Pharmaceutical Development Case Study: "ACE Tablets"

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Foreword

The last decade has seen a significant transformation in pharmaceutical quality regulation from an empirical process to a more science and risk based approach. This case study is an extremely important document for helping guide FDA and the industry toward the "desired state" of pharmaceutical quality envisioned for the 21st Century. It is through this and similar documents that we can determine how best to implement the principles of ICH Q8, Q9, and Q10 to meet the requirements of this new regulatory paradigm.

I believe this case study, and others like it, will provide a foundation for discussion with our scientific and regulatory constituents within industry and with our global regulatory colleagues in other agencies. Such documents are necessary to enable dialogue and understanding of what we all mean and expect from the ICH paradigms, and to ensure an appropriate framework for future regulatory processes, including both review and inspection of all pharmaceuticals. Not only does this case study provide a basis for understanding and commitment to the process, it also helps identify the opportunities that can be gained through the enhanced scientific experience and knowledge sharing.

I want to personally thank Conformia, FDA's CRADA partner, the CMC-IM Working Group team that Conformia convened and all of those individuals who contributed to creating this Pharmaceutical Development Case Study on ACE Tablets . I truly believe that it will be invaluable to all of us in moving forward in implementing a modern approach to the regulatory processes. This case study is a perfect example of how scientific collaboration can lead to synergism across our regulatory programs in order to better serve the public.

Helen Winkle, Director, Office of Pharmaceutical Sciences, CDER, FDA

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Anjali Kataria, Chief Marketing Officer and Founder of Conformia
Principal Investigator, FDA-Conformia CRADA

1. Report on the Pharmaceutical Development of Acetriptan Tablets

1.1 Introduction and Overview

This report presents a summary of the pharmaceutical development of acetriptan ("ACE") tablets. It emphasizes a science and risk-based approach to product and process development, and presents findings as a knowledge-based report. Where relevant, supporting data have been summarized in appropriate tables or illustrations

The scientific approach used begins with identification of the desired dosage form and performance attributes through the target product profile. From this target product profile, an initial list of critical quality attributes was developed. A risk assessment was undertaken to identify the variables and unit operations which are most likely to impact the critical quality attributes. This was then used to focus development activities on potential high risk areas. A risk assessment, starting with the physico-chemical characteristics of the API, led to the identification of a viable formulation and manufacturing approach. Formulation development involved the use of prior knowledge and structured experimentation to investigate the relationship between formulation component levels, API attributes and the drug product quality attributes. An interaction between API particle size and magnesium stearate level was demonstrated and acceptable formulation component levels and API particle size ranges were identified. Development of the manufacturing process focused on the unit operations posing greatest potential risk to drug product quality. Using prior knowledge, models, extrapolation and risk assessment processes, the material attributes and process parameters, which could have an impact upon final product quality, were identified. For each unit operation experimentation was undertaken to define the relationship between the input attributes, process parameters, output attributes and final drug product quality. The intermediate critical quality attributes, operating conditions and a control strategy were defined to mitigate risk and ensure final product quality. An *in-vivo* study was then conducted to compare formulation and manufacturing variables. This study revealed that the dissolution test procedure provided excellent prediction of biopharmaceutical performance, but that the initial acceptance criterion needed to be modified. Based on the pharmaceutical development work and *in-vivo* results, a design space and science and risk-based approaches to formulation component level adjustment, scale-up, site transfers and 'real time release' are proposed based on the enhanced product and process understanding.

1.2 Target Product Profile

ACE tablets are being developed for the treatment of migraine. The intent is to develop a rapid onset therapy which will provide relief of the symptoms of migraine.

The pharmaceutical target profile for acetriptan is a safe efficacious convenient dosage form, preferably a tablet, that will facilitate patient compliance. The tablet should be of an

appropriate size, with a single tablet per dose. The manufacturing process for the tablet should be robust and reproducible, and should result in a product that meets the appropriate drug product critical quality attributes, for example identity, assay, appearance, chemical and microbiological purity, disintegration and/or dissolution as well as content uniformity. The drug product should be packaged in a container closure system that will provide adequate protection from moisture vapour, protection through distribution and use as well as convenience of use for the patient.

A Target Product Profile is presented in the **Table 1:** below. From the profile, the initial Critical Quality Attributes which were used to define satisfactory quality were identified.

Table 1:Target Product Profile

Quality Attribute	Target	Criticality
Dosage form	Tablet, maximum weight 200mg	Not applicable
Potency	20 mg	Not applicable
Pharmacokinetics	Immediate release enabling Tmax in 2 hours or less	Related to dissolution
Appearance	Tablet conforming to description shape and size	Critical
Identity	Positive for acetriptan	Critical
Assay	95 – 105%	Critical
Impurities	ACE12345 NMT 0.5%, other impurities NMT 0.2%, total NMT 1%	Critical
Water	NMT 1%	Not critical – API not sensitive to hydrolysis
Content Uniformity	Meets USP	Critical
Resistance to Crushing (Hardness)	5-12kP	Not critical since related to dissolution
Friability	NMT 1.0%	Not critical
Dissolution	Consistent with immediate release, e.g., NLT 75% at 30mins	Critical
Disintegration	NMT 15mins	Not critical, a precursor to dissolution
Microbiology	If testing required, meets USP criteria	Critical only if drug product supports microbial growth

1.3 Formulation and Pharmaceutical Manufacturing Selection

The formulation type chosen was an oral standard release tablet, in consideration of the known PK characteristics of the molecule. A rapid onset is desirable for the treatment of migraine and a T_{max} of less than 2 hours was desired, and subsequently achieved, with this formulation.

A roller compaction granulation process was chosen based on prior scientific knowledge of products with similar physical and chemical properties, and available technologies and equipment. Factors that influenced the selection of a roller compaction process were: 1) degradation of the drug on exposure to heat precluding drying following wet granulation, and 2) poor flow properties precluding direct compression. Thermal degradation also precluded drying following film coating. Roller compaction was also chosen in the expectation of its meeting the expectation of its suitability for operating with excipients which are compatible with acetriptan, active pharmaceutical ingredient (API) processability and API stability requirements during manufacture, and since it should result in a tablet that will have a shelf life of at least 2 years.

The development of ACE tablets and the associated manufacturing process used prior knowledge from previous products and development projects. A risk analysis, in accordance with ICH Q9, was used to establish which variables and unit operations were likely to have the greatest impact on product quality. This initial risk assessment is shown in **Table 2** below.

Table 2: Risk Assessment to Identify Variables Potentially Impacting Product Quality

	Variables and Unit Operations					
DP CQAs	Formulation Composition	Blending I	Roller Compaction	Milling	Lubrication	Compresssion
Appearance	Low	Low	Low	Low	High	High
Identity	Low	Low	Low	Low	Low	Low
Assay	Low	Low	Low	Low	Low	High
Impurities	High	Low	Low	Low	Low	Low
Content Uniformity	High	High	High	High	Low	High
Dissolution	High	Low	High	High	High	High

The boxes shaded green were concluded, through prior knowledge, to present low risk to the product critical quality attributes. The red boxes represent potential risks to the product and formed areas for further study during development.

The proposed commercial formulation is an immediate release tablet. Only one tablet strength is proposed for commercialization, a 200 mg tablet containing 20 mg of acetriptan. Each tablet contains the following excipients: microcrystalline cellulose, lactose monohydrate, croscarmellose sodium, magnesium stearate and talc. The manufacturing process involves a preblending step, roller compaction of the acetriptan

with microcrystalline cellulose, croscarmellose sodium, magnesium stearate and lactose monohydrate, then milling to produce granules before blending with magnesium stearate, and talc. This is then followed by compression on a rotary tablet press. ACE tablets are proposed to be supplied as white, biconvex, round tablets containing 20 mg of acetriptan identified with "ACE" and "20" debossed on one side, in cartons containing a blister pack of 6 tablets, or in polypropylene bottles containing 10 tablets. Further information on the packaging is provided under Container Closure System, Section 5.

For the unit operations with the potential to impact quality, a further risk assessment was used to identify process parameters and materials' attributes that could impact product quality. Experimental studies were then defined and executed to develop additional scientific knowledge and understanding, to allow appropriate controls to be developed and implemented thereby mitigating the risk to quality.

1.4 Control Strategy

Process understanding developed around ACE tablets demonstrated that blending, roller compaction and compression are the critical unit operations that determine the quality of the final product.

Considerable experimentation has been undertaken to gain process understanding of the blending step. A blending design of experiments was used to determine the impact of API particle size, microcrystalline cellulose particle size and environmental humidity on the blending operation. Blend uniformity was found to be the intermediate critical quality attribute that directly impacts the critical quality attribute of content uniformity. Blend uniformity is monitored and controlled by use of NIR.

Roller compaction was studied using design of experiments investigating formulation factors and roller compaction process parameters. The design of experiments studies enabled cause and effect relationships to be identified between formulation variables, intermediate attributes, process parameters and final product attributes. Ribbon density was identified as the intermediate critical quality attribute which ensures drug product dissolution criteria are met. Ribbon density is measured in-line by NIR as part of the control strategy.

The compression design of experiments investigated the impact of input material attributes and compression process parameters on final product attributes and showed that tablet hardness is the output attribute that must be controlled because of its relationship to tablet dissolution, and tablet weight due to its relationship to content uniformity. Control of the compression step is ensured through in-process measurements at regular intervals throughout compression. The tablet weight is controlled via an inferential feedback loop with main compression force and fill-height.

2. Selection of the Components of the Drug Product

2.1 Drug Substance

The target product profile for ACE tablets was met by the investigation and selection of the free base of acetriptan. Acetriptan is a weak base with a pKa of 4.9. It forms crystalline tartrate, citrate, hydrochloride and sulphate salts. The tartrate and citrate salts show no solubility advantages. The hydrochloride and sulphate salts showed small improvements in solubility; but, each showed multiple polymorphic forms. Therefore, the free base was chosen for further development.

