot made with 21.5% water and 38%K (f2=60) which provided the fastest dissolution rates while still maintaining f2 similarity to the 600L baseline.

4.4 Correlation of Blend Attributes to Tablet Attributes

Values for tablet dissolution, average hardness, and friability were regressed against granulation blend and mean particle size for both the 25L and 1250L lots. For the 25L lots, no significant correlations of these parameters were detected, indicating limited potential of using blend characteristics to predict tablet characteristics. For the 1250L scale, two significant correlations were found as shown in Figures 17 and 18 on pages 87-88. Blend density appears to correlate with 30 minute dissolution values, while mean blend particle size appears to correlate with friability weight loss. Both correlations were not linear but fit a second degree polynomial well. These correlations make sense since these attributes were previously shown to be influenced by the same granulation process parameters. Blend density and water were both affected by water level, while particle size and friability were both affected by %K endpoint. These correlations, though specific to this system and product, do demonstrate benefits and predictive capability of certain blend characteristics on tablet characteristics.

Table 22: SUPAC f2 Values 1250L Vs. 600L Baseline

SUPAC f2 Values 1250L Vs. 600L Baseline				
		Water		
		20%	**21.5%**	**23.00%**
% K	**33**	64/60	**	87/59*
	41		72	
	48	73/74		71/64
NOTES: 1st number is lot using low density drug.				
2nd number is the high density drug lot.				
* Confirmation lots made at 23%W and 33%K show values of 57 and 86				
** Confirmation lot made at 21.5% W and 38%K showed a value of 60.				

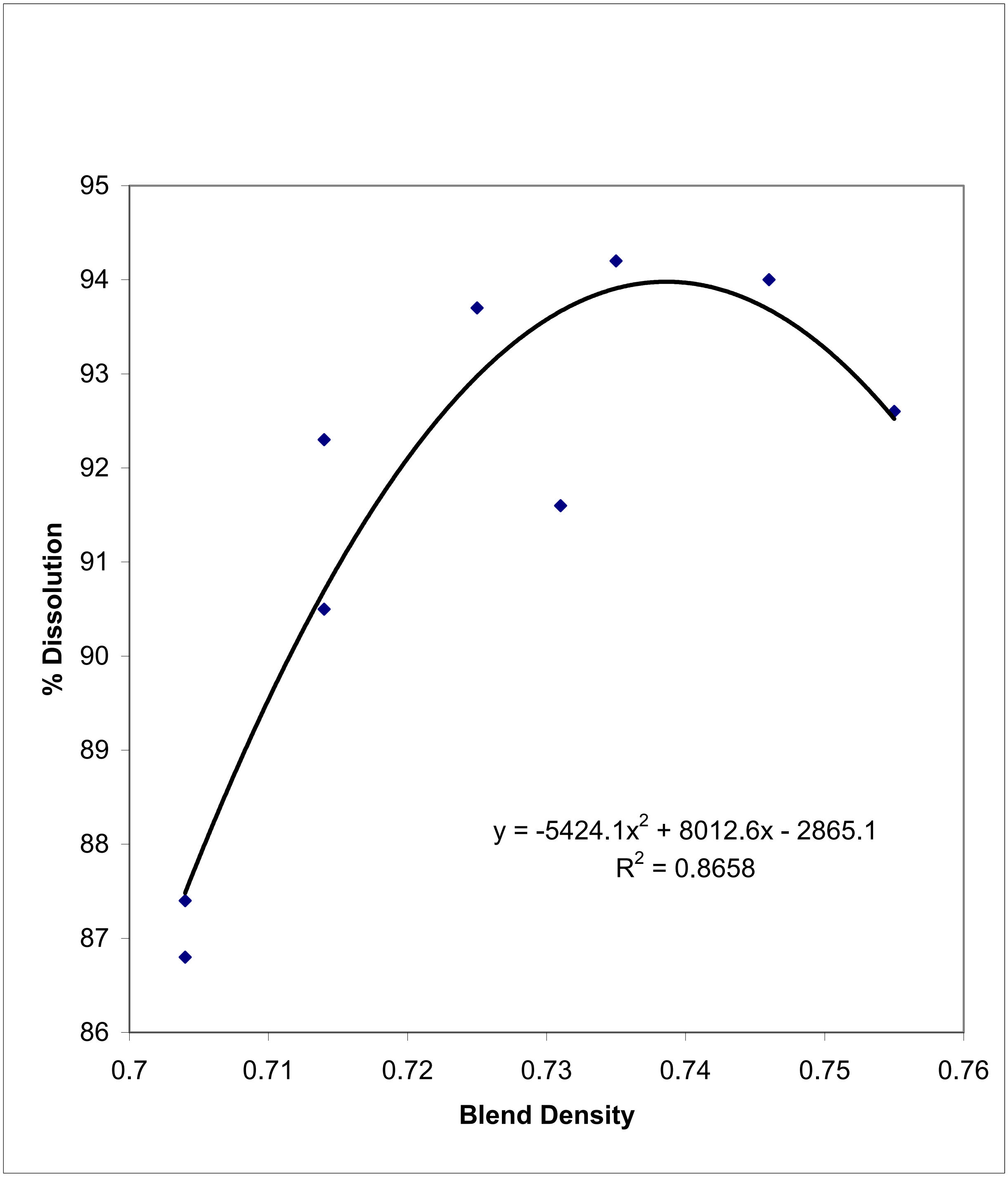


Figure 17: Correlation of Blend Density and 30 Minute Tablet Dissolution 1250L

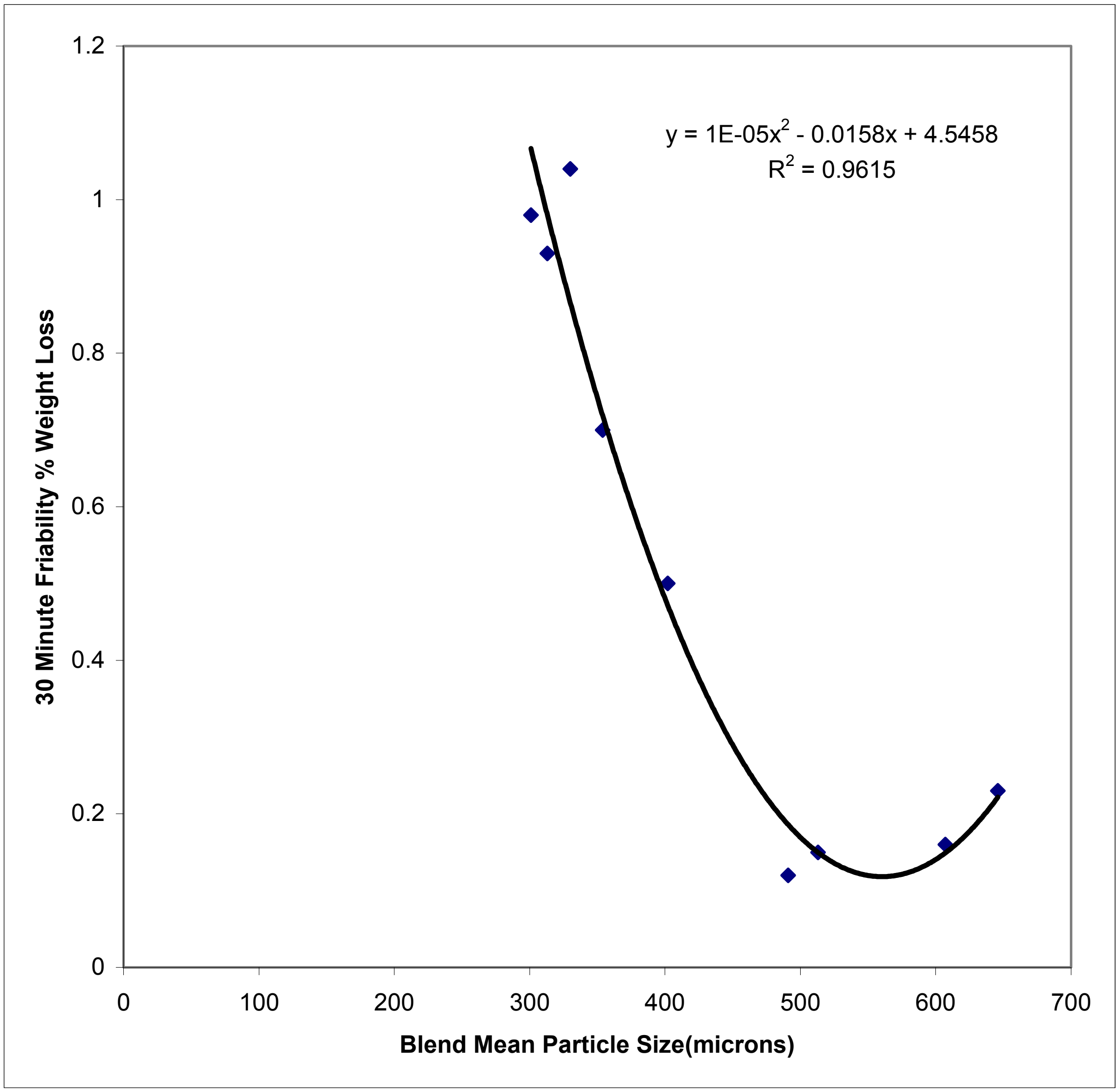


Figure 18: Correlation of Mean Blend Particle Size and 30 Minute Friability Weight Loss (1250L)

Chapter 5. SUMMARY AND CONCLUSIONS

5.1 Of the process variable studied, water level and granulation endpoint, measured either by torque or %K on a Diosna probe, are the most significant process factors in controlling granulation/blend and tablet characteristics. This is consistent with the work of Kornchankul (2000).

5.2 Atomization spray was studied at the 25L scale only and was only found to be a significant factor in friability results for the parameters studied. Atomizing spray did appear to lower weight loss during friability, providing some benefit for its use. Its importance in the 25L system may have been diminished due to the ability of the high amount of shear and intensive mixing action to provide adequate liquid dispersion. This conclusion may or may not hold on scale up depending on relatively mixing action at different scales. It was noted by Schaefer, *et al* (1986) that atomization does become more critical in larger scale mixers.

5.3 Raw material bulk density, which was studied at 1250L scale only, does not appear to be a major factor in controlling granulation/blend or tablet properties other than blend densities. This result verifies robustness of the process and product for the density ranges studied for drug substance PG690215.

5.4 While granulation endpoint and water level are primary controlling factors in blend and tablet characteristics at both scales, their relationship and impact to individual blend or tablet characteristics does differ in across the 25L and 1250L scales as shown in Table 23 on page 91. Differences range from the degree of magnitude of the effect (e.g. water level for dissolution) to differences in controlling factor overall (e.g. water for 25L tablet hardness versus granulation endpoint for 1250L tablet hardness). Perhaps this is not surprising due to basic differences in equipment for these scales, particularly for the tablet presses which may have been the main contributor to differences in behavior of hardness and friability.

Comparison of water and endpoint (or granulation time) effects from this work to past literature reveals some interesting similarities and differences. Water level does appear to scale linearly with size, i.e. similar percentages in water can be used to scale granulations as suggested by Leuenberger (1983) and Rekhi, *et al* (1996). Unlike Rekhi's work, lower amounts of moisture did not result in smaller particle size and density. In fact, lower amounts of moisture increased density and particle size. This affect appeared to be linked to longer granulation times for lower water amounts. While an effect of water level on particle size was seen for 1250L, it did not significantly affect flow as evidenced by similar tablet weight variation across the lots. Vojnovic, *et al* (1992) did see an effect of water on flow.

Table 23: Summary of Effect of Granulation Factors On Blend and Tablet Characteristics

Characteristic	25L	1250L
Blend Particle size	+ endpoint - water -water * endpoint	+ endpoint - water - water*endpoint
Blend Density	- water + endpoint	- water - drug density
Tablet Hardness	+ water	+ endpoint
Tablet Friability **(weight loss/chipped tablets)**	- atomizing spray (Wt loss only)	- endpoint + water - endpoint*water *
Tablet Dissolution	- water + endpoint (for vertice and centerpoints only)	- water

NOTE: + indicates characteristic increases with increase in factor
- indicates characteristics decreases with increase in factor

*** For the number of capped tablets, effects are "– endpoint, - water, and + endpoint*water".**

Granulation endpoint had strong affects on granulation size, density(25L only) and tablet hardness/friability(1250L) only. More granulated lots appeared to process just as well as less granulated lots, except for the extreme cases at 25L where increased weight variation was seen for the smallest , least granulated lots. No affect of endpoint, or granulation times, on dissolution was noted as opposed to the work of Ertel, *et al* (1990) and Zoglio, *et al* (1976) who suggested there could be a significant impact.

5.5 With regards to the 25L scale, it does appear that proper choice of water level and torque endpoint can result in similar granulation blend and tablet quality as the 600L or 1250L scales, though the match is not exact and some trade offs may be necessary. To best match 600L baseline made with 23% water, torque endpoints of 140 -150 in lbs provide similar ranges of particle size and density, while water levels near 23% should provide similar dissolution and highest hardness ranges. Tablet hardness will be lower than 600L on average (~20N). Tablet weight loss during friability is comparable to 600L, while tablet chipping during friability is much lower and not predictive of 600L.

5.6 To best match 25L lots with the 1250L lots optimized at 21.5% water and 38%K, torque endpoint of ~150 in lbs should provide similar ranges of density and particle size, while water level at ~21.5% appear to provide similar hardness and dissolution. Friability is much lower for the 25L scale, so friability issues were not well predicted at small scale.

5.7 With regards to the 600L to the 1250L comparison, the 1250L appears to provide slightly larger and denser granulation/blend, even at the lowest %K endpoint. This may be due in part to greater head pressure effect due to the higher load in the 1250L unit. Tablet hardness was lower than the 600L lots for a given compression force, and tablet friability became an issue (capping) when lower %K (33%) was used. Although dissolution is similar across all process ranges challenged here, it does seem to decrease with increasing water levels (21.5 to 23%). Therefore, it appears that an optimized product with comparable friability to 600L and faster dissolution can be obtained by utilizing a water level of 21.5% and an endpoint of 38%K. It also appears that the strategy outlined for scaling from a 600L to a 1250L Diosna can provide equivalent product if the adjustment in granulation endpoint is made to improve overall compressibility/ hardness and eliminate friability problems.

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APPENDIX

Table A1: Granulation Times For 25L Lots

Lot	Water Level (%)	Torque Endpoint (in lbs)	Spray	Run Duration (min:sec)
1	18	150	On	21:53
2	20	110	On	7:40
3	20	130	On	8:27
4	20	130	Off	9:27
5	20	140	On	10:13
6	20	160	On	19:01
7	20	170	On	Never Reached *
8	20	170	Off	Never Reached **
9	21.5	145	On	10:58
10	21.5	150	Intermediate	10:21
11	21.5	150	Intermediate	9:42
12	23	110	On	4:23
13	23	130	On	5:13
14	23	130	Off	4:40
15	23	140	On	5:49
16	23	160	On	8:08
17	23	170	On	10:03
18	23	170	Off	10:31
19	25	150	On	3:54

* Never reached 170. Stopped at 26:45 and 130 in-lb torque.
** Never reached 170. Stopped at 27:12 and 120-140 in-lb torque.

Table A2: Granulation Times For 1250L Lots

Water level (%w/w)	K level (%)	Drug Density Level	Run Duration (min:sec)
20	33	Low	18:55
20	33	High	12:18
20	48	Low	23:11
20	48	High	19:00
21.5	41	Middle	15:06
23	33	Low	11:00
23	33	High	9:50
23	48	Low	11:34
23	48	High	11:00

Table A3: Granulation Particle Size: Weight % Retained On Sieves (25L)

Water %		18	20	20	20	20	20
Torque In Lbs		150	110	130	130	140	160
Spray		On	On	On	Off	On	On
Screen Size	1190	1.0	1.1	0.4	0.6	0.5	1.7
(microns)	850	10.0	6.4	4.8	7.6	5.6	12.8
	500	22.6	15.3	14.3	15.2	11.8	20.0
	300	15.2	17.4	16.8	21.5	18.0	19.6
	212	10.0	12.4	9.8	16.3	15.5	13.9
	106	17.8	21.7	20.2	21.9	24.8	17.1
	0	23.4	25.8	33.7	16.9	23.9	14.9
	Total	100.0	100.0	100.0	100.0	100.0	100.0
Combined Data							
Screen Size	1190	1.0	1.1	0.4	0.6	0.5	1.7
(microns)	500	32.6	21.6	19.0	22.7	17.4	32.8
	212	25.2	29.8	26.6	37.8	33.5	33.5
	106	17.8	21.7	20.2	21.9	24.8	17.1
	0	23.4	25.8	33.7	16.9	23.9	14.9

Water %		21.5	21.5	21.5	23	23	23
Torque In Lbs		145	150	150	110	130	130
Spray		On	Inter-mediate	Inter-mediate	On	On	Off
Screen Size	1190						
(microns)	850	1.7	1.0	1.4	0.8	1.2	1.6
	500	19.2	11.8	11.5	8.8	10.1	11.5
	300	32.8	30.2	18.7	16.6	18.5	16.1
	212	15.2	22.2	19.5	15.8	15.2	13.9
	106	7.1	8.0	13.9	11.2	10.4	10.7
	0	12.3	12.8	19.6	18.3	26.1	20.7
		11.7	13.9	15.3	28.5	18.6	25.5
	Total	100.0	100.0	100.0	100.0	100.0	100.0
Combined Data							
Screen Size	1190	1.7	1.0	1.4	0.8	1.2	1.6
(microns)	500	52.0	42.0	30.3	25.5	28.6	27.6
	212	22.3	30.2	33.4	27.0	25.6	24.6
	106	12.3	12.8	19.6	18.3	26.1	20.7
	0	11.7	13.9	15.3	28.5	18.6	25.5

Water %		15	31	16	25	22
Torque In Lbs		23	23	23	23	25
Spray		140	160	170	170	150
Screen Size(microns)	1190	On	On	On	Off	On
	850	1.1	1.0	1.6	1.5	0.7
	500	8.9	12.5	18.6	26.3	9.1
	300	18.4	21.6	28.8	35.0	16.3
	212	18.5	19.0	17.9	13.8	14.4
	106	13.4	14.0	8.5	4.8	11.0
	0	22.5	17.5	9.5	5.9	17.3
		17.2	14.4	15.0	12.8	31.1
	Total	100.0	100.0	100.0	100.0	100.0
Combined Data						
Screen Size(microns)						
	1190	1.1	1.0	1.6	1.5	0.7
	500	27.3	34.1	47.4	61.3	25.4
	212	31.9	33.0	26.4	18.5	25.4
	106	22.5	17.5	9.5	5.9	17.3
	0	17.2	14.4	15.0	12.8	31.1

Table A4: Granulation Blend Particle Size: Weight % Retained On Sieve (1250L)

Water %		20	20	20	20	21.5
%K		33	33	48	48	41
Drug Bulk Density		Low	High	Low	High	Middle
Screen Size	1250	4.4	2.4	20.2	17.7	7.4
(microns)	800	10.9	9.4	31.6	26.1	17.5
	500	14.1	14.2	17.7	20.9	17.8
	315	20.5	22.5	7.8	12.2	18.7
	200	20.8	21.4	5.8	8.6	16.3
	100	18.7	20.5	7.5	8	13.8
	0	10.5	9.5	9.4	6.6	8.5
Combined Data						
Screen Size	1250	4.4	2.4	20.2	17.7	7.4
(microns)	500	25	23.6	49.3	47	35.3
	200	41.3	43.9	13.6	20.8	35
	100	18.7	20.5	7.5	8	13.8
	0	10.5	9.5	9.4	6.6	8.5

Water %		21.5	23	23	23	23
%K		38	33	33	48	48
Drug Bulk Density		Intermediate	Low	High	Low	High
Screen Size	1250	NA	7	7.6	11.5	11
(microns)	800	NA	14.4	15.2	23.9	25.2
	500	NA	13.8	15.2	20.7	19.7
	315	NA	14.8	15.9	15.6	13.2
	200	NA	18.2	17.5	11.5	10.4
	100	NA	21.4	18.3	9.8	11
	0	NA	10.5	10.3	7	9.4
Combined Data						
Screen Size	1250	5.3	7	7.6	11.5	11
(microns)	500	28.2	28.2	30.4	44.6	44.9
	200	37.2	33	33.4	27.1	23.6
	100	19.5	21.4	18.3	9.8	11
	0	9.8	10.5	10.3	7	9.4

Table A5: Granulation Blend Particle Size: Weight % Retained On Sieve (600L)

Water %		23	23	23
%K		35	35	35
Combined Data				
Screen Size	1250	1.6	1.5	2.7
(microns)	500	19.5	22.5	24.5
	200	29.4	33.2	36
	100	31.5	41.3	24.7
	0	18	1.7	13.3

Table A6:Granulation Blend Bulk Density (600L)

Water %	23	23	23
%K	35	35	35
Bulk Density (g/ml)	0.63	0.70	0.68

Table A7: Tablet Weights (Grams) - 25L

Lot	Force (kN)	Tab 1	Tab 2	Tab 3	Tab 4	Tab 5	Tab 6	Tab 7	Tab 8	Tab 9	Tab 10
18%H2O; 150 Torque	7*	0.527	0.536	0.525	0.521	0.523	0.527	0.522	0.506	0.522	0.528
	9	0.518	0.523	0.529	0.518	0.512	0.524	0.507	0.518	0.514	0.524
	10.5	0.515	0.520	0.524	0.523	0.516	0.524	0.516	0.512	0.515	0.509
	12*	0.511	0.522	0.508	0.528	0.514	0.523	0.521	0.508	0.511	0.518
	14	0.521	0.519	0.512	0.526	0.508	0.514	0.526	0.502	0.501	0.526
	* One extra tablet measured at 0.526 g.										
	** Two extra tablets measured at 0.524 and 0.530g.										
20% H2O; 110Torque	7	0.512	0.515	0.512	0.517	0.524	0.520	0.515	0.523	0.519	0.518
	9	0.519	0.524	0.515	0.516	0.517	0.511	0.517	0.517	0.512	0.520
	10.5*	0.519	0.524	0.522	0.514	0.524	0.518	0.514	0.517	0.524	0.513
	12	0.518	0.513	0.511	0.523	0.523	0.516	0.521	0.516	0.508	0.514
	14*	0.518	0.514	0.515	0.511	0.511	0.519	0.515	0.518	0.515	0.512
	* One extra tablet measured at 0.518 g.										
20% H2O; 130Torque	7	0.532	0.524	0.526	0.522	0.523	0.520	0.510	0.520	0.515	0.526
	9	0.528	0.515	0.520	0.520	0.526	0.522	0.517	0.518	0.525	0.521
	10.5	0.518	0.528	0.518	0.526	0.527	0.524	0.517	0.515	0.520	0.521
	12	0.519	0.517	0.528	0.508	0.509	0.525	0.517	0.526	0.525	0.522
	14	0.519	0.517	0.513	0.528	0.511	0.522	0.524	0.530	0.527	0.513

Lot	Force (kN)	Tab 1	Tab 2	Tab 3	Tab 4	Tab 5	Tab 6	Tab 7	Tab 8	Tab 9	Tab 10
20% H2O; 130Torque	7	0.519	0.520	0.520	0.518	0.520	0.523	0.523	0.515	0.519	0.526
No Spray	9	0.524	0.517	0.518	0.517	0.514	0.523	0.515	0.518	0.515	0.515
	10.5	0.524	0.515	0.512	0.519	0.513	0.521	0.510	0.508	0.517	0.511
	12	0.517	0.520	0.522	0.512	0.524	0.517	0.515	0.522	0.523	0.521
	14	0.524	0.510	0.508	0.516	0.514	0.517	0.519	0.524	0.515	0.523
20% H2O; 140Torque	7	0.519	0.514	0.516	0.515	0.519	0.523	0.535	0.524	0.522	0.524
	9	0.524	0.508	0.525	0.517	0.523	0.526	0.526	0.522	0.526	0.527
	10.5	0.527	0.528	0.529	0.518	0.521	0.513	0.521	0.521	0.524	0.523
	12	0.504	0.523	0.520	0.516	0.517	0.527	0.515	0.516	0.514	0.515
	14	0.527	0.510	0.522	0.527	0.511	0.518	0.522	0.517	0.521	0.517

Lot	Force(kN)	Avg.	SD	%RSD	Minimum	Maximum
18% H2O;150 Torque	7*	0.524	0.007	1.4	0.506	0.536
	9	0.519	0.007	1.3	0.507	0.529
	10.5	0.517	0.005	1.0	0.509	0.524
	12*	0.518	0.008	1.5	0.508	0.530
	14	0.515	0.010	1.9	0.501	0.526
	Overall	**0.519**	**0.008**	**1.5**	**0.501**	**0.536**
20% H2O;110Torque	7	0.518	0.004	0.8	0.512	0.524
	9	0.517	0.004	0.7	0.511	0.524
	10.5	0.519	0.004	0.8	0.513	0.524
	12	0.516	0.005	0.9	0.508	0.523
	14	0.515	0.003	0.6	0.511	0.519
	Overall	**0.517**	**0.004**	**0.8**	**0.508**	**0.524**
20% H2O;130Torque	7	0.522	0.006	1.2	0.510	0.532
	9	0.521	0.004	0.8	0.515	0.528
	10.5	0.521	0.005	0.9	0.515	0.528
	12	0.520	0.007	1.3	0.508	0.528
	14	0.520	0.007	1.3	0.511	0.530
	Overall	**0.521**	**0.006**	**1.1**	**0.508**	**0.532**
20% H2O;130Torque	7	0.520	0.003	0.6	0.515	0.526
No Spray	9	0.517	0.003	0.7	0.514	0.524
	10.5	0.515	0.005	1.0	0.508	0.524
	12	0.519	0.004	0.7	0.512	0.524
	14	0.517	0.006	1.1	0.508	0.524
	Overall	**0.518**	**0.005**	**0.9**	**0.508**	**0.526**
20% H2O;140Torque	7	0.521	0.006	1.2	0.514	0.535
	9	0.522	0.006	1.1	0.508	0.527
	10.5	0.522	0.005	1.0	0.513	0.529
	12	0.517	0.006	1.2	0.504	0.527
	14	0.519	0.006	1.1	0.510	0.527
	Overall	**0.520**	**0.006**	**1.2**	**0.504**	**0.535**

NOTE: Avg.=average; SD=Standard deviation; RSD=Relative standard deviation

Lot	Force (kN)	Tab 1	Tab 2	Tab 3	Tab 4	Tab 5	Tab 6	Tab 7	Tab 8	Tab 9	Tab 10
20% H2O; 160Torque	7	0.512	0.529	0.531	0.524	0.522	0.522	0.523	0.537	0.523	0.530
	9	0.523	0.523	0.531	0.531	0.516	0.525	0.527	0.511	0.527	0.528
	10.5	0.527	0.522	0.523	0.526	0.523	0.525	0.525	0.534	0.531	0.526
	12	0.528	0.519	0.523	0.518	0.517	0.522	0.527	0.509	0.525	0.520
	14	0.527	0.518	0.520	0.520	0.521	0.526	0.515	0.534	0.527	0.523
21.5% H2O; 145Torque	7	0.522	0.522	0.528	0.525	0.524	0.521	0.514	0.524	0.514	0.518
	9	0.517	0.525	0.517	0.515	0.518	0.507	0.518	0.512	0.528	0.516
	10.5	0.513	0.509	0.527	0.519	0.523	0.520	0.517	0.527	0.516	0.514
	12	0.525	0.520	0.516	0.522	0.525	0.522	0.516	0.524	0.529	0.511
	14	0.518	0.517	0.518	0.528	0.521	0.528	0.527	0.520	0.521	0.512
21.5% H2O; 150Torque	7	0.523	0.524	0.520	0.524	0.521	0.531	0.521	0.528	0.533	0.519
Intermediate Spray Level	9	0.526	0.530	0.529	0.527	0.514	0.532	0.527	0.532	0.530	0.518
	10.5	0.527	0.527	0.517	0.529	0.528	0.522	0.528	0.523	0.530	0.520
	12	0.523	0.523	0.515	0.532	0.529	0.531	0.525	0.532	0.516	0.517
	14	0.511	0.526	0.520	0.522	0.521	0.527	0.519	0.517	0.528	0.527
21.5% H2O; 150Torque	7*	0.510	0.517	0.515	0.515	0.521	0.496	0.508	0.510	0.518	0.512
Intermediate Spray Level	9	0.515	0.524	0.517	0.516	0.511	0.512	0.517	0.504	0.523	0.513
	10.5	0.507	0.512	0.512	0.511	0.517	0.514	0.519	0.516	0.526	0.505
	12	0.506	0.517	0.516	0.518	0.515	0.513	0.520	0.519	0.520	0.519
	14	0.520	0.520	0.525	0.511	0.528	0.529	0.518	0.521	0.511	0.515
	* Two extra tablets measured at 0.520 and 0.519 g.										
23% H2O; 110Torque	7	0.528	0.536	0.537	0.516	0.497	0.531	0.514	0.540	0.496	0.506
	9	0.538	0.520	0.522	0.538	0.516	0.523	0.515	0.516	0.522	0.514
	10.5*	0.509	0.517	0.540	0.505	0.514	0.519	0.509	0.514	0.533	0.535
	12	0.528	0.498	0.540	0.507	0.507	0.503	0.526	0.519	0.527	0.495
	14	0.516	0.494	0.512	0.519	0.518	0.512	0.543	0.511	0.533	0.520
	* Two extra tablets measured at 0.521 and 0.512 g.										