Table 3 shows an evaluation of the API attributes that present a risk with respect to final drug product quality. Those API attributes considered to have potential for impact on the product quality are coloured in red. The selection of acetriptan free base and polymorphic form took into consideration the attributes that could affect the drug product quality. The impact of the API attributes on drug product quality and the manufacturing process was evaluated during development and is detailed in Section.3. The API critical Quality attributes that must be controlled to ensure drug product quality are identity, solid state form, impurities, water content, residual solvents and particle size. The control strategy for the API manufacturing process, which ensures that acetriptan with appropriate quality attributes is produced, is detailed in API development reports.

Table 3: Potential impact of API Attributes on Drug Product Attributes

	API Attribute								
DP CQAs	Particle Size	Salt form	Moisture	Crystallinity	Morphology	Stability	Solvent content	Purity	Solubility
Appearance	Low	Low	Low	Low	Low	Low	Low	Low	Low
Identity	Low	High	Low	Low	High	Low	Low	Low	Low
Assay	Low	Low	Low	Low	Low	Low	Low	High	Low
Impurities	Low	Low	High	Low	Low	High	High	High	Low
Content Uniformity	High	Low	Low	Low	Low	Low	Low	Low	Low
Dissolution	High	High	Low	High	High	Low	Low	Low	High

2.2 Excipients

In order to meet the target product profile, tablet excipients with appropriate functionality were assessed based on scientific and prior knowledge. From IND 2-1234, dated February 30, 2007, the chosen excipients had been used successfully for a roller compacted formulation of an analogous agent. The excipients selected were microcrystalline cellulose, lactose monohydrate, croscarmellose sodium, magnesium stearate and talc.

Drug/excipient compatibility was assessed through HPLC analysis of binary mixtures of drug to excipient, at a 1:1 ratio in the solid state, stored at 25°C/60% RH and 40°C/75% RH (open and closed conditions) for 1 month. An interaction was seen with magnesium

stearate at 40°C/75% , however it was still used, as the drug-to-magnesium stearate ratio in the final product is an order of magnitude less, there will be less direct contact when the drug is diluted with other excipients and magnesium stearate is generally regarded to be a better lubricant than the standard alternatives. Subsequent assurance of compatibility was provided by stability data on formulations used in early clinical trials and the ongoing stability studies on the formulation proposed for commercialization . No compatibility issues were identified between acetriptan and the excipients in the final drug product.

The excipients included in the product for commercialization are listed together, with their functionalities, in **Table 4.**

Table 4: Excipients in ACE tablets

Excipient	Quantity per tablet (mg)	Quantity per tablet %	Function
Microcrystalline cellulose	80	40	Filler/Diluent
Lactose monohydrate	81.5*	40.75*	Filler/Diluent
Croscarmellose sodium	6-8	3-4	Disintegrant
Magnesium stearate intra-granular extra-granular	 2-4 0.5	 1-2 0.25	Lubricant
Talc	10	5	Glidant
*Quantity adjusted to compensate for amount of croscarmellose sodium and/or magnesium stearate used in order to ensure 200mg overall tablet weight. Each tablet contains 20 mg (10%) acetriptan			

Based on scientific and prior knowledge of the excipients used in ACE tablets, a risk assessment was conducted to determine the potential impact of the excipients on final product quality (see **Table 5**). The excipients identified as high risk were investigated in more detail throughout the formulation and manufacturing process development. The excipients used in the formulation for ACE Tablets, are conventional and the amounts per tablet are generally within standard quantities of usage. The specifications of the inactive ingredients comply with the United States Pharmacopeia/National Formulary (USP/NF), European and Japanese pharmacopoeias. Additional controls, above those in the pharmacopoeia, include particle size limits on the two major excipients (lactose and microcrystalline cellulose).

Table 5: **Potential impact of Excipients on Drug Product CQAs**

	Formulation Attributes				
DP CQAs	Microcrystalline Cellulose	Lactose Monohydrate	Croscarmellose Sodium	Magnesium stearate	Talc
Appearance	Low	Low	Low	High	Low
Identity	Low	Low	Low	Low	Low
Assay	Low	Low	Low	Low	Low
Impurities	Low	Low	Low	High	Low
Content Uniformity	High	Low	Low	High	Low
Dissolution	Low	Low	High	High	Low

3. Drug Product Formulation Development

3.1. Formulation Development Overview

The target product profile was to develop an immediate release tablet dosage form for oral dosing. The formulation should provide an acceptable tablet size. The manufacturing process must be robust and reproducible. The drug product will have to meet the critical quality attributes of identity, assay, appearance, impurities, microbiological, dissolution and content uniformity while also delivering suitable stability in order to not constrain commercialization in worldwide markets.

Identity – the API must be of the required chemical structure and solid state form in order to deliver the desired efficacy and safety profile (See ICH Q6A).

Assay- is related to dose delivery to the patient, thus to efficacy and needs to comply with appropriate limits for drug content (See ICH Q6A).

Appearance- the appearance of the tablets must be acceptable such that the patient will comply with the dosing regime (See ICH Q6A)

Microbiological – the tablets must conform to relevant microbiological limit tests to ensure patient safety. During development, it has been demonstrated that the water activity is below 0.4; therefore, it is too low to support microbial growth.

Dissolution –dissolution needs to comply with the requirement for an immediate release tablet as dictated by the target product profile. This requirement relates to efficacy of the product.

Content Uniformity - is related to consistency of the dose delivered to the patient, thus to efficacy and needs to comply with USP, JP and Ph.Eur acceptance criteria for Uniformity of Dosage Units.

Impurities (including Degradation Product Content) - may impact patient safety. Compound ACE12345 is the principal degradation product that was demonstrated to form, at low levels, during stability studies. This is an unqualified impurity. Therefore, its levels need to comply with the relevant ICH limits for unqualified, identified impurities. The levels of any unspecified degradation product will need to comply with the relevant ICH identification limits. In order to ensure patient safety, a limit for total degradation products is included.

3.2 Development of a Discriminatory Dissolution Method

As acetriptan is a BCS Class II compound displaying poor solubility (less than 0.015 mg/mL) across the physiological pH range (see Biopharmaceutics and Pharmacokinetics Section 2.1.3), it was recognized that development of a dissolution method that can act as a surrogate of pharmacokinetics was an important initial step to allow ACE tablets manufactured during development studies to be assessed in terms of *in vivo* performance. If such a test could be established then it could be used to help establish design space(s). By consideration of ICH Q6A guidance, the objective was a dissolution test method:

- that was able to distinguish amongst different input material, processing and formulation variables.
- that achieved significant (e.g. greater than 75%) dissolution within a timescale appropriate for a routine control test.
- that could demonstrate *in vivo* relevance.

A summary of the learning gained from the method development studies is provided below.

The dissolution of ACE tablets was assessed in aqueous buffers across the pH range 1.2 to 6.8. At all of the pH levels investigated, low recoveries were observed due to the low solubility of the 20 mg dose. From these studies, it was concluded that aqueous buffers did not provide the optimum conditions for use as a routine control test capable of differentiation between processing and formulation variables for ACE tablets.

In accordance with regulatory guidance documents, the use of surfactants was evaluated. The dissolution of ACE tablets was assessed in Tween 80 and sodium lauryl sulphate (SLS). Tween media were considered to be unsuitable due to coning of insoluble tablet excipients leading to incomplete disintegration of ACE tablets. Dissolution in SLS media exhibited the potential for: 1)differentiation between processing and formulation variables, and 2) use as a routine control test. Following assessment of SLS concentrations over the range 0.25% to 5.0% w/v SLS, the optimum surfactant concentration was identified as 1.0% w/v SLS in water. At this concentration, the rate of tablet dissolution was sufficiently slow to provide the potential for discrimination between tablet variants while still affording complete dissolution within a timescale appropriate for use as a finished product test.

The paddle speed was selected following evaluation of tablet dissolution at 50, 75 and 100 rpm. For all three paddle speeds investigated in 1.0% w/w SLS media, no coning of insoluble tablet excipients was observed; complete dissolution was achieved after 60 minutes. From these data, it was concluded that a paddle speed of 50 rpm provided the optimum conditions for use as a routine control test.

Therefore, the method proposed for ACE tablets uses dissolution apparatus equipped with paddles (speed 50 rpm) and a volume of 900 ml of SLS (1.0% w/v) maintained at a temperature of 37°C, followed by UV spectroscopy at a wavelength of 282 nm.

The acquired data demonstrated that 1.0% w/v SLS in is the most appropriate dissolution medium for discrimination between tablet batches manufactured by variation of the most relevant product attributes. At a paddle speed of 50 rpm, the 1.0% w/v SLS medium is capable of reproducibly discriminating between tablets manufactured by variation of most relevant input material, processing and formulation variables such as the API particle size, roller pressure and concentration of filler and lubricant. The data also demonstrated that the proposed method is suitable for use as a routine control test.

3.3. Biopharmaceutics and Pharmacokinetics of ACE

Acetriptan has been shown to be stable in gastrointestinal fluid, displays high permeability when investigated using Caco-2 monolayers, and is not susceptible to efflux by P-glycoprotein (P-gp). Solubility of acetriptan is low (0.015 mg/mL) and constant across the physiological pH range due to the lypophillic nature of the molecule. As such, acetriptan can be classified as Class II based on the biopharmaceutics classification system (BCS).

Acetriptan appears to exhibit linear single-dose pharmacokinetics across the investigated dose range 1 to 40 mg in both healthy volunteers and patients. The apparent mean clearance and volume of distribution were approximately 2.3 L/hr and 80 L, respectively. The mean elimination half-life was 24 hrs, and median T_{max} of 1.3 hrs.