Lot	Force(kN)	Avg.	SD	%RSD	Minimum	Maximum
20% H2O;160 Torque	7	0.525	0.007	1.3	0.512	0.537
	9	0.524	0.007	1.3	0.511	0.531
	10.5	0.526	0.004	0.7	0.522	0.534
	12	0.521	0.005	1.0	0.509	0.528
	14	0.523	0.006	1.1	0.515	0.534
	Overall	**0.524**	**0.006**	**1.1**	**0.509**	**0.537**
21.5% H2O;145 Torque	7	0.521	0.005	0.9	0.514	0.528
	9	0.517	0.006	1.1	0.507	0.528
	10.5	0.518	0.006	1.1	0.509	0.527
	12	0.521	0.005	1.0	0.511	0.529
	14	0.521	0.005	1.0	0.512	0.528
	Overall	**0.520**	**0.005**	**1.1**	**0.507**	**0.529**
21.5%W;150Torque	7	0.524	0.005	0.9	0.519	0.533
Intermediate Spray Level	9	0.526	0.006	1.1	0.514	0.532
	10.5	0.525	0.004	0.8	0.517	0.530
	12	0.524	0.007	1.3	0.515	0.532
	14	0.522	0.005	1.0	0.511	0.528
	Overall	**0.524**	**0.005**	**1.0**	**0.511**	**0.533**
21.5%W;150Torque	7	0.513	0.007	1.3	0.496	0.521
Intermediate Spray Level	9	0.515	0.006	1.1	0.504	0.524
	10.5	0.514	0.006	1.2	0.505	0.526
	12	0.516	0.004	0.9	0.506	0.520
	14	0.520	0.006	1.2	0.511	0.529
	Overall	**0.516**	**0.006**	**1.2**	**0.496**	**0.529**
23%W;110Torque	7	0.520	0.017	3.2	0.496	0.540
	9	0.522	0.009	1.7	0.514	0.538
	10.5	0.519	0.011	2.2	0.505	0.540
	12	0.515	0.015	2.9	0.495	0.540
	14	0.518	0.013	2.5	0.494	0.543
	Overall	**0.519**	**0.013**	**2.5**	**0.494**	**0.543**

NOTE: Avg.=average; SD=Standard deviation; RSD=Relative standard deviation

Lot	Force (kN)	Tab 1	Tab 2	Tab 3	Tab 4	Tab 5	Tab 6	Tab 7	Tab 8	Tab 9	Tab 10
23% H2O; 130Torque	7	0.514	0.512	0.527	0.522	0.524	0.514	0.522	0.518	0.522	0.517
	9	0.518	0.522	0.516	0.523	0.525	0.526	0.515	0.528	0.524	0.520
	10.5	0.516	0.523	0.523	0.523	0.526	0.519	0.515	0.527	0.522	0.513
	12	0.523	0.524	0.509	0.512	0.525	0.511	0.523	0.520	0.526	0.521
	14	0.516	0.520	0.512	0.513	0.519	0.527	0.513	0.520	0.525	0.514
23% H2O; 130Torque	7	0.524	0.523	0.514	0.516	0.509	0.517	0.520	0.530	0.501	0.518
No Spray	9	0.526	0.514	0.510	0.531	0.525	0.508	0.511	0.509	0.511	0.534
	10.5	0.526	0.533	0.510	0.524	0.514	0.516	0.514	0.516	0.529	0.516
	12	0.510	0.512	0.528	0.521	0.509	0.523	0.523	0.526	0.514	0.525
	14	0.514	0.506	0.513	0.521	0.527	0.503	0.508	0.515	0.513	0.515
23% H2O; 140Torque	7	0.526	0.514	0.529	0.519	0.519	0.509	0.527	0.516	0.527	0.518
	9	0.522	0.528	0.513	0.520	0.519	0.510	0.521	0.526	0.513	0.513
	10.5	0.514	0.521	0.510	0.520	0.521	0.521	0.525	0.522	0.526	0.524
	12	0.528	0.523	0.515	0.515	0.511	0.520	0.523	0.512	0.513	0.525
	14	0.526	0.510	0.521	0.521	0.515	0.523	0.520	0.520	0.516	0.522
23% H2O; 160Torque	7	0.529	0.533	0.514	0.516	0.513	0.516	0.525	0.516	0.528	0.522
	9	0.521	0.524	0.531	0.526	0.520	0.519	0.521	0.517	0.520	0.521
	10.5	0.507	0.530	0.529	0.521	0.528	0.526	0.528	0.523	0.516	0.515
	12	0.523	0.529	0.516	0.528	0.520	0.521	0.520	0.516	0.524	0.518
	14	0.531	0.522	0.529	0.514	0.525	0.516	0.526	0.523	0.521	0.516
23% H2O; 170Torque	7	0.521	0.520	0.510	0.523	0.521	0.517	0.521	0.528	0.520	0.520
	9	0.524	0.527	0.525	0.517	0.530	0.509	0.517	0.500	0.530	0.519
	10.5	0.519	0.508	0.506	0.520	0.527	0.516	0.521	0.508	0.507	0.514
	12	0.507	0.528	0.505	0.525	0.534	0.510	0.530	0.500	0.519	0.525
	14	0.526	0.524	0.521	0.527	0.530	0.519	0.527	0.524	0.525	0.515

Lot	Force(kN)	Avg.	SD	%RSD	Minimum	Maximum
23% H_2O; 130Torque	7	0.519	0.005	0.9	0.512	0.527
	9	0.522	0.004	0.8	0.515	0.528
	10.5	0.521	0.005	0.9	0.513	0.527
	12	0.520	0.006	1.2	0.509	0.526
	14	0.518	0.005	1.0	0.512	0.527
	Overall	**0.520**	**0.005**	**1.0**	**0.509**	**0.528**
23% H_2O; 130Torque	7	0.517	0.008	1.6	0.501	0.530
No Spray	9	0.518	0.010	2.0	0.508	0.534
	10.5	0.520	0.008	1.5	0.510	0.533
	12	0.519	0.007	1.4	0.509	0.528
	14	0.513	0.007	1.3	0.503	0.527
	Overall	**0.517**	**0.008**	**1.6**	**0.501**	**0.534**
23% H_2O; 140Torque	7	0.520	0.007	1.3	0.509	0.529
	9	0.518	0.006	1.1	0.510	0.528
	10.5	0.520	0.005	0.9	0.510	0.526
	12	0.518	0.006	1.2	0.511	0.528
	14	0.519	0.005	0.9	0.510	0.526
	Overall	**0.519**	**0.005**	**1.1**	**0.509**	**0.529**
23% H_2O; 160Torque	7	0.521	0.007	1.4	0.513	0.533
	9	0.522	0.004	0.8	0.517	0.531
	10.5	0.522	0.007	1.4	0.507	0.530
	12	0.522	0.005	0.9	0.516	0.529
	14	0.522	0.006	1.1	0.514	0.531
	Overall	**0.522**	**0.006**	**1.1**	**0.507**	**0.533**
23% H_2O; 170Torque	7	0.520	0.005	0.9	0.510	0.528
	9	0.520	0.010	1.8	0.500	0.530
	10.5	0.515	0.007	1.4	0.506	0.527
	12	0.518	0.012	2.3	0.500	0.534
	14	0.524	0.005	0.9	0.515	0.530
	Overall	**0.519**	**0.008**	**1.6**	**0.500**	**0.534**

NOTE: Avg.=average; SD=Standard deviation; RSD=Relative standard deviation

Lot	Force(kN)	Tab 1	Tab 2	Tab 3	Tab 4	Tab 5	Tab 6	Tab 7	Tab 8	Tab 9	Tab 10
23%H2O; 170Torque	7	0.502	0.522	0.527	0.525	0.528	0.527	0.531	0.518	0.502	0.528
No Spray	9	0.530	0.521	0.513	0.523	0.530	0.514	0.527	0.516	0.531	0.512
	10.5	0.506	0.519	0.516	0.514	0.506	0.515	0.529	0.526	0.524	0.526
	12	0.524	0.495	0.533	0.527	0.510	0.528	0.532	0.518	0.506	0.524
	14	0.521	0.534	0.523	0.511	0.523	0.529	0.524	0.504	0.513	0.528
Lot	Force(kN)	Tab 1	Tab 2	Tab 3	Tab 4	Tab 5	Tab 6	Tab 7	Tab 8	Tab 9	Tab 10
25%H2O; 150Torque	7	0.546	0.535	0.487	0.517	0.523	0.504	0.550	0.529	0.458	0.491
	9	0.537	0.523	0.545	0.470	0.467	0.503	0.512	0.539	0.534	0.544
	10.5	0.534	0.538	0.504	0.494	0.496	0.509	0.499	0.508	0.523	0.514
	12	0.490	0.499	0.523	0.521	0.540	0.518	0.526	0.498	0.516	0.542
	14	0.546	0.505	0.470	0.496	0.523	0.492	0.512	0.510	0.508	0.503

Lot	Force(kN)	Avg.	SD	%RSD	Minimum	Maximum
23%W; 170Torque	7	0.521	0.011	2.1	0.502	0.531
No Spray	9	0.522	0.007	1.4	0.512	0.531
	10.5	0.518	0.008	1.6	0.506	0.529
	12	0.520	0.012	2.4	0.495	0.533
	14	0.521	0.009	1.7	0.504	0.534
	Overall	**0.520**	**0.009**	**1.8**	**0.495**	**0.534**
Lot	**Force(kN)**	**Avg.**	**SD**	**%RSD**	**Minimum**	**Maximum**
25%W; 150Torque	7	0.514	0.029	5.6	0.458	0.550
	9	0.517	0.029	5.6	0.467	0.545
	10.5	0.512	0.015	3.0	0.494	0.538
	12	0.517	0.017	3.4	0.490	0.542
	14	0.507	0.020	3.9	0.470	0.546
	Overall	**0.513**	**0.022**	**4.3**	**0.458**	**0.550**

NOTE: Avg.=average; SD=Standard deviation; RSD=Relative standard deviation

Table A8: Tablet Weights (milligrams) – 1250L

Lot	Force (kN)	Tab 1	Tab 2	Tab 3	Tab 4	Tab 5	Tab 6	Tab 7	Tab 8	Tab 9	Tab 10
20% H2O	7.8	526	528	519	523	526	527	523	528	533	520
33%K	9.3	520	524	532	530	531	526	528	534	529	534
Low Density	10.7	514	519	521	518	528	519	534	526	522	529
	13	503	500	505	505	514	510	510	515	505	503
	14.5	500	500	493	497	488	490	504	499	500	494
20% H2O	7.8	536	530	522	526	530	530	518	526	518	527
33%K	9.3	513	526	525	522	525	524	530	519	524	526
High Density	11.3	516	520	521	514	530	526	520	526	524	528
	13	509	496	503	512	518	508	510	504	510	508
	14.5	493	498	495	491	492	491	502	499	492	485
20% H2O	7.8	521	536	542	517	527	518	523	531	520	526
48%K	9.3	517	538	527	525	522	525	514	513	524	531
Low Density	13	505	509	520	500	505	514	497	507	506	513
	14.2	524	524	511	515	522	519	514	514	511	523
	14.5	491	485	500	493	491	497	491	498	499	484
20% H2O	9.3	518	527	528	522	523	526	531	527	522	527
48%K	13	507	506	506	510	502	501	507	514	506	507
High Density	10.4	516	513	528	529	521	514	521	509	519	516
21.5% H2O	7.8	520	518	518	524	521	522	522	519	519	523
41%K	9.3	524	530	531	527	531	525	527	526	530	530
Middle Density	11.2	517	513	518	520	522	523	521	527	521	523
	13	522	520	525	514	505	518	506	518	508	511
	14.5	492	490	495	493	496	498	491	490	491	490

Lot	Average	St. Deviation	%RSD	Minimum	Maximum
20% H2O	525	4.2	0.8	519	533
33%K	529	4.5	0.8	520	534
Low Density	523	6.1	1.2	514	534
	507	5.0	1.0	500	515
	497	5.1	1.0	488	504
Overall	**516**	**13.3**	**2.6**	**488**	**534**
20% H2O	526	5.7	1.1	518	536
33%K	523	4.6	0.9	513	530
High Density	523	5.2	1.0	514	530
	508	5.9	1.2	496	518
	494	4.9	1.0	485	502
Overall	**515**	**13.4**	**2.6**	**485**	**536**
20% H2O	526	8.1	1.5	517	542
48%K	524	7.7	1.5	513	538
Low Density	508	6.8	1.3	497	520
	518	5.3	1.0	511	524
	493	5.6	1.1	484	500
Overall	**514**	**13.9**	**2.7**	**484**	**542**
20% H2O	525	3.8	0.7	518	531
48%K	507	3.7	0.7	501	514
High Density	519	6.4	1.2	509	529
Overall	**517**	**9.1**	**1.8**	**501**	**531**
21.5% H2O	521	2.1	0.4	518	524
41%K	528	2.6	0.5	524	531
Middle Density	521	3.8	0.7	513	527
	515	7.0	1.4	505	525
	493	2.8	0.6	490	498
Overall	**515**	**12.8**	**2.5**	**490**	**531**

Lot	Force (kN)	Tab 1	Tab 2	Tab 3	Tab 4	Tab 5	Tab 6	Tab 7	Tab 8	Tab 9	Tab 10
23% H2O	7.8	522	525	521	526	518	517	527	525	522	529
33%K	9.3	532	518	522	523	530	524	529	524	522	529
Low Density	10.5	519	526	522	527	529	520	511	526	522	531
	13	512	512	507	511	510	511	510	513	516	507
	14.5	490	492	495	492	500	495	490	498	495	494
23% H2O	7.8	526	528	525	527	525	521	532	524	530	524
33%K	9.3	524	532	525	527	530	532	528	531	526	532
High Density	13	513	507	511	509	509	519	509	503	507	507
	14.2	512	512	529	523	526	525	528	514	519	516
	14.5	498	496	498	489	497	500	493	501	498	493
23% H2O	7.8	503	505	493	500	501	502	496	508	502	495
48%K	9.3	524	517	532	525	524	524	525	525	528	524
Low Density	10.7	519	520	527	522	513	521	519	512	517	521
	13	506	509	511	513	508	514	500	509	511	510
	14.5	491	491	501	496	490	498	497	500	496	491
23% H2O	9.3	522	536	523	521	529	531	530	529	529	515
48%K	13	520	514	512	508	510	514	508	510	521	500
High Density	10.4	537	517	518	528	517	514	519	532	531	530

Lot	Average	St. Deviation	%RSD	Minimum	Maximum
23% H2O	523	3.9	0.7	517	529
33%K	525	4.4	0.8	518	532
Low Density	523	5.8	1.1	511	531
	511	2.7	0.5	507	516
	494	3.2	0.7	490	500
Overall	**515**	**12.6**	**2.4**	**490**	**532**
23% H2O	526	3.2	0.6	521	532
33%K	529	3.1	0.6	524	532
High Density	509	4.3	0.8	503	519
	520	6.6	1.3	512	529
	496	3.7	0.7	489	501
Overall	**516**	**12.8**	**2.5**	**489**	**532**
23% H2O	501	4.6	0.9	493	508
48%K	525	3.7	0.7	517	532
Low Density	519	4.4	0.8	512	527
	509	4.0	0.8	500	514
	495	4.1	0.8	490	501
Overall	**510**	**11.9**	**2.3**	**490**	**532**
23% H2O	527	6.1	1.2	515	536
48%K	512	6.1	1.2	500	521
High Density	524	8.1	1.5	514	537
Overall	**521**	**9.4**	**1.8**	**500**	**537**

Table A9: Tablet Hardness Values (25L)

Lot	Force (kN)	Tab 1	Tab 2	Tab 3	Tab 4	Tab 5	Tab 6	Tab 7	Tab 8	Tab 9	Tab 10
18%H2O 150 Torque	7*	74	87	76	67	73	76	74	56	62	79
	9	87	95	97	90	81	85	64	81	87	93
	11	98	97	76	75	94	103	98	101	96	74
	12**	107	94	84	104	106	117	116	101	106	67
	14	132	116	120	125	112	117	126	105	101	133
20%H2O 110Torque	7	46	68	70	72	71	73	69	73	43	70
	9	81	91	56	79	83	75	87	87	42	89
	10.5*	96	100	99	97	106	95	91	88	97	92
	12	106	95	85	108	110	97	103	102	95	101
	14**	120	113	118	112	115	116	109	118	112	112
20%H2O 130Torque	7	86	75	81	72	79	75	64	70	69	78
	9	92	50	89	98	92	91	88	84	88	87
	11	98	108	100	105	106	104	80	70	93	100
	12	105	104	123	95	97	108	105	110	112	110
	14	120	116	116	131	112	124	124	127	123	85
20%H2O 130Torque	7	66	68	70	68	67	42	75	67	71	75
No Spray	9	88	79	81	74	78	88	73	67	83	79
	11	95	88	87	97	89	93	88	81	85	86
	12	91	110	101	92	108	95	101	108	105	101
	14	114	104	95	107	87	106	113	117	105	120
20%H2O 140Torque	7	64	63	61	60	64	60	77	70	67	72
	9	90	55	83	78	88	95	92	89	79	92
	11	102	107	99	81	96	88	95	80	106	103
	12	93	119	93	108	87	117	68	103	76	63
	14	110	124	84	96	101	121	118	109	111	119

Lot	Force (kN)	Average	%RSD
18%H2O 150 Torque	7*	73	11.4
	9	86	11.2
	11	91	12.6
	12**	103	14.7
	14	119	9.1
20%H2O 110Torque	7	65	17.2
	9	77	20.7
	10.5*	96	4.9
	12	100	7.4
	14**	111	9.7
20%H2O 130Torque	7	75	8.8
	9	86	15.4
	11	96	12.7
	12	107	7.3
	14	118	11.1
20%H2O 130Torque	7	67	13.9
No Spray	9	79	8.4
	11	89	5.4
	12	101	6.9
	14	107	9.5
20%H2O 140Torque	7	66	8.9
	9	84	13.9
	11	96	10.2
	12	93	21.2
	14	109	11.2

	Force (kN)	Tab 1	Tab 2	Tab 3	Tab 4	Tab 5	Tab 6	Tab 7	Tab 8	Tab 9	Tab 10
20%H2O;160Torque	7	65	83	89	85	40	89	83	89	82	85
	9	102	96	104	106	89	89	89	84	106	94
	11	110	100	108	106	93	117	117	117	97	110
	12	126	120	104	110	119	126	119	91	106	106
	14	135	120	118	123	126	129	118	114	132	125
21.5%H2O;150Torque	7	74	75	79	80	65	74	59	80	65	66
	9	87	92	85	80	78	81	94	75	97	72
	11	86	87	80	89	103	98	96	98	99	89
	12	107	104	102	119	115	104	106	108	118	87
	14	118	110	109	121	114	120	122	110	122	108
21.5%H2O;150Torque	7	72	73	69	64	71	83	59	72	87	68
Intermediate Spray	9	90	97	94	90	78	96	94	97	95	85
	11	99	107	85	100	89	97	106	100	103	100
	12	108	106	83	111	112	116	72	113	107	110
	14	98	112	116	122	114	114	107	116	122	112
21.5%H2O;150Torque	7*	69	74	70	72	65	58	61	60	79	67
Intermediate Spray	9	94	93	88	95	82	88	93	73	97	85
	11	95	97	83	99	106	101	101	94	104	91
	12	93	107	102	101	113	115	105	117	109	123
	14	131	123	134	121	132	130	115	117	118	105
	* Two extra tablets measured at 71 and 65N										
23%H2O;110Torque	7	81	90	85	69	57	77	58	87	52	63
	9	103	89	93	116	84	107	94	95	100	94
	11*	91	107	129	24	99	95	63	87	126	121
	12	128	88	145	92	85	93	120	117	72	78
	14	132	97	125	126	128	119	160	113	135	135
	* Two extra tablets measured at 108 and 100N										

	Force (kN)	Average (N)	% RSD
20%H2O;160Torque	7	79	19.6
	9	96	8.4
	11	107	8.1
	12	113	10.1
	14	124	5.4
21.5%H2O;150Torque	7	72	10.2
	9	84	9.9
	11	93	8.0
	12	107	8.6
	14	115	5.1
21.5%H2O;150Torque	7	72	11.3
Intermediate Spray	9	92	6.8
	11	99	7.0
	12	104	13.8
	14	113	6.1
21.5%H2O;150Torque	7*	67	9.2
Intermediate Spray	9	89	8.3
	11	97	7.1
	12	109	8.2
	14	122	7.5
23%H2O;110Torque	7	72	19.6
	9	97	9.7
	11*	96	30.3
	12	102	23.7
	14	127	12.8

	Force (kN)	Tab 1	Tab 2	Tab 3	Tab 4	Tab 5	Tab 6	Tab 7	Tab 8	Tab 9	Tab 10
23%H2O;130Torque	7	71	68	78	75	78	65	78	74	75	71
	9	88	92	88	97	72	101	92	98	99	92
	11	99	105	105	107	110	102	96	113	105	96
	12	119	120	109	105	120	105	108	106	113	112
	14	127	124	112	122	120	132	117	124	127	117
23% H2O;130Torque	7	91	88	78	80	73	85	87	95	69	81
No Spray	9	103	96	92	107	112	86	60	89	87	117
	11	116	127	97	106	103	102	110	107	118	106
	12	112	103	129	110	114	118	126	128	114	135
	14	130	115	118	129	137	106	130	130	112	131
23% H2O;140Torque	7	83	68	81	65	74	67	59	76	79	74
	9	98	101	68	89	95	78	65	95	88	92
	11	96	83	89	101	106	106	114	104	112	113
	12	125	122	110	111	108	119	109	109	105	122
	14	134	120	113	130	118	129	134	128	124	132
23% H2O;160Torque	7	83	89	68	78	68	59	77	57	78	81
	9	102	98	110	97	87	76	98	88	97	100
	11	100	93	114	114	118	108	114	107	91	107
	12	119	109	105	120	106	117	114	106	96	111
	14	139	130	136	115	127	83	125	128	135	126
23% H2O;170Torque	7	88	91	77	81	94	50	92	95	89	90
	9	109	114	112	101	121	89	102	77	111	107
	11	118	101	101	112	106	111	118	99	102	109
	12	107	138	107	137	144	118	130	106	130	125
	14	155	143	144	149	155	119	141	147	147	127
23% H2O;170Torque	7	68	86	86	87	97	92	95	82	62	73
No Spray	9	107	101	87	99	113	101	112	94	111	89
	11	94	103	103	105	96	105	121	119	113	115
	12	128	92	131	130	81	130	116	117	104	122
	14	116	157	126	117	133	145	137	107	124	138

	Force (kN)	Tab 1	Tab 2	Tab 3	Tab 4	Tab 5	Tab 6	Tab 7	Tab 8	Tab 9	Tab 10
25% H2O;150Torque	7	54	93	129	60	139	105	95	76	77	50
	7(b)	145	121	57	101	94	91	149	52	42	71
	9	155	119	150	69	61	108	105	135	142	161
	11	63	164	119	104	109	130	116	125	147	134
	12	102	127	156	150	173	148	167	125	144	178
	14	205	114	95	132	168	127	153	147	141	136

	Force (kN)	Average (N)	% RSD
23% H2O;130Torque	7	73	6.1
	9	92	9.0
	11	104	5.4
	12	112	5.5
	14	122	4.8
23% H2O;130Torque	7	83	9.6
No Spray	9	95	17.3
	11	109	8.3
	12	119	8.5
	14	124	8.1
23% H2O;140Torque	7	73	10.6
	9	87	14.5
	11	102	10.1
	12	114	6.3
	14	126	5.8
23% H2O;160Torque	7	74	14.4
	9	95	9.7
	11	107	8.8
	12	110	6.7
	14	124	12.8
23% H2O;170Torque	7	85	15.9
	9	104	12.4
	11	108	6.6
	12	124	11.3
	14	143	8.2
23% H2O;170Torque	7	83	14.1
No Spray	9	101	9.2
	11	107	8.6
	12	115	15.2
	14	130	11.5

	Force (kN)	Average (N)	% RSD
25% H2O;150Torque	7	88	34.8
	7(b)	92	40.9
	9	120	29.1
	11	121	22.4
	12	147	16.1
	14	142	21.1

Table A10: Tablet Hardness Values (1250L)

Lot	Force (kN)	Tab 1	Tab 2	Tab 3	Tab 4	Tab 5	Tab 6	Tab 7	Tab 8	Tab 9	Tab 10
20% H2O;33%K	7.8	64	70	74	71	73	68	60	81	76	66
Low Density	9.3	83	96	86	92	95	89	79	92	89	83
	10.7	107	104	107	100	98	112	88	102	102	107
	13	112	100	90	86	110	101	83	109	88	94
	14.5	83	92	68	90	61	94	80	97	94	94
20% H2O;33%K	7.8	60	65	69	69	73	64	69	75	62	76
High Density	9.3	90	84	87	97	89	90	93	79	83	92
	11.3	109	115	110	122	106	111	106	117	105	104
	13	119	103	99	104	110	88	117	107	100	108
	14.5	95	82	95	95	95	70	91	95	109	78
20% H2O;48%K	7.8	91	83	83	91	75	100	96	90	79	81
Low Density	9.3	93	87	102	94	97	104	108	103	82	127
	13	135	95	138	124	113	147	135	122	140	142
	14.2	131	148	130	152	153	153	138	122	138	143
	14.5	124	126	136	121	148	122	135	138	134	117
20% H2O;48%K	9.3	93	99	88	97	95	98	91	87	90	92
High Density	10.4	101	100	108	127	115	97	111	95	97	100
	13	130	119	121	119	118	114	119	119	122	127
21.5% H2O;41%K	7.8	76	73	79	74	76	76	79	73	79	76
Middle Density	9.3	103	105	100	99	97	99	99	96	101	95
	11.2	111	111	110	105	111	108	111	113	98	108
	13	117	112	118	115	115	115	108	117	114	115
	14.5	106	97	91	102	108	104	88	108	105	111
23% H2O;33%K	7.8	78	72	55	72	68	71	77	72	74	70
Low Density	9.3	85	88	93	82	91	92	80	95	84	99
	10.5	121	106	95	98	111	115	107	108	109	97
	13	123	77	78	117	105	78	93	124	118	105
	14.5	115	125	82	94	106	114	73	102	84	108

Lot	Force (kN)	Average (N)	RSD (%)
20%H2O;33%K	7.8	70	8.7
Low Density	9.3	88	6.3
	10.7	103	6.4
	13	97	10.9
	14.5	85	14.4
20% H2O;33%K	7.8	68	8.0
High Density	9.3	88	6.0
	11.3	111	5.3
	13	106	8.5
	14.5	91	12.2
20% H2O;48%K	7.8	87	9.1
Low Density	9.3	100	12.5
	13	129	12.3
	14.2	141	7.7
	14.5	130	7.4
20% H2O;48%K	9.3	93	4.5
High Density	10.4	105	9.6
	13	121	3.8
21.5% H2O;41%K	7.8	76	3.1
Middle Density	9.3	99	3.1
	11.2	109	4.0
	13	115	2.5
	14.5	102	7.5
23% H2O;33%K	7.8	71	9.0
Low Density	9.3	89	6.9
	10.5	107	7.7
	13	102	18.8
	14.5	100	16.6

	Force (kN)	**Tab 1**	**Tab 2**	**Tab 3**	**Tab 4**	**Tab 5**	**Tab 6**	**Tab 7**	**Tab 8**	**Tab 9**	**Tab 10**
23% H2O;33%K	7.8	79	71	64	74	67	73	74	74	80	80
High Density	9.3	96	91	85	92	90	95	95	95	91	96
	13	110	119	103	122	116	109	112	118	104	109
	14.2	112	122	102	115	123	111	123	121	124	109
	14.5	119	99	103	104	115	99	98	106	103	103
23%H2O;48%K;LD	7.8	60	54	58	62	51	57	51	62	59	54
Low Density	9.3	95	88	101	98	87	105	100	92	100	96
	10.7	112	110	116	114	107	104	93	101	104	116
	13	115	102	121	102	118	124	99	118	121	116
	14.5	89	107	109	97	113	104	105	112	97	106
23% H2O ;48%K	9.3	90	112	95	100	96	102	107	101	95	90
High Density	10.4	124	108	105	124	104	97	115	121	119	119
	13	146	144	133	138	136	143	138	123	150	123

Lot	Force (kN)	Average (N)	RSD (%)
23% H2O;33%K	7.8	74	7.2
High Density	9.3	93	3.8
	13	112	5.7
	14.2	116	6.5
	14.5	105	6.6
23%H2O;48%K	7.8	57	7.3
Low Density	9.3	96	6.0
	10.7	108	6.9
	13	114	8.0
	14.5	104	7.2
23% H2O ;48%K	9.3	99	7.2
High Density	10.4	114	8.3
	13	137	6.6

Table A11: Tablet Hardness Values (600L)