3.4 Prototype Formulation and Process Selection

Initial evaluation of physico-chemical properties of the drug substance provided the basis for the selection of roller compaction as the dry manufacturing process. The API is sensitive to heat and as such would not be chemically stable during a drying process required for a wet granulation manufacturing process. Given the target clinical dose of 20 mg and in order to obtain an acceptable size tablet, drug concentrations of approximately 10% were required in the tablet. The flow properties of acetriptan and excipient blends were not acceptable at a concentration of 10% acetriptan, indicating that acetriptan's physical properties were not suitable for direct compression. The roller compaction process allows for higher drug loads even with acetriptan properties that are not generally acceptable for direct compression. A roller compaction manufacturing process does not

expose the acetriptan to excessive heat and results in granules that are acceptable for compression with reliable weight control. A roller compaction process was predicted to achieve the required product attributes with the minimum process complexity and the lowest risk, based on the API liabilities.

The initial prototype formulation component levels were selected based on prior manufacturing platform knowledge, the properties of acetriptan and acceptable compatibility with acetriptan. The prototype formulation has been utilized in other drug products and resulted in acceptable large scale manufacturing process attributes. Microcrystalline cellulose and lactose monohydrate are among the commonly used diluents for dry granulation formulations, individually and in combination with each other, as they exhibit appropriate flow and compression properties. The initial magnesium stearate level was selected based on knowledge of this formulation and levels required to produce acceptable ejection forces. The disintegrant level was selected to produce short disintegration times that would be expected to produce an acceptable dissolution rate for the immediate release of the poorly soluble drug.

The initial prototype formulation, which was also used in the pivotal clinical trials, contained the following components:

Intra-granular:	**% w/w Total tablet weight**
Acetriptan	10%
Lactose monohydrate	40.25%
Microcrystalline Cellulose	40%
Croscarmellose Sodium	3.0%
Magnesium Stearate	1.5%
Extra – granular:	
Talc	5.0%
Magnesium Stearate	0.25%
Total	**100.0%**

A risk assessment on formulation composition is shown in **Table 6** below. From this assessment it was concluded that the input variables potentially having the greatest impact on the drug product attributes were the API particle size and concentration, and the levels of the disintegrant and lubricant.

Table 6: **Formulation Composition Risk Assessment**

	Formulation Attributes						
DP CQAs	API level	API particle size	Lactose level	Disintegrant level	MCC particle size	Glidant level	Mg St level
Appearance	Low	Low	Low	Low	Low	Low	High
Identity	Low	Low	Low	Low	Low	Low	Low
Assay	Low	Low	Low	Low	Low	Low	Low
Impurities	Low	Low	Low	Low	Low	Low	Low
Content Uniformity	High	High	Low	Low	High	Low	Low
Dissolution	High	High	Low	High	Low	Low	High

The risk assessment also indicated that hardness, dissolution and dose uniformity should be used as the response variables. It was expected that these would also indicate whether friability or disintegration would be impacted by composition changes. All formulation development experiments were conducted at small scale at either 2 kg or 5 kg. The manufacturing process used to conduct the formulation experiments was a standard roller compaction process, that included the following manufacturing unit operations:

- Mixing / blending prior to roller compaction
- Roller compaction / milling
- Blending / lubrication
- Tablet compression

The parameters used for these unit operations were representative of parameters that would be used as a center point for the process development and all manufacturing parameters were held constant throughout the formulation development experiments.

Knowledge from two key formulation development studies is presented in the following sections. The first study is a formulation component level definition study designed to establish component levels for the key excipients. The second study was an API particle size and magnesium stearate interaction study: its design was based on the results of the first study and was utilized to establish the acceptable magnesium stearate range.

3.4.A Formulation Component Level Definition Study

The formulation component level definition study was designed with the objectives of establishing preliminary formulation component levels and demonstrating the rationale for selection of the excipient levels and the target drug concentration. The study was also utilized to determine if acceptable product attribute responses were obtained over the range of excipient and drug concentrations studied.

A central composite response surface design was used with 17 trial runs to study the impact of three formulation factors on the three key response variables. The factors studied were as follows:

- Drug Concentration (Load): 5% - 15%
- Disintegrant (Croscarmellose Na) Level: 1% - 4% (intragranular)
- Lubricant (Magnesium Stearate) Level: 0.75% - 2.25 (intragranular)

One lot of acetriptan (d_{90} 20 micron) was employed in the study; therefore, API particle size was constant in all experiments.

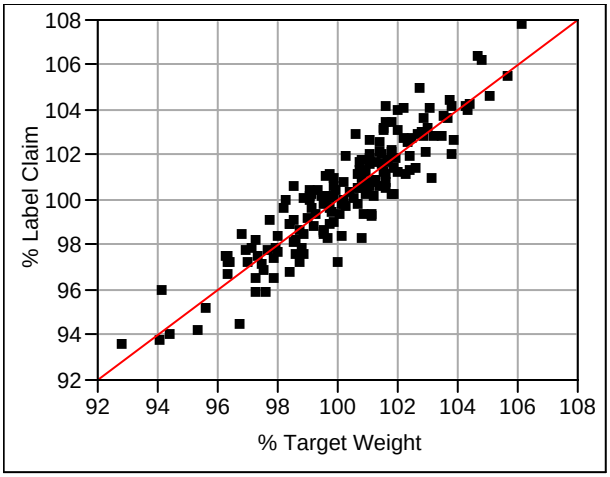
The response variables studied were as follows:

- Tablet hardness at a fixed compression pressure
- Dissolution average at a fixed tablet hardness of 12 kP
- Tablet weight uniformity (based on correlation to content uniformity)

Tablets were compressed at three compression pressures and samples were also collected at a target hardness of 12 kP , the compression pressure was adjusted to achieve this hardness. A constant tablet weight of 200 mg was used with the filler amount adjusted to achieve the target weight.

Figure 1 contains a plot of the % target tablet weight vs the % label claim for individual tablets tested in this study. For each of the 17 experimental runs, 10 tablets were individually weighed and then tested for drug content. The results compiled in **Figure 1** demonstrate that tablet weight correlates with % label claim and that most of the variability observed in dose uniformity is accounted for by the weight variability. These results indicate that weight uniformity can be used as a predictive surrogate for drug content uniformity, assuming blend uniformity going into compression. Based on this correlation, 100 tablets were individually weighed for each experimental run in order to obtain a more accurate measure of variability for each trial. The tablet weight uniformity data is utilized in the analysis of the data from this study.

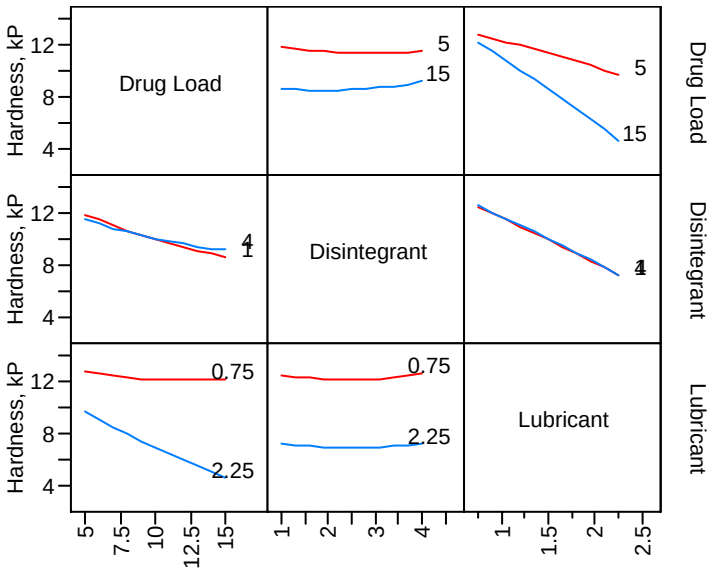
Figure 1: Plot of % Target Tablet Weight vs % Label Claim for Individual Tablets Tested from Formulation Definition Study



Note in **Figure 1:** Red line shows theoretical line of perfect agreement between weight and drug content.

Figure 2 presents the interaction profile for the hardness response at a fixed compression pressure. The interaction profile illustrates the effect of drug load and magnesium stearate level on tablet hardness. Increasing both variables results in a decrease in hardness with some interaction between these two variables. The higher drug load shows a larger decrease in hardness with increasing magnesium stearate level.

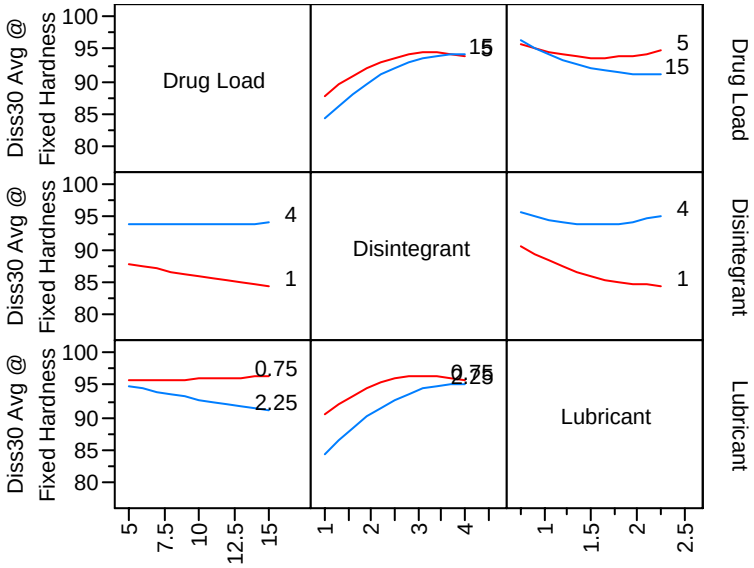
Figure 2: **Interaction profile for Hardness Response at Fixed Compression Pressure.**



In order to understand the impact of the formulation variables on dissolution, the relationship was examined at a fixed tablet hardness of 12 kP. The hardness was fixed at 12 kP because a high hardness would be expected to be the worst case for the dissolution response. If dissolution were studied at a fixed compression pressure the results could be confounded by the impact of drug load and magnesium stearate level on the tablet hardness. As both variables are increased the tablet hardness decreases at a fixed compression pressure as presented in **Figure 2.** This decrease in hardness would confound any potential impact the variables have on dissolution because the associated decrease in hardness usually results in an increase in dissolution.