Lot	Force (kN)	Tab 1	Tab 2	Tab 3	Tab 4	Tab 5	Tab 6	Tab 7	Tab 8	Tab 9	Tab 10	Avg. (N)	% RSD
Lot 1	8.5	106	95	102	97	106	101	100	107	105	106	103	4.1
	10.6	124	129	128	127	123	126	127	111	126	124	125	4.1
	12	138	137	139	130	135	141	146	132	141	142	138	3.5
	13	144	143	137	135	136	136	149	144	132	140	140	3.8
	14.5	136	141	142	160	154	146	136	133	137	142	143	6.0
Lot 2	8.5	101	111	113	107	108	112	115	104	105	109	109	4.0
	10.6	124	134	129	136	129	130	123	124	126	128	128	3.3
	12	136	136	125	147	137	147	140	118	109	155	135	10.4
	13	130	133	142	144	144	150	136	144	140	148	141	4.5
	14.5	150	157	140	132	147	151	150	151	139	137	145	5.4
Lot 3	8.5	108	107	105	109	119	113	106	109	105	102	108	4.4
	10.6	114	124	132	123	116	138	124	132	130	127	126	5.9
	12	127	143	134	135	128	140	140	141	143	149	138	5.0
	13	158	146	142	118	150	141	150	153	148	144	145	7.4
	14.5	150	151	158	150	151	156	141	143	147	156	150	3.7

Table A12: Tablet Friability Results (25L)

% Water	18	20	20	20	20	20	21.5	21.5	21.5
Torque in lbs	**150**	**110**	**130**	**130**	**140**	**160**	**145**	**150**	**150**
Spray	**On**	**On**	**On**	**Off**	**On**	**On**	**On**	**Inter-med-iate**	**Inter-Med-iate**
% Friability - 10 min	0.35	0.36	0.38	0.36	0.33	0.38	0.38	0.40	0.33
% Friability - 20 min	0.63	0.51	0.54	0.56	0.51	0.55	0.60	0.61	0.52
% Friability - 30 min	0.78	0.66	0.68	1.09	0.78	0.73	1.13	1.04	0.78
No. Capped Tablets - 10 min	0	0	0	0	0	0	0	0	0
No. Capped Tablets - 20 min	0	0	0	0	0	0	0	0	0
No. Capped Tablets - 30 min	0	0	0	0	0	0	0	0	0
No. Chipped Tablets - 10 min	0	0	0	0	0	0	0	0	0
No. Chipped Tablets - 20 min	1	0	0	4	2	0	2	5	2
No. Chipped Tablets - 30 min	8	3	3	60	24	4	53	57	19

% Water	23	23	23	23	23	23	23	25
Torque in lbs	**110**	**130**	**130**	**140**	**160**	**170**	**170**	**150**
Spray	**On**	**On**	**Off**	**On**	**On**	**On**	**Off**	**On**
% Friability - 10 min	0.32	0.33	0.88	0.42	0.35	0.37	0.41	0.33
% Friability - 20 min	0.47	0.48	1.03	0.58	0.52	0.54	0.62	0.49
% Friability - 30 min	0.47	0.59	1.17	0.73	0.52	0.54	0.78	0.64
No. Capped Tablets - 10 min	0	0	0	0	0	0	0	0
No. Capped Tablets - 20 min	0	0	0	0	0	0	0	0
No. Capped Tablets - 30 min	0	0	0	0	0	0	0	0
No. Chipped Tablets - 10 min	0	0	0	0	0	0	0	0
No. Chipped Tablets - 20 min	0	0	0	0	0	0	0	0
No. Chipped Tablets - 30 min	6	1	2	3	15	15	3	3

Table A13: Tablet Friability Results (1250L)

% Water	20	20	23	23	21.5	21.5
%K	48	48	48	48	41	38
Drug Bulk Density	Low	High	Low	High	Middle	Inter-mediate
% Wt Loss - 10 min	0.11	0.23	0.16	0.12	0.04	0.05
% Wt Loss - 30 min	0.23	0.16	0.15	0.12	0.50	0..38
No. Capped Tablets - 10 min	0	0	0	0	0	0
No. Capped Tablets - 20 min	0	0	0	0	0	0
No. Capped Tablets - 30 min	0	0	0	0	0	0
No. Chipped Tablets - 10 min	0	0	0	0	2	0
No. Chipped Tablets - 20 min	10	0	3	1	26	16
No. Chipped Tablets 30 min	48	37	25	25	130	137

% Water	20	20	23	23	23	23
%K	33	33	33	33	33	33
Drug Bulk Density	Low	High	Low	High	Inter-mediate	Inter-mediate
% Wt Loss - 10 min	0.11	0.09	0.13	0.11	0.11	0.13
% Wt Loss - 30 min	0.93	0.98	1.04	0.7	0.07	3.34
No. Capped Tablets - 10 min	1	1	0	0	2	0
No. Capped Tablets - 20 min	6	3	0	0	6	8
No. Capped Tablets - 30 min	9	5	0	1	10	11
No. Chipped Tablets - 10 min	1	2	0	0	0	4
No. Chipped Tablets - 20 min	23	40	94	56	35	65
No. Chipped Tablets - 30 min	95	102	175	146	155	168

Table A14: Tablet Friability Results (600L)

				Average
% Water	23	23	23	
%K	35	35	35	
Drug Bulk Density	Intermediate	Intermediate	Intermediate	
% Wt Loss - 10 min	0.06	0.09	0.07	0.07
% Wt Loss - 30 min	0.72	1.32	0.24	0.76
No. Capped Tablets - 10 min	0	0	0	0.00
No. Capped Tablets - 20 min	0	0	0	0.00
No. Capped Tablets - 30 min	0	0	0	0.00
No. Chipped Tablets- 10 min	0	1	0	0
No. Chipped Tablets- 20 min	34	30	38	34
No. Chipped Tablets- 30 min	126	126	139	130

Table A15: Tablet % Dissolution Results (25L)

Water %	Torque In-Lbs	Spray	Time (min)	Tab 1	Tab 2	Tab 3	Tab 4	Tab 5	Tab 6	Average	%RSD
18	150	On	0	0.1	-1.2	-0.1	-0.1	-0.2	0.0	-0.3	-187.1
			5	35.5	52.0	55.5	47.4	35.7	50.3	46.1	18.4
			10	61.8	72.8	77.1	82.2	62.9	83.7	73.4	12.8
			15	76.3	82.6	87.3	95.0	76.5	92.4	85.0	9.3
			20	84.9	86.7	91.8	99.1	86.3	96.2	90.8	6.4
			25	91.6	91.0	95.2	101.2	92.6	98.8	95.1	4.4
			30	94.9	93.1	97.6	101.9	95.6	100.4	97.2	3.5
			35	96.9	94.5	99.0	102.8	97.3	101.3	98.6	3.1
			40	98.7	96.6	100.2	103.1	99.2	101.8	99.9	2.3
			45	100.3	97.5	100.7	103.3	100.4	102.3	100.8	2.0
			50	101.7	99.2	101.2	103.4	101.5	102.5	101.6	1.4
			55	102.6	99.1	101.4	103.4	102.2	102.6	101.9	1.5
			60	103.4	100.7	101.5	103.6	102.8	102.8	102.5	1.1
			65	104.0	100.7	101.8	103.6	102.9	103.0	102.6	1.2
			70	104.4	100.7	101.8	103.7	103.0	102.9	102.7	1.3
			75	104.6	100.7	102.0	103.8	103.2	103.0	102.9	1.4
			80	104.9	101.1	102.2	103.8	103.3	103.1	103.1	1.3
			85	105.1	100.8	102.3	104.0	103.4	103.2	103.1	1.4
			90	105.1	101.2	102.3	104.0	103.4	103.2	103.2	1.3

Water %	Torque In-Lbs	Spray	Time (min)	Tab 1	Tab 2	Tab 3	Tab 4	Tab 5	Tab 6	Average	%RSD
20	110	On	0	0.1	0.4	0.1	0.2	0.2	0.0	0.2	82.0
			5	29.9	29.2	50.0	40.8	29.2	33.3	35.4	23.7
			10	52.8	51.8	66.0	60.3	51.8	55.6	56.4	10.2
			15	64.2	63.2	74.7	71.2	65.4	70.4	68.2	6.7
			20	74.4	72.8	80.8	81.4	76.5	80.3	77.7	4.7
			25	81.8	80.0	85.6	89.6	84.5	87.8	84.9	4.2
			30	88.0	85.8	88.8	94.4	90.2	92.6	90.0	3.5
			35	92.2	90.9	92.1	97.9	93.4	96.0	93.8	2.9
			40	95.2	93.6	93.6	99.6	95.8	97.8	95.9	2.5
			45	97.7	96.3	95.3	100.3	97.4	99.0	97.7	1.9
			50	99.2	98.0	96.6	100.8	98.4	99.7	98.8	1.5
			55	100.2	99.2	97.3	100.9	99.2	100.1	99.5	1.3
			60	100.7	100.3	98.0	101.0	99.7	100.3	100.0	1.1
			65	101.1	100.6	98.6	101.0	99.9	100.6	100.3	0.9
			70	101.5	101.7	99.1	101.2	100.3	100.7	100.8	0.9
			75	101.7	101.5	99.5	101.3	100.4	100.8	100.9	0.8
			80	101.9	102.2	99.8	101.3	100.7	100.9	101.1	0.9
			85	102.1	102.0	99.8	101.3	100.7	101.1	101.2	0.9
			90	102.1	102.4	100.1	101.5	100.9	101.1	101.4	0.8

Water %	Torque In-Lbs	Spray	Time (min)	Tab 1	Tab 2	Tab 3	Tab 4	Tab 5	Tab 6	Average	%RSD
20	130	On	0	0.5	0.5	0.5	0.5	0.5	0.3	0.5	17.4
			5	42.2	44.0	44.5	40.0	33.2	42.6	41.1	10.2
			10	68.9	68.3	69.5	68.1	61.9	69.3	67.6	4.3
			15	81.2	79.2	79.7	83.4	77.4	84.9	81.0	3.5
			20	87.7	85.9	86.7	91.5	86.4	94.1	88.7	3.7
			25	92.9	90.7	91.9	95.5	92.6	98.4	93.7	3.0
			30	95.9	94.4	95.0	98.2	95.9	100.3	96.6	2.3
			35	97.7	96.9	97.6	100.0	97.9	101.3	98.5	1.7
			40	98.9	98.7	99.4	100.9	99.2	101.5	99.8	1.2
			45	100.1	99.9	100.9	101.6	100.4	101.9	100.8	0.8
			50	100.7	100.3	101.5	102.0	100.7	101.8	101.2	0.7
			55	101.2	100.7	102.2	102.4	101.3	102.0	101.6	0.7
			60	101.4	100.9	102.6	102.5	101.4	101.9	101.8	0.6
			65	101.4	100.9	103.0	102.6	101.5	101.8	101.9	0.8
			70	101.7	101.2	103.1	102.7	101.6	101.9	102.0	0.7
			75	101.8	101.3	103.6	102.7	101.8	102.0	102.2	0.8
			80	101.7	101.2	103.4	102.8	101.7	102.1	102.2	0.8
			85	101.8	101.4	103.7	102.8	101.8	101.9	102.2	0.8
			90	101.7	101.3	103.7	102.7	101.8	101.9	102.2	0.8

Water %	Torque In-Lbs	Spray	Time (min)	Tab 1	Tab 2	Tab 3	Tab 4	Tab 5	Tab 6	Average	%RSD
20	130	Off	0	-0.1	-0.1	-0.1	-0.1	-0.2	-0.1	-0.1	-35.0
			5	32.9	43.4	29.5	32.9	36.2	52.9	38.0	23.0
			10	57.1	66.2	54.7	57.6	58.7	73.5	61.3	11.6
			15	70.2	76.3	70.3	73.0	73.1	80.2	73.9	5.2
			20	78.6	82.3	79.9	82.9	80.8	85.0	81.6	2.8
			25	85.2	86.6	86.3	89.0	86.8	89.1	87.2	1.8
			30	89.8	90.5	91.2	93.4	90.8	92.3	91.4	1.4
			35	93.9	93.3	94.1	96.2	93.6	94.6	94.3	1.1
			40	96.6	95.7	96.6	97.9	95.7	96.4	96.5	0.8
			45	98.1	97.2	98.0	99.5	97.1	98.1	98.0	0.9
			50	99.3	98.6	99.2	100.4	98.7	99.3	99.2	0.7
			55	100.3	100.2	100.0	101.1	99.4	100.2	100.2	0.5
			60	100.8	100.4	100.5	101.4	100.0	101.2	100.7	0.5
			65	101.2	101.1	100.8	101.6	100.3	101.5	101.1	0.5
			70	101.4	101.2	101.1	101.7	100.6	101.7	101.3	0.4
			75	101.6	101.4	101.2	101.9	100.8	101.8	101.5	0.4
			80	101.8	101.6	101.3	102.0	101.0	101.9	101.6	0.4
			85	101.9	101.8	101.3	102.0	101.2	102.0	101.7	0.4
			90	102.2	101.8	101.4	102.2	101.3	102.2	101.8	0.4

Water %	Torque In-Lbs	Spray	Time (min)	Tab 1	Tab 2	Tab 3	Tab 4	Tab 5	Tab 6	Average	%RSD
20	140	On	0	-0.1	0.0	-0.1	-0.2	-0.1	-0.3	-0.1	-77.5
			5	49.6	38.3	57.5	43.6	38.8	29.4	42.9	22.8
			10	73.2	73.3	79.8	81.9	75.5	65.5	74.8	7.7
			15	87.6	84.6	90.1	93.1	88.4	81.4	87.5	4.7
			20	92.0	90.8	95.7	96.9	93.4	90.8	93.3	2.8
			25	95.5	95.3	98.3	100.0	96.5	97.1	97.1	1.8
			30	98.0	97.8	99.6	101.8	98.5	99.8	99.3	1.5
			35	99.7	99.7	100.6	102.2	99.6	100.9	100.5	1.0
			40	100.5	101.1	101.5	102.6	100.7	101.6	101.3	0.7
			45	101.6	101.7	101.9	102.7	101.4	101.9	101.8	0.4
			50	101.9	102.1	102.1	102.7	101.6	101.9	102.0	0.4
			55	102.3	102.5	102.2	102.8	101.9	101.9	102.3	0.3
			60	102.6	102.7	102.5	102.9	102.1	102.0	102.5	0.3
			65	102.8	103.1	102.6	102.9	102.3	102.2	102.7	0.3
			70	103.0	103.3	102.7	102.9	102.5	102.3	102.8	0.4
			75	103.0	103.4	102.7	103.0	102.5	102.2	102.8	0.4
			80	103.1	103.6	102.7	103.0	102.5	102.3	102.9	0.4
			85	103.1	103.6	102.7	103.0	102.5	102.3	102.9	0.4
			90	103.1	103.9	102.8	103.1	102.6	102.5	103.0	0.5
20	160	On	0	0.0	-0.8	0.0	0.1	-0.1	-0.1	-0.1	-215.6
			5	41.1	38.2	30.2	46.4	45.9	34.9	39.4	16.1
			10	73.9	71.4	59.5	80.9	83.2	68.3	72.9	11.8
			15	86.7	84.6	78.3	96.9	94.7	88.5	88.3	7.7
			20	92.6	91.0	87.4	100.8	98.7	95.3	94.3	5.3
			25	96.1	95.0	91.4	102.4	100.9	98.3	97.3	4.2
			30	98.4	97.8	94.1	103.1	102.0	100.2	99.3	3.3
			35	99.8	99.6	96.5	103.5	103.1	101.6	100.7	2.6
			40	101.1	101.5	98.7	103.8	103.7	102.2	101.8	1.8
			45	102.0	101.3	100.5	103.8	103.9	102.6	102.3	1.3
			50	102.7	101.9	101.6	104.0	104.5	103.0	102.9	1.1
			55	103.1	102.8	102.2	103.9	104.5	103.0	103.3	0.8
			60	103.5	102.1	102.4	103.9	104.6	103.1	103.3	0.9
			65	103.7	102.2	102.8	103.9	104.8	103.1	103.4	0.9
			70	103.7	102.2	102.8	104.0	104.9	103.2	103.5	0.9
			75	103.8	102.5	102.8	104.0	104.9	103.2	103.5	0.9
			80	103.9	102.6	103.1	104.0	104.8	103.1	103.6	0.8
			85	103.7	103.1	102.9	104.0	104.8	103.2	103.6	0.7
			90	103.9	102.5	103.0	103.9	104.9	103.2	103.6	0.8