Figure 3 presents the interaction profile for dissolution at a set target tablet hardness of 12kP. This interaction profile demonstrates that the magnesium stearate level has minor effects on dissolution with the different drug loads. There is a small decrease in dissolution with increasing magnesium stearate when the disintegrant level is at 1%. This interaction profile also shows that there is no effect of disintegrant level between 3-4% for both lubricant levels and drug loads. The dissolution response is 80% or above for all drug loads, disintegrant and lubricant levels studied, meeting the attribute target criteria of >75%.

Figure 3: Interaction Profile for Dissolution Response at a Set Target Tablet Hardness of 12kP.



A contour plot for the 30 minute dissolution response for the 10% drug load at a fixed tablet hardness is presented in **Figure 4.** This figure illustrates that the predicted average dissolution is 93% or higher, when the disintegrant level is 3% - 4%, across all levels of magnesium stearate. The figure also shows a relatively small decrease in dissolution with increasing lubricant levels at the low disintegrant levels. The predicted average dissolution response is 85% or above for all regions of the contour plot demonstrating that

at the 10% drug load all levels of disintegrant and lubricant will produce tablets meeting the attribute target criteria of >75%.

Figure 4: **Contour plot of Dissolution response for 10% drug load at a set Target Tablet Hardness of 12kP**

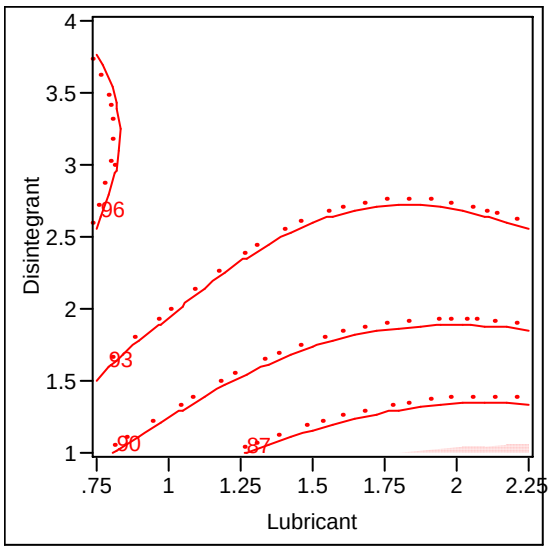
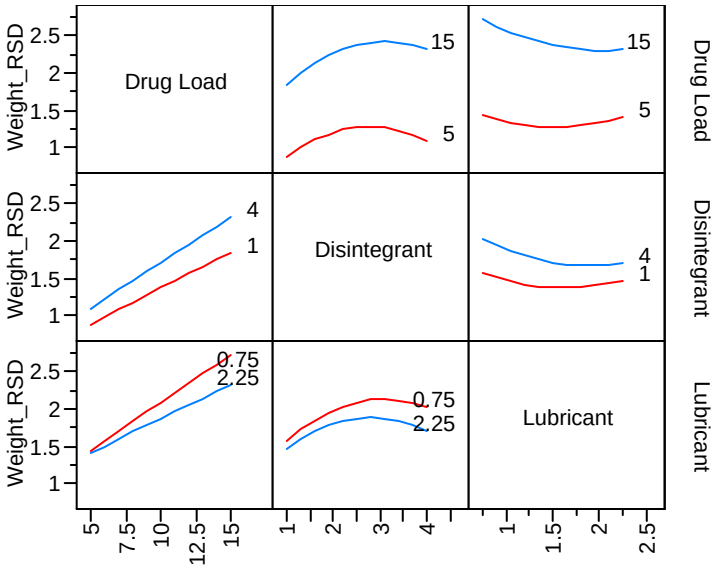


Figure 5 presents the interaction profile for the weight %RSD response at a fixed compression pressure. The only trend identified for this response is that increasing drug load increases tablet weight % RSD. This trend indicates that physical properties of the API could impact the weight uniformity, which would be expected. The predicted tablet weight uniformity % RSD responses are 2.6% or lower, which meets the attribute target criteria of < 3.0%.

Figure 5: Interaction profile for Weight %RSD Response at Fixed Compression Pressure.



The conclusions from the formulation component level definition study provided the basis for formulation component level selection. An acceptable predicted response was demonstrated for weight variation % RSD over the ranges studied. The dissolution response at a fixed tablet hardness of 12 kP shows only minor effects when the lubricant level is between 0.75 and 2.25% and the disintegrant level is between 3 – 4%. The expected commercial dosage is 20 mg such that a 10% drug load would provide a tablet size that is acceptably small enough for patients to swallow. The response surface for the 10% drug load was robust for dissolution performance and therefore 10% was selected for use in the formulation. An interaction was observed between the drug load and magnesium stearate levels with regard to the hardness response. This interaction indicated the need for further study to determine if API physical properties (particularly particle size) could impact the hardness response and what level of magnesium stearate should be used in the commercial formulation.

3.4.B API Particle Size and Magnesium Stearate Interaction Study

The API particle size and magnesium stearate interaction study was primarily designed based on the interaction observed in the formulation component level study between acetriptan concentration and magnesium stearate level. The objectives of the interaction study were to: 1) fully characterize how the acetriptan particle size could impact drug product critical quality attributes; 2) establish the acceptable particle size limits for acetriptan; and 3) to establish an acceptable magnesium stearate range. The study was required to fully understand the impact of this interaction for a poorly soluble drug. Either of these two variables could potentially impact the dissolution rate. Due to the

impact on tablet hardness and the potential impact on dissolution, a tighter range of lubricant was selected for use in this study.

A response surface design was used to study the impact of two factors at three levels plus center points, for a total of 11 trial runs. The formulation selected from the component level definition study with 10% drug load and 3% croscarmellose sodium, was utilized with a 200 mg total tablet weight. The factors studied were as follows:

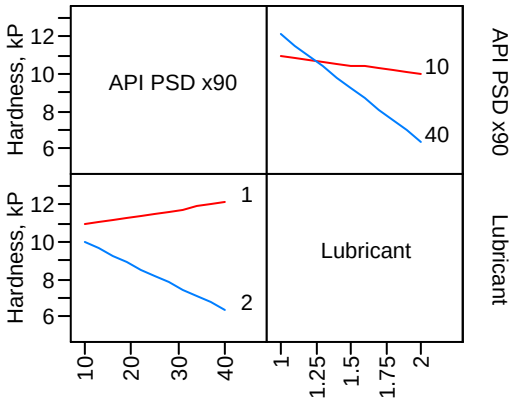
- Acetriptan Particle size d_{90}: 10, 25 & 40 microns
- Lubricant (Magnesium Stearate) Level: 1%, 1.5% & 2% (intragranular)

The response variables studied were as follows:

- Tablet hardness at a fixed compression pressure
- Dissolution average at 30 minutes at a set target hardness of 12kP
- Tablet weight uniformity (based on correlation to content uniformity)

Figure 6 presents the interaction profile for the hardness response at a fixed compression pressure. The interaction profile illustrates the effect of API particle size and magnesium stearate level on tablet hardness. Increasing both variables results in a decrease in hardness with an interaction between these two variables. The decrease in hardness with increasing API particle size is larger at the 2% lubricant level; and the impact of magnesium stearate level is larger with API particle size of 40 microns. Harder tablets are produced at lower levels of lubricant or lower API particle size. This figure also illustrates that an increase in particle size can be compensated for with a decrease in magnesium stearate level to produce a harder tablet. All hardness responses do meet the minimum criteria of 5 kP over the ranges studied.

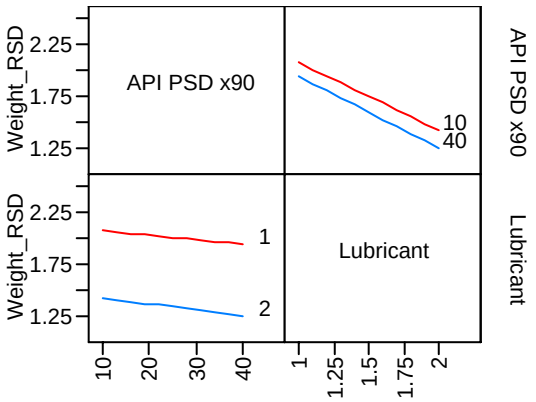
Figure 6: **Interaction profile for Hardness Response at Fixed Compression Pressure.**



The interaction profile for the tablet weight %RSD is presented in Figure 7. The interaction profile illustrates that the magnesium stearate level has no effect on predicted weight %RSD (although RSD at 1% magnesium stearate is higher than at 2%) and the

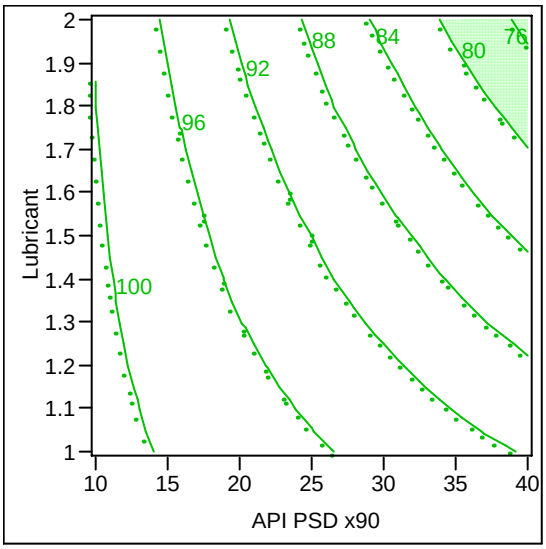
acetriptan particle size has a relatively small impact on predicted weight %RSD. All predicted weight % RSD results are below 2.25% over the ranges studied for these two variables.

Figure 7: **Interaction profile for Tablet Weight % RSD Response at Fixed Compression Pressure.**



A contour plot of the dissolution response at a target tablet hardness of 12 kP is presented in **Figure 8.** As in the previous study, the hardness was fixed at 12 kP because a high hardness would be expected to be the worst case for the dissolution response. An interaction between the API particle size and the lubricant level is evident in this figure. The dissolution response is acceptable over the lubricant range of 1-2% when the particle size is at the lower end of the range studied. From Figure 8, it can be seen that all combinations result in dissolutions exceeding the initial target value of 75%. However, a later in-vivo study showed that a target value for dissolution of 80% was required. The combination of higher particle size and high lubricant level (upper right hand corner of Figure 8) results in unacceptable dissolution below the target of NLT 80%. The shaded area represents the region of unacceptable dissolution, while the large unshaded area represents acceptable dissolution.

Figure 8: **Contour Plot of Dissolution at a Set Target Tablet Hardness of 12kP.**



The conclusions from the API particle size and magnesium stearate interaction study and the in-vivo study are as follows. Product attributes were acceptable over nearly the full range of magnesium stearate level and acetriptan particle size. The most significant effects were observed for dissolution and tablet hardness. There is an interaction between the acetriptan particle size and the lubricant level. Higher lubricant levels or larger particle size result in reduced tablet hardness at a fixed compression pressure. At a fixed tablet hardness of 12 kP, the combination of high lubricant and high acetriptan particle size results in unacceptable dissolution, which is only a small portion of the design space. In order to account for the range of acetriptan particle size, the proposed magnesium stearate range will be linked to the acetriptan particle size to ensure that: 1) acceptable minimum tablet hardness can be achieved and 2) dissolution meets the criterion of not less than 80%.

3.5 Summary of Formulation Component Studies

The formulation composition is concluded to be:

Acetriptan particle size	d_{90} 10-35 microns	d_{90} 35-40 microns
Acetriptan concentration	10%	10%
Croscarmellose level	3-4%	3-4%
Mg Stearate level	1-2% (intragranular) 0.25% (extragranular)	1-1.75% (intragranular) 0.25% (extragranular)
Microcrystalline cellulose	40% (intragranular)	40% (intragranular)
Lactose monohydrate	38.75 - 40.75%*	39.00 – 40.75%*
Talc	5%	5%

* Quantity adjusted to compensate for amount of croscarmellose sodium and/or magnesium stearate

Formulations containing component levels within the ranges above are predicted to have the following attributes: 1) average dissolution at 30 minutes will be greater than 80%; 2) tablet hardness will be greater than 5 kP, and 3) weight variation will be less than 3.0% RSD (ensuring acceptable drug content uniformity given the low concentration variation). The knowledge presented demonstrates that there is an interaction between the acetriptan particle size and the magnesium stearate level impacting tablet hardness and dissolution. The acetriptan particle size impact can be compensated for, if necessary, by adjusting the magnesium stearate level. Acetriptan with higher particle size decreases dissolution, and this can be compensated for by decreasing the magnesium stearate level. There is no significant impact of magnesium stearate on the critical quality attributes of dose uniformity within the ranges proposed. There is no impact on dissolution over the range of disintegrant levels established (3 – 4%). The impact of varying levels of formulation components on tablet quality was further studied during development of the compression step and in-vivo investigations.

4. Manufacturing Process Development

4.1 Overview

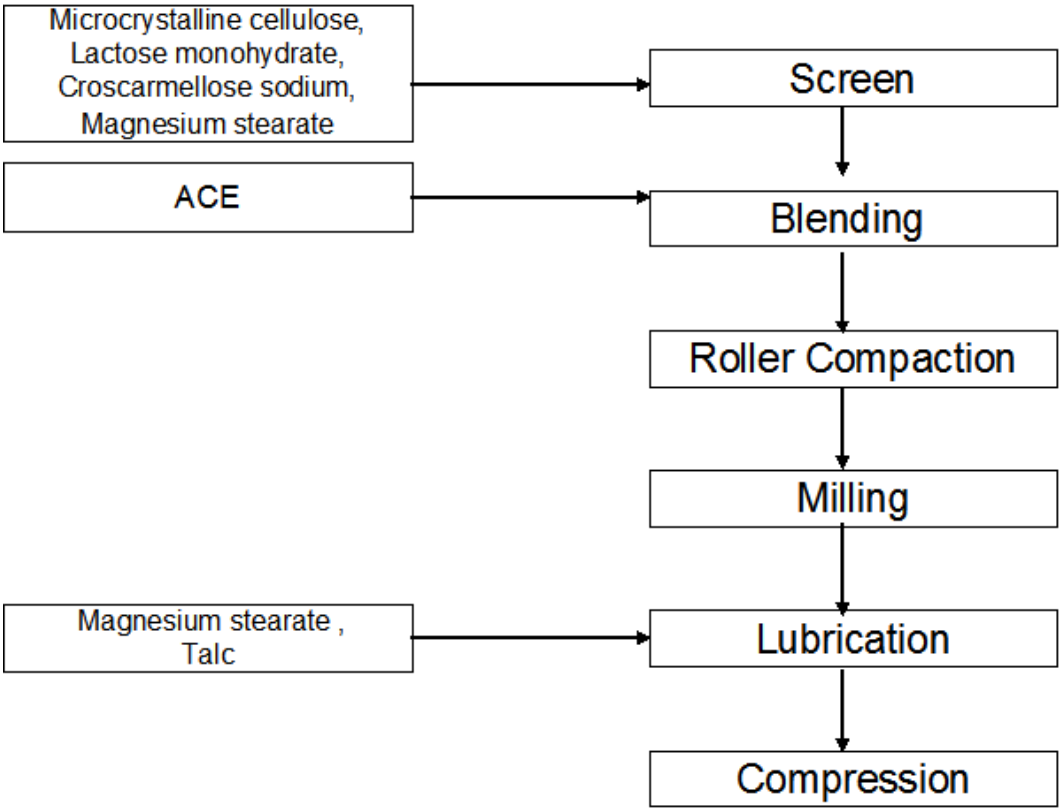
This section presents the process knowledge and understanding obtained during development of the manufacturing process. The relationship between the input attributes and process parameters and the output attributes, for the unit operations that define the Design Space for the ACE tablet manufacturing process is discussed. This then leads to definition of the control strategy that must be implemented in order to ensure that drug product of appropriate quality is produced.

The target product profile states that the manufacturing process should be robust and reproducible. The drug product produced must meet the specification for the drug product CQAs of identity, assay, appearance, microbiological, impurities, dissolution and content uniformity and deliver suitable stability in order not to constrain commercialization in worldwide markets.

4.1.A Summary of the selected process

Based on the physico-chemical properties of the API, roller compaction was selected as the most appropriate manufacturing process. The API is sensitive to heat which would preclude wet granulation, due to chemical instability during a drying process. In addition, the API physical properties (flow) precluded direct compression at the concentrations required. Tablet coating was also precluded due to chemical instability during drying. A flow diagram of the manufacturing process for ACE tablets is provided in **Figure 9**. Microcrystalline cellulose, lactose monohydrate, croscarmellose sodium and magnesium stearate are separately weighed and screened and then blended with API. The blend is then roller compacted to produce a ribbon which is milled to give active granules. Extragranular ingredients (magnesium stearate, and talc) are separately weighed and screened and then blended with the granules. The blend is then compressed into tablets.

Figure 9: Manufacturing Process Flow for ACE tablets



Based on scientific understanding and prior knowledge, a risk assessment of the potential impact of the unit operations on the drug product CQAs was completed. **Table 7** shows the result of the risk assessment and identifies the unit operations which require further investigation to determine the appropriate control strategy.

Table 7: Risk Matrix for Drug Product CQAs for each unit operation

	Unit Operations				
DP CQAs	Blending I	Roller Compaction	Milling	Lubrication	Compresssion
Appearance	Low	Low	Low	High	High
Identity	Low	Low	Low	Low	Low
Assay	Low	Low	Low	Low	High
Impurities	Low	Low	Low	Low	Low
Content Uniformity	High	High	High	Low	High
Dissolution	Low	High	High	High	High

4.2 Process Optimization – Blending Unit Operation

The manufacturing process uses a blending step followed by roller compaction to obtain granules for compression. The blend includes approximately 10% active and 90% diluent, which is mostly lactose monohydrate and microcrystalline cellulose. Despite the presence of another blending step (lubrication) later in the process train, this processing step was deemed critical because development studies indicated that material insufficiently blended at this stage ultimately leads to unacceptable content uniformity of the finished drug product. Based on the development data, the NIR endpoint parameters listed in **Table 8** are acceptable

Table 8: Process Parameter Ranges for Blending

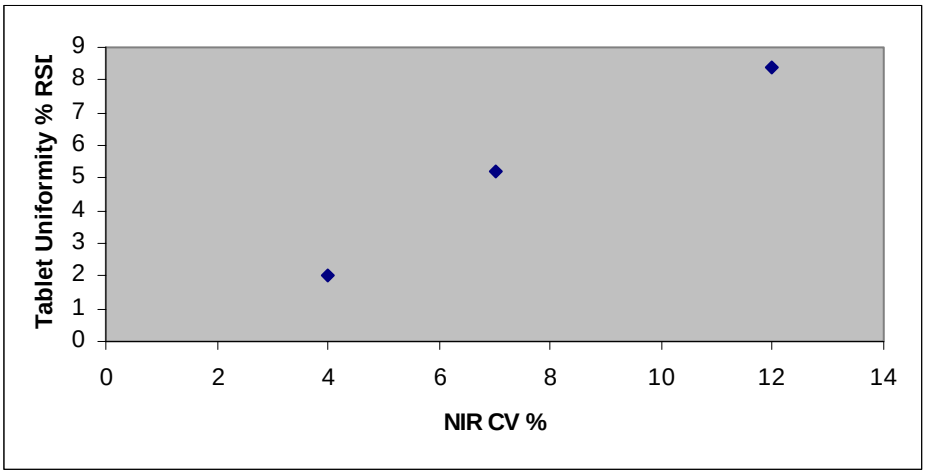
Process Parameter	Proposed process range
% CV	NMT 5
Moving window size	NLT 10 revolutions

4.2.A Method for Determining Blend Homogeneity

NIR was used for determining the endpoint for blending for the majority of the development work, since it provides real time response and eliminates the challenges and errors associated with sampling blends. Diffusive blenders of different sizes were fitted with a NIR sensor. NIR measurements are made once every revolution and the spectroscopic data is analyzed using a chemometric model. Assessment of the NIR spectra of the API and excipients indicated that sufficient specificity for the drug can be obtained, and that NIR is a suitable tool for monitoring this blending process. Using the chemometric model developed, the moving standard deviation of 6 consecutive spectra is calculated over the appropriate range of wavelength. The average of the standard deviations (A_s) is then used to determine the endpoint. The %CV (ratio of standard deviation to mean) of the A_s is calculated. Once 10 consecutive %CV values are below 5%, the blend is considered homogeneous. The criteria that the %CV stay below 5% for 10 revolutions is to ensure brief excursions below the 5% threshold are not used to terminate the blending operation.