Water %	Torque In-Lbs	Spray	Time (min)	Tab 1	Tab 2	Tab 3	Tab 4	Tab 5	Tab 6	Average	%RSD
21.5	145	On	0	0.0	-0.2	-0.1	0.0	0.0	-0.1	-0.1	-122.5
			5	31.9	33.8	40.3	46.3	35.6	35.2	37.2	14.2
			10	56.5	60.2	66.7	73.7	58.6	58.0	62.3	10.7
			15	71.2	73.8	75.5	82.9	72.2	72.7	74.7	5.7
			20	79.5	81.9	81.5	89.4	79.8	82.2	82.4	4.4
			25	85.6	86.8	86.4	94.3	85.7	89.7	88.1	3.8
			30	90.9	91.2	89.9	97.9	90.6	93.7	92.4	3.3
			35	95.3	94.2	93.2	100.3	93.4	96.3	95.4	2.8
			40	98.7	96.8	95.5	101.8	95.9	98.6	97.9	2.4
			45	101.1	98.8	97.5	102.7	98.1	99.9	99.7	2.0
			50	102.6	99.9	98.8	103.4	99.4	100.9	100.8	1.8
			55	103.7	101.5	100.3	103.9	100.8	101.7	102.0	1.5
			60	104.3	102.0	101.1	104.1	101.3	102.1	102.5	1.3
			65	104.7	102.9	101.8	104.5	102.1	102.6	103.1	1.2
			70	105.0	103.1	102.4	104.4	102.6	102.8	103.4	1.0
			75	105.0	103.7	102.7	104.5	103.0	102.8	103.6	0.9
			80	105.1	103.7	103.0	104.5	103.3	102.8	103.7	0.9
			85	105.4	104.4	103.4	104.7	103.7	103.3	104.1	0.8
			90	105.4	104.0	103.5	104.5	103.6	103.0	104.0	0.8

Water %	Torque In-Lbs	Spray	Time (min)	Tab 1	Tab 2	Tab 3	Tab 4	Tab 5	Tab 6	Average	%RSD
21.5	150	Inter-med.	0	0.1	0.3	0.1	0.2	0.1	-0.1	0.1	113.9
			5	29.7	40.7	28.5	44.8	37.0	50.5	38.5	22.2
			10	56.9	62.3	52.4	77.9	64.1	81.4	65.8	17.5
			15	73.3	75.1	68.0	87.5	76.2	87.3	77.9	10.2
			20	81.9	83.6	78.6	94.6	82.0	91.4	85.3	7.3
			25	90.1	89.6	85.0	98.5	87.4	95.3	91.0	5.5
			30	94.7	94.2	90.4	101.5	91.3	97.9	95.0	4.4
			35	97.8	97.8	94.1	103.1	94.6	100.0	97.9	3.5
			40	100.0	99.7	96.3	104.2	97.0	101.5	99.8	2.9
			45	101.5	101.5	98.6	104.9	99.1	102.6	101.4	2.3
			50	102.8	102.0	100.0	105.4	100.8	103.3	102.4	1.9
			55	103.6	102.9	100.9	105.7	101.8	103.7	103.1	1.6
			60	104.5	103.5	101.8	106.1	102.6	104.2	103.8	1.5
			65	104.7	103.9	102.4	106.3	103.1	104.6	104.2	1.3
			70	105.0	103.9	103.0	106.3	103.5	104.8	104.4	1.2
			75	105.1	104.0	103.2	106.3	103.7	104.9	104.5	1.1
			80	105.4	104.3	103.6	106.4	104.0	105.1	104.8	1.0
			85	105.4	104.3	103.7	106.3	104.1	105.3	104.9	0.9
			90	105.6	104.3	103.7	106.4	104.2	105.2	104.9	1.0

Water %	Torque In-Lbs	Spray	Time (min)	Tab 1	Tab 2	Tab 3	Tab 4	Tab 5	Tab 6	Average	%RSD
21.5	150	Inter-med.	0	0.0	-0.2	0.0	0.0	0.0	-0.1	-0.1	-167.3
			5	32.2	58.4	40.0	30.9	29.2	29.2	36.7	31.1
			10	60.1	81.2	76.3	59.5	55.9	55.8	64.8	17.1
			15	73.8	87.7	87.0	76.3	75.1	71.4	78.6	8.9
			20	80.8	91.5	90.6	85.6	83.8	81.0	85.5	5.4
			25	84.9	94.0	93.2	90.6	88.1	88.2	89.8	3.8
			30	89.3	96.1	95.1	94.5	90.8	92.3	93.0	2.8
			35	92.5	97.9	96.9	97.1	93.9	95.8	95.7	2.2
			40	94.3	99.4	98.1	99.4	96.1	97.8	97.5	2.1
			45	96.1	100.3	98.9	101.1	97.5	99.6	98.9	1.9
			50	97.5	101.1	99.6	101.8	99.1	100.4	99.9	1.5
			55	98.6	101.4	100.2	102.5	100.2	101.0	100.6	1.3
			60	99.6	101.9	100.4	102.8	101.0	101.3	101.2	1.1
			65	100.5	102.3	100.6	102.9	101.3	101.6	101.5	0.9
			70	101.0	102.5	100.6	103.0	101.4	101.6	101.7	0.9
			75	101.5	102.7	100.6	103.1	101.7	101.7	101.9	0.9
			80	101.9	103.1	100.8	103.2	101.8	101.8	102.1	0.9
			85	102.3	102.9	100.8	103.2	102.0	102.0	102.2	0.8
			90	102.3	103.4	100.7	103.1	101.9	101.9	102.2	0.9

Water %	Torque In-Lbs	Spray	Time (min)	Tab 1	Tab 2	Tab 3	Tab 4	Tab 5	Tab 6	Average	%RSD
23	110	On	0	0.0	0.0	0.0	0.0	0.1	0.1	0.0	154.9
			5	46.4	33.2	42.8	40.0	37.6	53.3	42.2	16.6
			10	67.6	60.3	66.6	65.4	60.2	73.0	65.5	7.4
			15	79.7	76.8	81.4	81.4	74.0	85.4	79.8	5.0
			20	87.4	87.2	89.8	90.7	84.6	91.2	88.5	2.9
			25	92.8	94.4	94.9	95.6	91.0	95.8	94.1	2.0
			30	95.9	98.5	98.0	98.6	96.2	97.6	97.5	1.2
			35	98.2	100.8	99.5	100.3	99.3	98.7	99.5	1.0
			40	99.3	102.8	100.9	101.0	101.0	99.5	100.8	1.3
			45	100.5	103.0	101.7	101.5	102.5	99.9	101.5	1.1
			50	100.8	104.2	102.2	101.8	103.2	100.0	102.1	1.5
			55	101.3	103.5	102.4	101.9	103.6	100.2	102.1	1.3
			60	101.4	104.9	102.8	102.1	104.0	100.3	102.6	1.7
			65	101.4	104.7	102.8	102.2	104.1	100.2	102.6	1.6
			70	101.6	104.0	102.9	102.1	104.2	100.3	102.5	1.5
			75	101.7	105.0	102.9	102.2	104.3	100.4	102.8	1.7
			80	101.7	104.6	103.1	102.2	104.5	100.4	102.7	1.6
			85	101.7	104.7	103.1	102.2	104.6	100.5	102.8	1.6
			90	101.8	104.1	103.1	102.4	104.5	100.5	102.7	1.4

Water %	Torque In-Lbs	Spray	Time (min)	Tab 1	Tab 2	Tab 3	Tab 4	Tab 5	Tab 6	Average	%RSD
23	130	On	0	0.0	0.3	0.3	0.2	0.4	0.0	0.2	83.7
			5	30.6	22.1	22.6	31.6	33.5	29.1	28.2	17.0
			10	50.1	38.0	41.6	50.2	54.5	51.4	47.6	13.4
			15	58.3	49.6	50.1	58.8	65.4	65.0	57.9	11.9
			20	64.3	59.9	57.9	66.4	73.8	75.2	66.3	10.7
			25	69.8	68.5	65.0	72.1	81.5	82.6	73.2	9.8
			30	74.9	75.5	71.1	77.5	86.7	88.9	79.1	8.9
			35	79.0	80.4	75.8	81.5	90.2	93.2	83.3	8.2
			40	82.5	85.0	81.0	85.3	93.1	96.3	87.2	7.0
			45	85.3	88.5	84.5	87.9	95.4	98.8	90.1	6.4
			50	88.0	90.9	87.1	89.9	97.1	100.8	92.3	5.9
			55	90.5	92.9	89.9	92.0	98.2	101.8	94.2	5.0
			60	92.3	95.3	92.2	93.5	99.4	102.5	95.9	4.4
			65	94.3	96.5	94.2	95.1	100.3	103.1	97.2	3.8
			70	96.2	97.6	95.8	96.4	100.8	103.5	98.4	3.1
			75	97.4	99.0	97.4	97.5	101.4	103.7	99.4	2.6
			80	98.4	99.5	98.6	98.4	101.7	103.8	100.1	2.2
			85	99.5	100.1	99.5	99.0	101.9	103.9	100.7	1.9
			90	100.4	100.6	100.4	99.7	102.1	103.9	101.2	1.5
23	130	Off	0	0.1	-0.2	0.1	0.2	0.2	0.1	0.1	176.6
			5	42.5	27.8	30.1	35.9	35.4	51.2	37.2	23.1
			10	60.6	49.7	51.8	57.7	56.2	65.9	57.0	10.4
			15	69.0	62.3	61.8	68.7	66.7	74.1	67.1	6.9
			20	75.3	70.2	70.2	76.8	73.9	81.1	74.6	5.6
			25	81.0	77.9	77.7	83.9	80.4	86.5	81.2	4.2
			30	86.3	83.3	84.1	89.3	86.5	90.7	86.7	3.3
			35	90.4	88.2	88.7	93.7	90.7	93.7	90.9	2.6
			40	93.3	91.1	92.5	96.3	94.5	95.4	93.9	2.0
			45	96.2	94.4	95.0	98.5	96.9	97.3	96.4	1.6
			50	97.9	96.2	97.0	100.1	98.7	98.1	98.0	1.4
			55	99.2	98.0	98.7	101.1	100.0	99.2	99.4	1.1
			60	100.3	99.0	99.7	101.9	101.1	99.8	100.3	1.0
			65	100.9	100.4	100.3	102.1	101.7	100.2	100.9	0.8
			70	101.4	100.7	100.9	102.4	101.9	100.6	101.3	0.7
			75	101.8	101.8	101.5	102.4	102.3	100.7	101.7	0.6
			80	101.9	101.5	101.8	102.5	102.5	100.8	101.8	0.6
			85	102.2	102.5	102.3	102.5	102.9	101.0	102.2	0.6
			90	102.4	102.4	102.3	102.5	103.0	101.0	102.3	0.7

Water %	Torque In-Lbs	Spray	Time (min)	Tab 1	Tab 2	Tab 3	Tab 4	Tab 5	Tab 6	Average	%RSD
23	140	On	0	0.0	0.0	0.2	0.0	0.0	0.0	0.0	244.9
			5	22.5	36.7	25.2	33.0	31.0	36.4	30.8	19.0
			10	44.9	60.5	50.2	58.2	56.0	69.5	56.6	15.0
			15	62.6	72.2	66.7	73.7	71.0	78.4	70.8	7.8
			20	73.5	80.8	77.4	83.0	79.5	84.2	79.7	4.9
			25	81.4	86.0	85.6	90.1	85.7	88.8	86.3	3.5
			30	88.2	91.7	91.6	94.7	91.0	93.2	91.7	2.4
			35	92.6	94.2	95.1	97.8	94.7	95.9	95.0	1.9
			40	95.9	96.4	97.8	100.2	97.4	98.1	97.6	1.5
			45	98.2	97.7	99.6	101.5	99.2	99.6	99.3	1.3
			50	100.0	99.9	100.7	102.0	100.4	100.6	100.6	0.7
			55	101.3	99.7	101.4	102.5	101.3	101.4	101.2	0.9
			60	101.9	101.3	101.8	102.8	101.7	101.8	101.9	0.5
			65	102.6	100.7	102.1	103.1	102.1	102.1	102.1	0.8
			70	102.9	102.0	102.4	103.2	102.2	102.5	102.5	0.4
			75	103.3	101.3	102.2	103.2	102.4	102.5	102.5	0.7
			80	103.3	102.5	102.5	103.2	102.5	102.5	102.7	0.4
			85	103.7	101.7	102.6	103.5	102.7	102.8	102.8	0.7
			90	103.7	102.8	102.7	103.5	102.8	102.8	103.0	0.4
23	160	On	0	0.0	0.3	0.0	0.0	0.0	-0.2	0.0	964.7
			5	43.5	55.9	31.4	34.6	33.6	49.5	41.4	23.8
			10	69.0	79.0	60.1	65.7	60.4	79.3	68.9	12.5
			15	80.8	85.2	72.8	81.7	74.2	90.5	80.9	8.3
			20	86.9	90.1	81.3	89.4	84.4	95.1	87.8	5.5
			25	91.6	92.7	87.3	94.4	89.4	97.3	92.1	3.9
			30	95.2	95.4	90.8	96.9	92.9	98.9	95.0	3.0
			35	97.6	97.1	94.1	98.9	95.6	100.0	97.2	2.2
			40	99.4	98.8	96.7	100.1	97.6	100.7	98.9	1.5
			45	100.6	99.9	98.1	101.2	98.9	101.2	100.0	1.3
			50	101.4	100.3	99.4	101.8	100.0	101.7	100.8	1.0
			55	102.1	101.7	100.2	102.1	100.7	102.0	101.5	0.8
			60	102.5	101.9	100.9	102.2	101.3	102.1	101.8	0.6
			65	103.0	102.4	101.4	102.4	101.9	102.3	102.2	0.5
			70	103.0	102.5	101.9	102.3	102.0	102.2	102.3	0.4
			75	103.0	102.7	102.2	102.4	102.1	102.4	102.5	0.3
			80	103.2	103.1	102.5	102.5	102.3	102.4	102.7	0.4
			85	103.2	103.2	102.7	102.5	102.5	102.6	102.8	0.3
			90	103.4	103.2	102.9	102.6	102.5	102.6	102.9	0.3