At the laboratory scale, several batches were blended to %CV values of the NIR predictions of 7% and 12%. These batches were processed through compression and found to result in elevated tablet content uniformity values of 5.2% and 8.4% RSD, respectively. Similar batches that were blended to a NIR %CV of 4% were processed through compression and maintained a tablet RSD less than 2% **(Figure 10).** Based on these results, the NIR is shown to be capable of accurately assessing the homogeneity of the blend and can be used to control the endpoint of the blending process. An NIR %CV value of 5% is predicted to produce tablets with a RSD of approximately 3% **(Figure 10).**

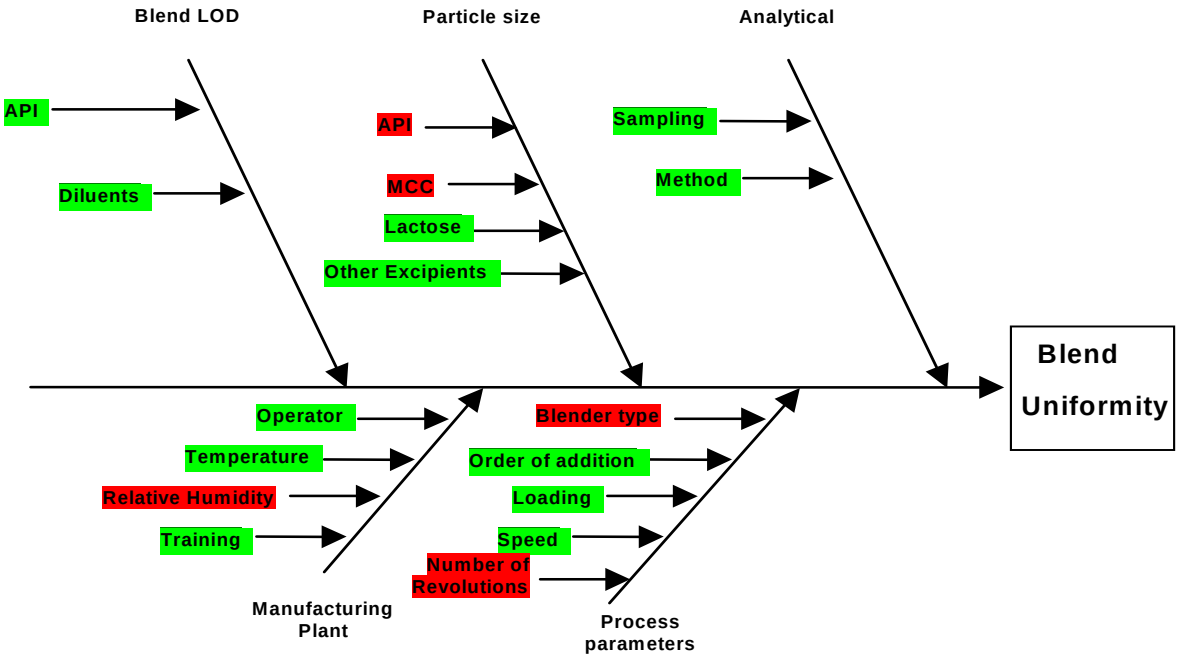
Figure 10: Correlation of Blend NIR CV with Tablet Content Uniformity RSD



4.2.B Critical Parameters Affecting the blend homogeneity

Blending was identified to be a potential risk to content uniformity if appropriate controls are not in place as indicated in **Table 7**. The blending process was evaluated with a cause and effect diagram as shown in **Figure 11.**

Figure 11: Cause and Effect Diagram for Blend Uniformity



Low Risk: Based on scientific understanding or prior knowledge Potential Higher Risk

The factors potentially affecting blend uniformity were identified. Based on previous knowledge, it was determined that blend moisture content is affected by the relative humidity in the manufacturing area and not by the initial water content of the materials. From prior knowledge, it was known that the particle size of the materials present at significant levels could play an important role in determining the appropriate blend time for this type of formulation (API, MCC, lactose). The lactose selected for the formulation is known to have a consistent particle size distribution, controlled by the material specification. Therefore the risk of an effect of lactose particle size was low and was not evaluated further. Based on this cause and effect analysis, a DoE was designed to study the effects of the most significant factors at the pilot scale: Particle sizes of acetriptan and MCC as well as the environmental humidity. The results of the DoE are discussed below.

Table 9: Risk Matrix Table for Blending Unit Operation

Drug Product Critical Quality Attributes	Blending Unit Operation
Identity	**Low**
Content Uniformity	**High**
Assay	**Low**
Dissolution	**Low**
Impurities	**Low**
Appearance	**Low**

Low Risk: Based on scientific understanding or prior knowledge
Potential Higher Risk

The DoE used was a central composite response surface design appropriate for gauging the relative impact of the listed properties on blend time. A screening design was not employed because prior experience with this type of formulation gave a reasonable likelihood that all three factors would be significant to some extent. Ranges of humidity from 20-70%RH, acetriptan particle size (d_{90}) from 10-40 micron and a MCC particle size (d_{50}) of 30-90 micron were studied. Contour plots for these factors are provided as **Figure 12**. From these data, an acceptable blend can be produced over the expected operating range of humidity (20-70 %RH) and particle size (10-40 micron for API and 40-80 micron for MCC), but the blend time can change dramatically (see **Figure 13**). On the pilot scale the extreme ends of this range would be from 8 minutes to 36 minutes. The NIR output was used to determine the blend endpoint in all of these cases, and despite the wide range of blend times, product of suitable quality could be produced under all conditions.

Figure 12: Blend Contour plots

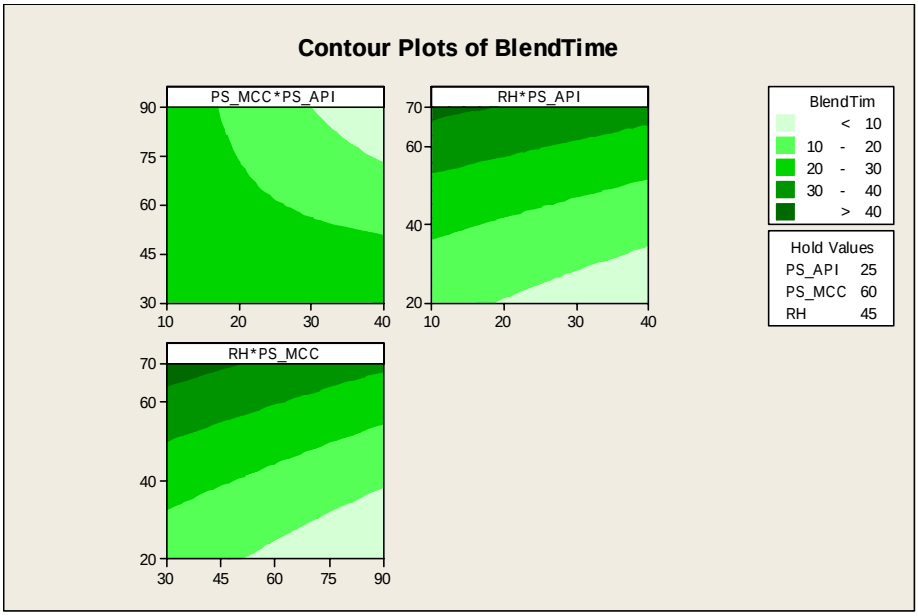
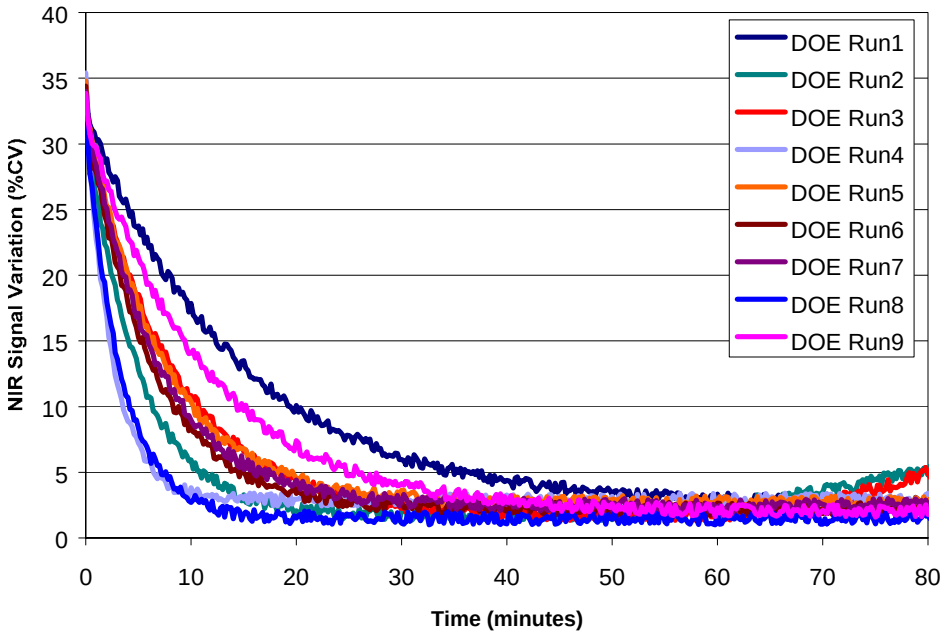


Figure 13: NIR output of DoE Blending Experiments (Representative Results)



In two of the DoE experiments with disparate particle sizes for the API and MCC, some segregation was seen after blending much longer than the minimum blend time determined by the NIR method. Because of this risk of demixing, blending beyond the

point where homogeneity is achieved is to be avoided, and instead, the process should be terminated when uniformity is first achieved, as determined by the NIR method.

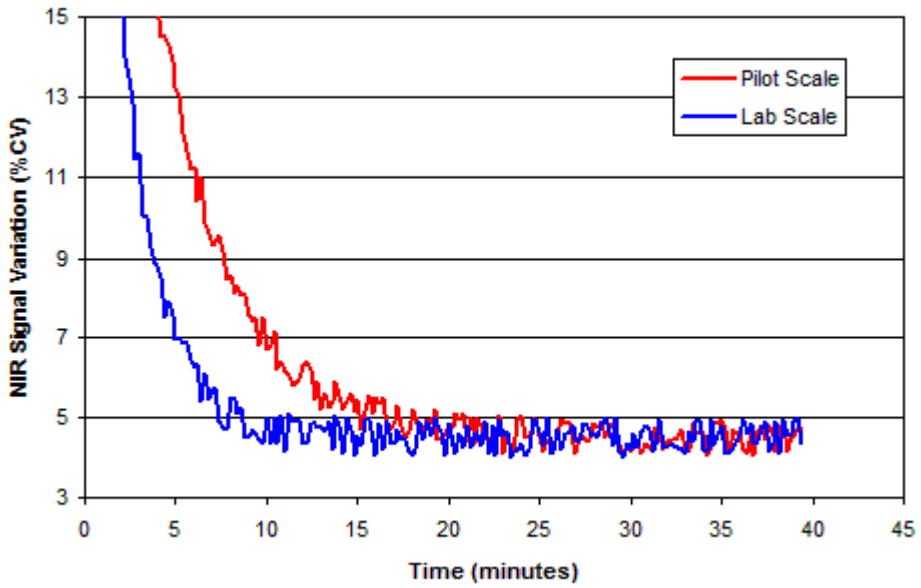
4.2.C Scale-up of the Blending Process

Development of the blending operation was performed at the 1 kg lab scale with a 5 L capacity diffusive blender operated at 9 rpm and at the 50 kg pilot plant scale with a 200 L capacity diffusive blender operated at 5 rpm (see **Table 10**). For these scales, the volume fill ratio was maintained within the range of 40-50% of working volume. At each scale, the blending was performed until the %CV was less than 5% based on the NIR measurements. Because traditional scaling rules typically apply to non-cohesive materials, they were not applicable for this process because of the cohesive nature of this API. This became apparent during development where the blend times at pilot scale were longer than expected. In the lab scale batches with 1 kg of material, the NIR endpoint criteria were reached at approximately 90 revolutions, occurring at 10 minutes (**Figure 14**). Upon scaling up to the pilot scale (**Table 10**) the NIR-based endpoint was likewise reached by 125 revolutions at 25 minutes under similar processing conditions (**Figure 14**). Based on the number of revolutions from lab scale, blending should have been achieved in 18 minutes. Although the blend times were different, the end point was always achieved, and the 5%CV endpoint as determined by the NIR method results in acceptable tablet content uniformity (RSD values ranging from 1.5 to 3.0%). Therefore, for commercial production, the on-line NIR will be routinely used to determine the blend endpoint for each batch.

Table 10: Summary of Scale Up Blending Parameters

Scale	Amount (kg)	Blender Capacity (L)	Blending Speed (rpm)	Volume Fill Ratio
Laboratory	1	5	9	40%
Pilot	50	200	5	50%

Figure 14: Blending Control Data



4.2.D Conclusion for Blending

The blending step discussed here is considered critical to the quality of the product. The parameters that can significantly affect the time to the endpoint of the process are:1) environmental humidity and 2) particle size of the API and MCC. **Table 11** exemplifies the input attributes that are known to produce blend of acceptable quality.

Table 11: **Input attributes for Blending Operation**

Input Attributes	Range
Humidity	20-70% RH
API (d_{90})	10-40 micron
MCC (d_{50})	30 - 90 micron
Equipment	Any diffusive blender
Lactose (d_{50})	70 – 100 micron
Scale	Any

In all cases, acceptable blending is achieved although blend times may vary. It is proposed that NIR be used for routine determination of the endpoint of the blending

process. Blending will terminate as soon as uniformity is achieved. Because NIR monitoring of the blend ensures that adequate mixing is performed, it obviates the need to specify any of the process parameters such as rotation speed, time, scale, excipient sources or equipment (provided a diffusive blender is employed).

A risk matrix table (**Table 12**) for the blending operation demonstrates that the identified risk to the quality attributes has been mitigated by: 1) control of acetriptan, 2) lactose and MCC particle size, 3) environmental humidity and 4) online NIR control.

Table 12: Risk Matrix Table for Blending Unit Operation after Controls

Critical Quality Attributes	Blending Unit Operation
Identity	**Prior Knowledge**
Content Uniformity	**NIR End Point Control**
Assay	**Prior Knowledge**
Dissolution	**Prior Knowledge**
Impurities	**Prior Knowledge**
Appearance	**Prior Knowledge**

Low Risk
High Risk

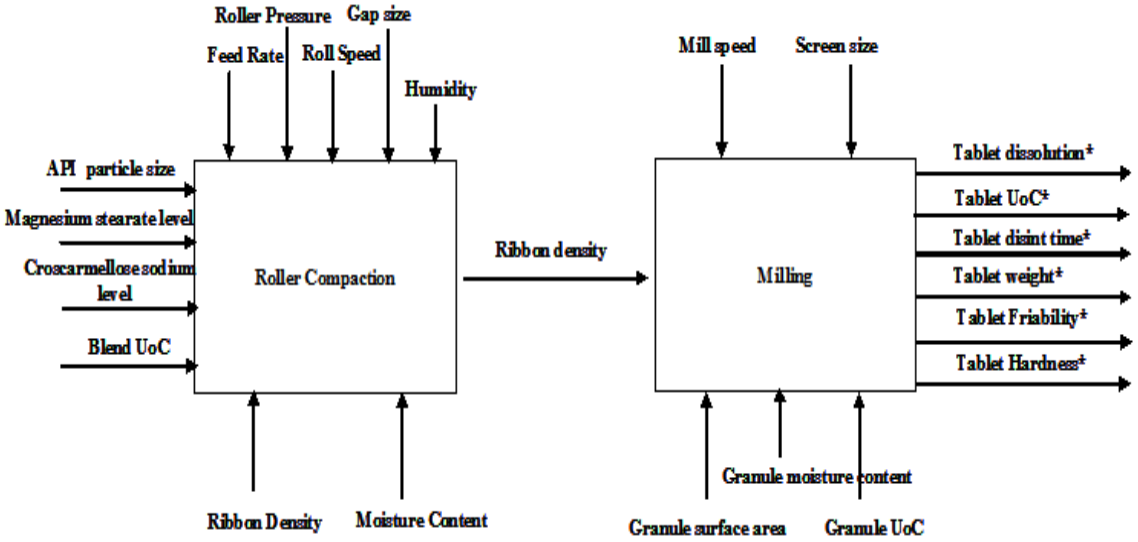
4.3 Process Optimization – Roller Compaction Unit Operation

4.3.A Introduction

The purpose of the roller compaction and milling stages is to produce granulated product that is suitable for subsequent blending and compression. The initial blend is transferred to the roller compactor where a screw-feeder drives it between two rollers, which compact the material. The compacted ribbon is then broken up and passes through a rotating impellor screen mill.

A process map for roller compaction and milling is presented in **Figure 15**. This was used to map the inputs, process parameters, product measures and outputs for both roller compaction and milling.

Figure 15: Process Map for Roller Compaction and Milling



* Final product attributes, not direct outputs from milling

This process map and prior scientific knowledge were used to perform the initial Quality Risk Assessment (QRA-1) from which factors that might affect product quality were proposed and then risk-scored. Subsequently, experimental studies were designed and executed to develop new scientific knowledge and allow further refinement of the risk assessment (QRA-2), thus enabling risk reduction through increased understanding and establishment of appropriate controls.

4.3.B Failure Modes, Effects and Criticality Analysis (FMECA) approach to Roller Compaction

A Failure Modes, Effects and Criticality Analysis (FMECA) approach was used to identify the most relevant raw materials attributes and process parameters in the roller compaction and milling steps that have the potential to impact product quality, and to allow each failure mode to be scored and ranked in terms of risk.

Each variable (potential failure mode) was scored in terms of probability, severity and detectability. Once defined, these scores were multiplied together to produce a "Risk Priority Number" (RPN), which represents the overall magnitude of the risk.