Water %	Torque In-Lbs	Spray	Time (min)	Tab 1	Tab 2	Tab 3	Tab 4	Tab 5	Tab 6	Average	%RSD
23	170	On	0	0.4	1.0	0.1	0.3	0.2	0.1	0.4	90.4
			5	22.8	29.9	30.3	26.4	27.5	38.6	29.3	18.2
			10	50.7	55.0	59.5	57.6	53.9	73.4	58.4	13.6
			15	70.8	70.2	75.9	79.4	68.6	86.6	75.2	9.1
			20	84.0	79.8	84.5	88.6	80.8	92.0	85.0	5.5
			25	91.8	86.3	89.5	93.2	87.4	95.3	90.6	3.8
			30	96.5	89.6	93.7	97.1	92.8	98.1	94.6	3.4
			35	99.2	93.3	96.7	99.5	96.3	100.3	97.6	2.7
			40	101.1	95.6	98.7	101.0	98.9	101.8	99.6	2.3
			45	102.4	98.0	100.4	102.1	100.8	102.6	101.0	1.7
			50	103.1	99.2	101.6	102.9	101.9	103.3	102.0	1.5
			55	103.7	101.0	102.2	103.3	102.7	103.8	102.8	1.0
			60	103.9	101.6	102.7	103.7	102.9	104.0	103.1	0.9
			65	104.0	102.5	102.9	103.8	103.0	104.1	103.4	0.7
			70	104.1	102.9	103.2	103.9	103.1	104.3	103.6	0.6
			75	104.0	103.5	103.1	104.0	103.0	104.2	103.6	0.5
			80	104.2	103.6	103.3	104.0	103.1	104.3	103.8	0.5
			85	104.2	104.0	103.5	104.1	103.2	104.5	103.9	0.5
			90	104.2	104.0	103.6	104.2	103.3	104.6	104.0	0.4
23	170		0	0.0	0.0	-0.1	0.0	0.0	-0.2	-0.1	-167.3
			5	27.8	52.2	57.6	39.7	32.9	34.4	40.8	28.7
			10	51.4	69.4	72.4	66.9	59.5	62.8	63.7	11.9
			15	68.1	76.7	79.7	75.3	72.7	72.8	74.2	5.3
			20	79.0	81.9	84.4	82.2	79.6	81.2	81.4	2.4
			25	86.7	86.6	88.1	88.1	85.3	87.0	87.0	1.2
			30	92.4	89.8	90.9	91.1	89.7	90.9	90.8	1.1
			35	95.5	92.6	93.1	94.3	93.1	94.5	93.8	1.2
			40	98.3	94.6	94.8	96.6	95.4	96.7	96.1	1.5
			45	99.8	96.5	96.2	98.3	97.1	98.4	97.7	1.4
			50	101.2	97.6	97.5	99.8	98.4	99.5	99.0	1.5
			55	101.9	98.7	98.2	100.6	99.3	100.6	99.9	1.4
			60	102.2	99.0	99.0	101.5	100.2	100.9	100.5	1.3
			65	102.5	99.7	99.6	102.0	100.9	101.5	101.0	1.2
			70	102.9	99.6	100.2	102.3	101.5	101.8	101.4	1.2
			75	102.9	99.8	100.5	102.6	101.8	101.7	101.6	1.2
			80	102.9	100.0	100.7	102.9	102.1	101.7	101.7	1.2
			85	103.0	100.5	100.9	103.1	102.3	102.0	102.0	1.0
			90	103.0	100.2	101.0	103.0	102.4	101.9	101.9	1.1

Water %	Torque In-Lbs	Spray	Time (min)	Tab 1	Tab 2	Tab 3	Tab 4	Tab 5	Tab 6	Average	%RSD
25	150	On	0	0.1	0.3	0.1	0.0	0.2	0.0	0.1	100.1
			5	38.9	34.2	41.2	44.7	38.6	33.7	38.6	10.9
			10	69.3	63.1	64.9	71.2	65.8	61.3	65.9	5.7
			15	80.4	77.3	78.1	83.7	79.5	76.3	79.2	3.3
			20	87.8	86.2	86.3	92.1	88.9	87.0	88.1	2.5
			25	93.1	92.6	91.0	96.2	93.8	93.1	93.3	1.8
			30	96.7	96.0	94.3	98.8	97.0	96.9	96.6	1.5
			35	99.5	98.0	95.7	100.0	99.0	99.0	98.5	1.5
			40	101.1	99.4	96.8	100.7	100.1	100.0	99.7	1.5
			45	102.3	100.2	97.4	100.9	101.1	100.6	100.4	1.6
			50	103.1	100.8	97.7	101.2	101.5	100.9	100.9	1.7
			55	103.6	101.4	97.9	101.5	102.0	101.1	101.3	1.8
			60	104.1	101.5	98.1	101.7	102.3	101.3	101.5	1.9
			65	104.2	101.5	98.3	101.8	102.3	101.2	101.5	1.9
			70	104.4	102.1	98.1	101.8	102.4	101.1	101.7	2.0
			75	104.6	101.9	98.3	101.9	102.5	101.3	101.7	2.0
			80	104.7	101.9	98.4	102.0	102.6	101.5	101.9	2.0
			85	104.8	102.0	98.4	101.9	102.6	101.5	101.9	2.0
			90	104.8	102.0	98.4	102.0	102.8	101.5	101.9	2.1

Table A16: Average %Tablet Dissolution (1250L)

Water %	20	20	20	20	21.5	23	23	23	23
%K	33	33	48	48	41	33	33	48	48
Drug Density	Low	High	Low	High	Middle	Low	High	Low	High
Time (min)									
0	-0.2	0.1	0.0	0.0	-0.1	0.0	0.0	0.1	-0.1
2	5.9	5.1	8.2	9.2	8.5	9.9	6.2	9.0	8.2
4	17.9	16.6	22.7	23.9	23.0	26.3	18.2	22.5	20.0
5	**23.8**	**22.1**	**30.0**	**30.8**	**29.6**	**33.4**	**24.3**	**28.8**	**26.1**
6	29.6	27.6	37.3	37.7	36.2	40.4	30.4	35.1	32.2
8	40.6	37.6	49.6	50.0	47.7	51.3	39.7	44.7	43.4
10	50.7	47.1	58.7	60.1	57.2	60.2	47.6	53.2	52.4
12	59.9	56.6	66.8	68.8	66.5	67.5	55.2	61.0	60.1
14	67.7	64.9	73.2	75.1	73.8	72.2	61.9	68.7	66.7
15	**71.0**	**68.3**	**76.0**	**77.8**	**76.4**	**74.2**	**64.7**	**71.4**	**69.4**
16	74.3	71.7	78.8	80.5	79.0	76.2	67.5	74.0	72.0
18	79.3	77.2	83.0	84.4	82.7	79.6	72.1	77.9	75.5
20	82.8	81.3	86.1	87.0	85.3	82.5	75.5	80.9	78.2
22	85.8	84.2	88.5	89.1	87.6	85.0	78.2	83.3	80.6
24	87.8	86.4	90.3	90.8	89.5	87.3	80.7	85.4	82.6
25	**88.7**	**87.4**	**91.1**	**91.5**	**90.4**	**88.2**	**81.8**	**86.4**	**83.5**
26	89.7	88.4	91.8	92.2	91.2	89.1	83.0	87.5	84.4
28	91.2	90.1	93.0	93.2	92.5	90.8	85.0	89.3	86.1
30	92.6	91.6	94.0	94.2	93.7	92.3	86.8	90.5	87.4
32	93.7	92.7	94.8	95.2	94.8	93.4	88.5	91.9	88.7
34	94.7	93.9	95.6	95.9	95.7	94.5	90.0	93.2	89.9
35	**95.2**	**94.4**	**95.9**	**96.3**	**96.1**	**95.0**	**90.6**	**93.6**	**90.3**
36	95.6	94.9	96.2	96.6	96.5	95.5	91.2	94.1	90.8
38	96.4	95.9	96.8	97.2	97.3	96.3	92.4	94.9	91.7
40	97.1	96.8	97.2	97.8	97.9	96.8	93.4	95.6	92.6
42	97.6	97.4	97.7	98.2	98.6	97.4	94.5	96.4	93.4
44	98.1	97.9	98.1	98.6	99.1	98.0	95.1	97.0	94.0
45	**98.4**	**98.2**	**98.3**	**98.8**	**99.2**	**98.3**	**95.4**	**97.1**	**94.3**
46	98.6	98.5	98.5	99.1	99.4	98.5	95.7	97.2	94.7
48	99.2	99.1	98.8	99.3	99.7	98.8	96.4	97.8	95.3
50	99.6	99.4	99.2	99.6	100.1	99.1	97.0	98.1	95.9

Water %	20	20	20	20	21.5	23	23	23	23
%K	33	33	48	48	41	33	33	48	48
Drug Density	Low	High	Low	High	Middle	Low	High	Low	High
Time (min)									
52	99.7	99.7	99.4	99.9	100.4	99.3	97.4	98.5	96.4
54	99.9	100.0	99.7	100.0	100.7	99.5	97.9	98.9	96.8
55	**100.0**	**100.1**	**99.8**	**100.0**	**100.8**	**99.6**	**98.1**	**99.0**	**97.0**
56	100.2	100.2	99.9	100.1	100.9	99.7	98.3	99.1	97.2
58	100.4	100.4	100.1	100.4	101.1	99.9	98.7	99.2	97.4
60	100.5	100.5	100.2	100.4	101.1	100.2	99.0	99.5	97.8
62	100.6	100.6	100.5	100.7	101.3	100.2	99.3	99.6	98.0
64	100.7	100.7	100.6	100.7	101.4	100.2	99.4	99.8	98.3
65	**100.8**	**100.8**	**100.5**	**100.7**	**101.5**	**100.3**	**99.6**	**99.8**	**98.5**
66	100.8	100.8	100.5	100.8	101.6	100.4	99.8	99.8	98.6
68	101.0	100.9	100.7	100.9	101.6	100.4	100.0	100.1	98.9
70	101.0	100.9	100.9	101.0	101.8	100.4	100.1	100.1	99.0
72	101.1	101.1	100.9	101.1	101.8	100.5	100.3	100.2	99.2
74	101.1	101.2	100.9	101.1	101.8	100.5	100.4	100.3	99.3
75	**101.1**	**101.2**	**101.0**	**101.1**	**101.9**	**100.5**	**100.5**	**100.3**	**99.3**
76	101.2	101.2	101.0	101.1	102.0	100.4	100.6	100.3	99.4
78	101.2	101.2	101.1	101.2	101.9	100.5	100.7	100.3	99.6
80	101.3	101.3	101.2	101.3	101.9	100.5	100.7	100.5	99.9
82	101.2	101.3	101.3	101.3	101.9	100.6	100.8	100.5	99.9
84	101.4	101.3	101.2		101.9	100.6	100.9	100.5	100.0
85	**101.4**	**101.3**	**101.2**		**101.9**	**100.6**	**100.9**	**100.5**	**100.0**
86	101.4	101.4	101.2		101.9	100.6	100.9	100.6	100.0
88	101.3	101.3	101.2		102.0	100.6	100.9	100.6	100.2
90	101.3	101.3	101.4		101.9	100.6	101.0	100.6	100.1

NOTE: Values at 15,25,35,45,55,65,75, and 85 minutes in bold were calculated by averaging values immediately above and below these time points. Graphs were prepared with data recorded for each 5 minute interval.

Table A17: Tablet % Dissolution (1250L Confirmation Lots 1-3

1250L Confirmation Lot 1:

% Water	23%							
%K	33%							
Drug Density	Intermediate							
Time	Tab 1	Tab 2	Tab 3	Tab 4	Tab 5	Tab 6	Average	%RSD
0	0.0	0.0	0.0	0.0	0.1	0.1	0.0	154.9
5	27.0	23.7	19.7	30.2	25.4	21.1	24.5	15.8
10	52.8	46.0	38.3	51.5	49.6	44.1	47.0	11.5
15	68.4	63.5	53.9	67.0	66.8	60.1	63.3	8.7
20	74.8	71.1	65.2	76.2	77.2	72.2	72.8	6.0
25	79.8	77.1	74.0	84.5	82.9	80.9	79.9	4.8
30	84.1	81.7	80.9	91.2	88.5	87.5	85.7	4.8
35	87.5	86.3	86.5	94.8	92.9	93.2	90.2	4.3
40	90.1	89.2	90.5	97.0	95.8	96.8	93.2	3.9
45	92.2	91.5	93.6	98.2	97.6	99.0	95.4	3.5
50	94.3	93.5	95.5	98.8	98.9	100.4	96.9	2.9
55	95.8	95.3	97.0	99.4	99.8	101.2	98.1	2.4
60	97.2	96.3	98.2	99.5	100.2	101.6	98.8	2.0
65	98.1	97.4	99.7	99.7	100.7	101.9	99.6	1.6
70	99.0	97.9	100.6	99.7	100.9	102.0	100.0	1.5
75	99.5	98.4	101.1	99.7	101.0	102.0	100.3	1.3
80	99.9	98.8	101.4	99.7	101.0	102.0	100.5	1.2
85	100.2	99.3	101.7	99.7	101.0	102.2	100.7	1.1
90	100.4	99.4	101.7	99.7	101.0	102.1	100.7	1.1

1250L Confirmation Lot 2:

% Water	23%							
%K	33%							
Drug Density	Intermediate.							
Time	Tab 1	Tab 2	Tab 3	Tab 4	Tab 5	Tab 6	Average	%RSD
0	-0.1	0.0	-0.1	0.0	-0.1	0.0	-0.1	-109.5
5	28.6	32.1	24.1	32.7	36.4	45.9	33.3	22.3
10	54.8	57.7	52.1	58.3	63.4	74.9	60.2	13.5
15	70.7	69.5	68.2	73.2	75.7	83.0	73.4	7.4
20	77.3	75.6	76.3	80.7	81.4	88.0	79.9	5.8
25	83.2	81.2	82.5	87.6	86.5	92.3	85.5	4.8
30	87.9	85.6	86.7	92.1	90.6	95.3	89.7	4.1
35	91.5	89.1	90.8	95.1	93.5	96.9	92.8	3.1
40	94.2	91.6	93.2	97.2	95.5	98.3	95.0	2.6
45	96.1	93.5	95.5	98.5	96.7	98.9	96.5	2.1
50	97.9	95.3	96.9	99.4	97.5	99.6	97.7	1.7
55	98.9	96.6	97.9	99.8	98.4	99.7	98.5	1.2
60	100.1	98.0	98.7	100.6	98.9	99.9	99.4	1.0
65	100.9	98.8	99.4	100.7	99.5	100.0	99.9	0.8
70	101.6	99.5	100.0	100.8	99.6	100.0	100.3	0.8
75	102.1	100.2	100.6	100.9	99.8	100.0	100.6	0.8
80	102.5	100.8	100.7	101.0	99.9	100.1	100.8	0.9
85	102.6	101.3	100.7	101.1	99.8	100.1	100.9	1.0
90	102.8	102.0	100.7	101.1	99.9	100.1	101.1	1.1

1250L Confirmation Lot 3:

% Water	21.5%					
%K	38%					
Drug Density	Intermediate					
Time (min)	Tab 1	Tab 2	Tab 3	Tab 4	Tab 5	Tab 6
0	0.0	0.1	0.0	0.1	0.8	-0.1
5	35.1	33.4	34.4	44.4	33.9	49.7
10	64.2	57.4	59.6	73.3	63.6	82.7
15	79.7	73.3	78.3	85.1	79.0	91.0
20	87.0	81.8	85.8	91.0	87.2	95.7
25	92.4	86.7	90.3	94.7	93.5	98.9
30	95.7	90.5	93.7	97.4	97.8	100.6
35	97.8	92.7	96.1	98.9	99.9	101.7
40	100.0	95.1	98.1	100.0	101.4	101.9
45	101.3	96.5	100.2	100.7	102.0	102.0
50	102.3	97.7	101.4	101.3	102.5	102.0
55	103.1	98.6	103.4	101.7	102.8	102.3
60	103.8	99.1	103.0	101.7	102.9	102.1
65	104.3	99.5	103.2	101.9	103.0	102.3
70	104.9	99.9	104.5	101.9	103.2	102.4
75	105.0	100.1	104.2	102.0	103.2	102.4
80	105.0	100.2	104.9	102.0	103.2	102.4
85	105.2	100.3	104.2	102.1	103.2	102.4
90	105.2	100.5	105.2	102.1	103.2	102.5

1250L Confirmation Lot 3:

% Water	21.5%							
%K	38%							
Drug Density	Intermed-iate							
Time (min)	Tab 7	Tab 8	Tab 9	Tab 10	Tab 11	Tab 12	Avg. of 12	%RSD of 12
0	0.0	0.0	-2.8	0.0	0.0	0.1	-0.2	-564.8
5	47.4	26.4	48.9	44.8	35.7	48.4	40.2	19.5
10	79.3	49.4	80.3	78.3	63.2	77.1	69.0	15.7
15	88.6	66.8	85.4	86.2	79.0	88.5	81.7	8.6
20	93.7	79.1	89.3	91.3	85.9	95.2	88.6	5.8
25	96.4	85.0	92.6	94.9	91.4	99.0	93.0	4.6
30	98.5	88.9	93.8	97.0	95.0	100.6	95.8	3.8
35	100.2	91.9	96.4	98.5	97.9	101.1	97.8	3.1
40	101.4	94.1	97.6	99.5	99.9	101.4	99.2	2.5
45	102.1	96.1	98.1	100.4	101.0	101.4	100.2	2.1
50	102.7	97.9	99.2	101.1	101.8	101.7	101.0	1.7
55	103.1	99.2	98.0	101.5	102.3	101.6	101.5	1.8
60	103.3	100.0	99.7	101.8	102.6	101.7	101.8	1.5
65	103.7	100.5	99.9	101.9	102.9	101.5	102.1	1.5
70	103.9	101.0	99.0	101.9	102.8	101.7	102.3	1.7
75	104.1	101.4	98.8	101.9	102.9	101.7	102.3	1.7
80	104.0	101.6	100.2	101.9	103.0	101.7	102.5	1.5
85	104.0	101.8	100.2	102.0	103.1	101.7	102.5	1.5
90	104.2	101.9	100.3	101.9	103.1	101.7	102.7	1.6

Table A18: Tablet %Dissolution (600L)

Lot 1	Time (min)	Tab 1	Tab 2	Tab 3	Tab 4	Tab 5	Tab 6
	0	0.1	0.2	0.1	0.1	0.0	0.1
	5	50.2	40.5	42.5	32.8	40.4	38.8
	10	69.4	63.2	65.7	59.4	64.2	68.3
	15	76.7	71.5	75.7	73.2	74.1	78.3
	20	82.3	78.3	82.0	82.5	82.1	85.0
	25	86.2	83.0	86.7	88.3	86.9	89.6
	30	90.5	87.7	90.5	92.9	90.8	94.0
	35	93.4	91.6	93.5	95.1	93.8	97.0
	40	95.4	93.8	96.1	96.6	95.9	99.7
	45	96.5	95.2	97.4	97.4	97.2	100.9
	50	97.6	96.6	98.4	98.2	98.8	102.3
	55	98.6	98.2	99.5	98.9	99.7	102.9
	60	98.9	98.8	100.0	99.4	100.0	102.9
	65	99.6	99.8	100.8	99.8	100.7	103.3
	70	99.9	100.2	100.9	100.0	101.1	103.5
	75	100.1	100.6	101.2	100.1	101.4	103.5
	80	100.6	101.0	101.5	100.3	101.9	103.7
	85	100.6	101.1	101.7	100.6	101.9	103.6
	90	100.7	101.2	101.7	100.6	102.0	103.7

Lot 1	Time (min)	Tab 7	Tab 8	Tab 9	Tab 10	Tab 11	Tab 12	Avg. of 12	% RSD of 12
	0	-1.0	0.0	-2.9	-4.2	0.5	-0.8	-0.6	-227.8
	5	33.2	34.5	21.2	28.1	44.5	45.5	37.7	21.5
	10	57.0	54.5	42.8	51.2	67.8	66.2	60.8	13.3
	15	67.2	65.5	55.9	62.6	75.9	74.1	70.9	9.5
	20	74.3	73.5	66.4	72.0	81.5	79.5	78.3	7.1
	25	80.6	78.8	77.0	78.2	86.0	83.8	83.8	5.0
	30	85.0	83.6	83.5	82.8	89.4	87.3	88.2	4.3
	35	89.3	86.9	89.4	86.5	92.2	90.0	91.6	3.5
	40	91.0	90.0	92.0	88.6	94.7	92.1	93.8	3.4
	45	92.7	92.3	95.8	90.6	96.1	94.0	95.5	2.9
	50	94.7	93.9	97.9	92.0	97.2	95.6	96.9	2.7
	55	96.3	95.6	99.2	93.3	98.2	97.5	98.1	2.4
	60	97.0	96.7	99.5	94.0	99.1	97.7	98.7	2.2
	65	97.7	97.5	100.6	94.7	99.5	98.8	99.4	2.1
	70	98.1	97.9	100.9	95.1	99.8	99.2	99.7	2.1
	75	98.5	98.5	101.2	95.4	100.1	99.7	100.0	2.0
	80	98.6	98.5	101.1	97.2	100.1	100.1	100.4	1.7
	85	98.6	98.6	101.2	95.4	100.2	100.2	100.3	2.0
	90	98.8	99.0	101.3	99.6	100.6	100.4	100.8	1.3

Lot 2	Time (min)	Tab 1	Tab 2	Tab 3	Tab 4	Tab 5	Tab 6
	0	-0.1	-0.2	-0.2	-0.1	-0.1	-0.1
	5	26.3	47.0	40.4	37.4	40.9	47.1
	10	50.0	67.5	66.6	63.2	67.9	68.8
	15	67.5	74.9	76.2	75.4	76.0	79.9
	20	78.0	79.2	82.3	84.8	82.6	85.8
	25	85.7	83.7	86.9	91.1	87.7	90.7
	30	90.5	87.2	91.0	95.4	92.2	94.2
	35	94.6	90.5	93.9	97.5	94.4	97.0
	40	96.6	92.6	95.9	98.9	96.3	98.5
	45	99.2	94.1	97.4	99.6	97.8	99.7
	50	100.0	95.3	98.9	99.7	100.0	99.7
	55	100.8	96.3	99.9	99.9	101.7	100.1
	60	101.4	97.5	100.7	100.1	102.4	100.6
	65	101.5	97.8	101.1	100.0	102.7	100.7
	70	101.6	98.4	101.4	100.3	101.5	100.9
	75	101.9	98.7	101.5	100.3	101.7	100.9
	80	101.7	98.9	101.4	100.3	101.7	100.8
	85	101.9	99.1	101.5	100.3	102.9	100.8
	90	101.7	99.0	101.4	100.2	102.4	100.7

Lot 2	Time (min)	Tab 7	Tab 8	Tab 9	Tab 10	Tab 11	Tab 12	Avg. Of 12	% RSD of 12
	0	0.1	0.4	0.1	-0.5	0.1	0.2	0.0	-680.2
	5	33.5	24.7	29.5	38.1	38.7	40.2	37.0	19.6
	10	60.2	45.9	53.4	61.1	62.8	60.7	60.7	12.1
	15	72.0	62.0	68.1	74.6	73.6	75.4	73.0	6.7
	20	79.6	70.8	76.5	84.8	80.0	85.0	80.8	5.4
	25	85.0	79.2	84.8	91.1	85.9	91.7	86.9	4.3
	30	89.8	85.7	90.7	94.5	90.4	95.4	91.4	3.4
	35	92.6	89.1	94.2	96.7	93.3	98.3	94.3	2.9
	40	95.5	92.0	96.9	98.2	95.7	99.5	96.4	2.4
	45	97.3	94.0	98.7	99.0	97.3	100.1	97.9	2.1
	50	99.0	95.5	99.4	99.2	98.3	100.4	98.8	1.7
	55	99.9	96.8	100.1	99.3	99.7	101.0	99.6	1.6
	60	100.4	97.6	100.5	99.3	100.0	101.0	100.1	1.4
	65	100.9	98.4	100.6	99.4	100.5	101.2	100.4	1.3
	70	101.2	99.1	100.8	99.6	100.9	101.1	100.6	1.0
	75	101.5	99.5	101.0	99.5	101.0	101.2	100.7	1.0
	80	101.6	99.8	100.9	99.6	101.0	101.2	100.8	0.9
	85	101.8	99.9	101.2	99.6	101.0	101.0	100.9	1.1
	90	101.8	99.9	101.1	99.6	101.2	101.1	100.8	1.0

Lot 3	Time (min)	Tab 1	Tab 2	Tab 3	Tab 4	Tab 5	Tab 6
	0.0	0.0	0.0	-0.1	0.0	-0.5	0.0
	5.0	25.9	28.7	40.3	36.6	35.0	27.1
	10.0	51.0	53.2	62.5	60.8	66.5	54.0
	15.0	67.9	67.8	72.2	72.4	76.2	70.0
	20.0	77.1	75.7	78.5	79.9	82.6	80.1
	25.0	83.3	82.2	84.5	87.1	87.1	88.6
	30.0	88.9	87.8	88.0	91.9	90.7	94.2
	35.0	92.4	91.6	90.5	95.5	93.2	97.8
	40.0	94.5	94.2	92.7	97.7	96.0	99.9
	45.0	96.4	96.2	94.5	99.0	97.3	101.3
	50.0	97.4	97.5	95.7	99.6	98.9	102.0
	55.0	98.0	98.0	96.6	99.7	99.2	102.2
	60.0	98.7	98.4	97.4	99.9	99.9	102.4
	65.0	99.1	98.7	98.3	100.1	99.4	102.5
	70.0	99.6	99.0	98.6	100.1	101.4	102.6
	75.0	99.8	99.1	98.8	100.1	100.4	102.7
	80.0	100.1	99.4	99.2	100.2	100.9	102.7
	85.0	100.3	99.4	99.5	100.2	101.7	102.8
	90.0	100.4	99.5	99.7	100.3	101.4	102.8

Lot 3	Time (min)	Tab 7	Tab 8	Tab 9	Tab 10	Tab 11	Tab 12	Avg.	% RSD
	0.0	-0.2	-0.1	1.0	-0.2	-0.2	-0.1	0.0	-779.0
	5.0	25.9	39.3	37.5	25.0	28.8	36.5	32.2	18.1
	10.0	47.6	62.9	57.4	48.9	53.5	62.7	56.8	11.0
	15.0	63.4	71.1	70.0	67.7	66.3	74.6	70.0	5.2
	20.0	72.8	76.0	77.9	80.2	72.9	82.9	78.1	4.3
	25.0	81.2	80.8	84.0	88.2	78.7	88.1	84.5	3.9
	30.0	87.1	84.5	88.8	94.1	83.6	91.5	89.3	3.8
	35.0	90.7	87.6	93.1	97.7	87.0	94.0	92.6	3.7
	40.0	93.6	89.6	96.4	100.1	89.9	95.6	95.0	3.5
	45.0	96.2	91.7	98.4	101.8	91.7	97.0	96.8	3.3
	50.0	97.9	93.1	100.0	102.8	93.4	97.8	98.0	3.0
	55.0	99.0	94.4	101.6	103.4	95.1	98.5	98.8	2.7
	60.0	99.7	95.1	102.8	103.8	96.4	99.2	99.5	2.6
	65.0	99.8	95.5	103.2	103.6	96.8	99.3	99.7	2.4
	70.0	100.4	96.5	103.8	103.9	97.5	99.7	100.3	2.3
	75.0	100.4	96.9	104.0	104.0	98.0	99.9	100.4	2.2
	80.0	100.4	97.8	104.1	104.0	98.4	100.0	100.6	2.0
	85.0	100.6	97.9	104.2	104.0	98.8	100.0	100.8	2.0
	90.0	100.5	98.1	104.0	103.8	98.8	99.9	100.8	1.9

Time (min)	600L Combined Average	600L Grand Combined. Deviation	600L Combined %RSD
0	-0.24	0.89	-374
5	35.6	7.34	20.6
10	59.4	7.31	12.3
15	71.3	5.24	7.35
20	79	4.56	5.77
25	85.1	3.92	4.61
30	89.6	3.61	4.03
35	92.8	3.28	3.53
40	95.1	3.09	3.25
45	96.7	2.8	2.89
50	97.9	2.55	2.6
55	98.9	2.29	2.32
60	99.4	2.15	2.16
65	99.8	2.01	2.01
70	100	1.88	1.87
75	100	1.78	1.78
80	101	1.58	1.57
85	101	1.74	1.73
90	101	1.41	1.4