4.3.C Initial Quality Risk Assessment (QRA-1) for the roller compaction and milling stages

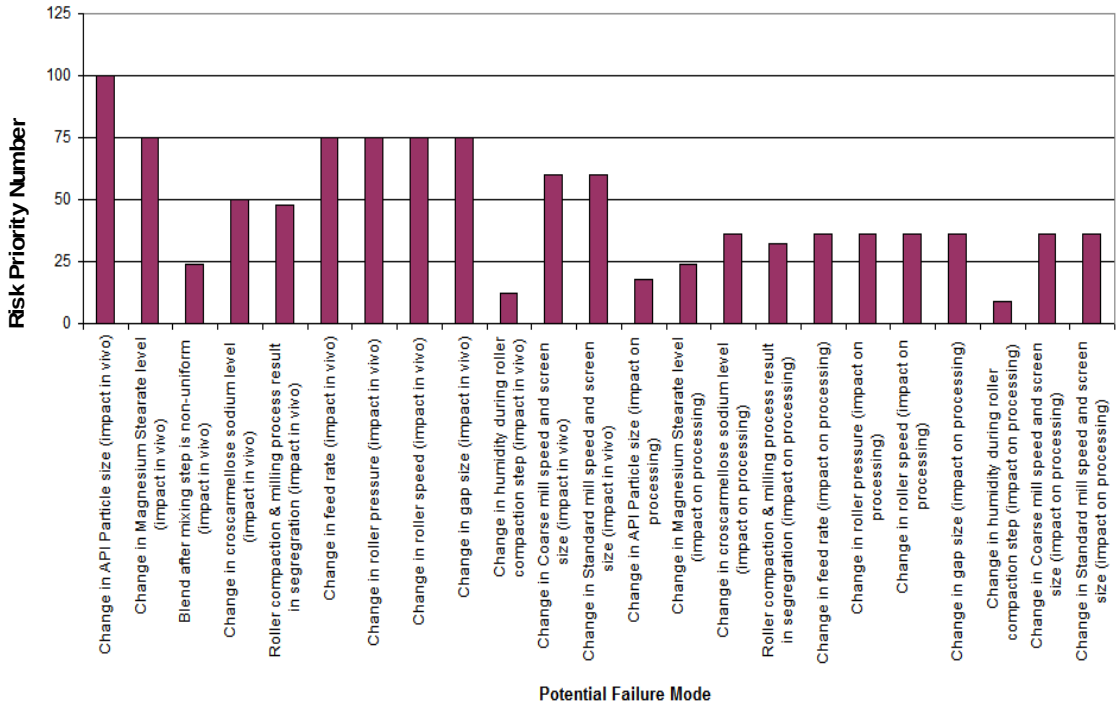
The starting point for the initial quality risk assessment (QRA-1) was the process map for the roller compaction and milling stages, see **Figure 15**. The process map was used to identify input material attributes and process parameters that had the potential to have an impact on product quality.

Based on prior knowledge and the outcome of development studies to investigate the preceding unit operations the following conclusions were reached:

1. The only formulation variables to consider from the formulation component level ranges are:
    a. Acetriptan particle size (d_{90}=10 to 40 µm)
    b. Croscarmellose sodium (CCS) level (3 to 4% w/w)
    c. Magnesium stearate level (1.25 to 2.25% w/w)
2. Initial blend uniformity of content will be routinely assured. Endpoint will be continuously verified using in line NIR (% CV < 5%). Furthermore, a diffusive blender will always be used. Therefore it was considered that uniformity of content would be acceptable at the point of roller compaction.

The outcome of the initial quality risk assessment (QRA-1) is summarized in **Figure 16.**

Figure 16: Initial Quality Risk Assessment (QRA-1) for the Roller Compaction and Milling stages



From this risk assessment, it can be seen that the failure effects fell into two high-level categories; those that could have an impact on *in vivo* performance, and those that could have an impact on processing (e.g. granule flow) and product physical quality.

Furthermore, those that could affect *in vivo* performance have generally been scored higher than those that could affect processing or product physical quality. This difference in scoring is linked to both the detectability and severity associated with each failure effect. For those failure effects that could have an impact on processing and product physical quality, detectability was high, occurring either: 1) during the unit operation, 2) during a subsequent unit operation or in some cases, 3) at finished product testing. As a consequence, the severity score could often be limited by rejection of the affected batch. However for those failure effects that could have an impact on *in vivo* performance, higher severity scores were given.

Due to the controls introduced at the blending stage, the risk of the input blended material having a non-uniform distribution was low. Based on prior knowledge, it was unlikely that the roller compaction and milling stages would cause segregation. Testing to confirm this would form part of experimental studies to increase product understanding of the roller compaction and milling stages.

Changes to humidity leading to variability in product moisture content were considered to be low risk because previous studies to assess the kinetic and equilibrium moisture content of the drug substance, excipients and formulation blends (which cover the extremes of the formulation component levels) demonstrated that there was no significant impact on the product output attributes across relative humilities of 20 to 70% RH. Based on this, relative humidity and product moisture content would not be investigated further.

The initial quality risk assessment (QRA-1) has allowed the highest risks to be identified. The highest risks have been identified as those associated with changes to the input raw materials (changes in API particle size, change to magnesium stearate level and change to CCS level) and process parameters for both the roller compaction and milling steps. Consequently an experimental approach was defined that allowed these risks to be investigated further, to determine if any controls would need to be applied.

4.3.D Process Development Work

Investigation of the formulation and process variables identified in QRA-1 was undertaken in two stages. Firstly, the effects of these six factors were investigated in a two-level, factorial, screening design, which consisted of 32 batches. After identification of the most relevant cause and effect relationships, the identified factors were further investigated using a response surface model design to elucidate the opportunity for control if required. These investigations were performed at a 1kg scale. This is described in more detail in the following sections.

4.3.D.1 Roller Compaction and Milling: DoE-1

Factors Investigated

The following six factors were investigated to better understand their effects, including interactions, on intermediate and final product attributes:

- Acetriptan particle size (10 and 40 μm)
- Magnesium Stearate level (1.25 and 2.25% w/w)
- Croscarmellose Sodium level (3 and 4% w/w)
- Roller pressure (50 and 150 bar)
- Mill screen size (0.039 and 0.062 inches)
- Mill speed (600 and 1200 rpm)

Acetriptan particle size and magnesium stearate level were known to interact from the formulation study. The purpose of this investigation was to evaluate the impact of roller compaction on the interaction between acetriptan particle size and magnesium stearate level. At the roller compaction stage, only roller pressure was investigated because prior knowledge has shown that varying the respective roller compaction process variables leads to the same effect, i.e. changes in ribbon density, meaning investigating the other factors adds no value. Furthermore, roller pressure is the process variable likely to have the greatest effect on ribbon density and is also straightforward to control. As ribbon density is the product attribute at this stage that is most likely to impact downstream processing and product performance, this was considered an appropriate approach.

For the purposes of DoE-1, the parameters of the subsequent unit operations (e.g. blending and compression) were fixed in order to enable correlation of any differences observed in drug product quality with variation introduced at the roller compaction and milling stages. For example, tablets with a hardness of 12 Kp were used in all evaluations. Previous work had suggested that tablet hardness has an impact on tablet dissolution and therefore worst-case interactions between variables at the roller compaction, milling and compression stages could be investigated.

Responses

Based on previous experience with similar formulations, the following responses (which include both intermediate and final product attributes) were measured to assess the impact of varying input materials and process parameters during the roller compaction and milling steps:

In-process Product Attributes

- Ribbon density
- Granule surface area
- Granule uniformity of content

Final Product Attributes

- Tablet weight
- Tablet hardness
- Tablet friability
- Tablet disintegration time

- Tablet dissolution
- Tablet uniformity of content

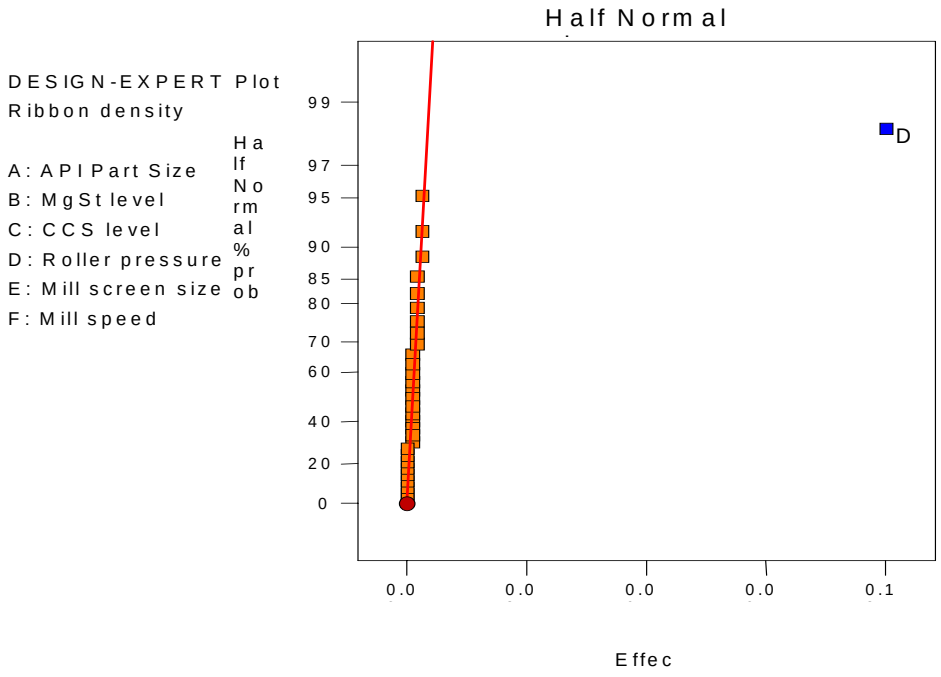
DoE- 1: Results and Discussion

These data were analyzed and significant cause and effect relationships identified. These will be presented in two stages; 1) those factors shown to impact on in-process product attributes, and 2) those factors shown to impact on final product attributes.

Significant Factors for In-process Product Attributes

The only significant factor affecting ribbon density was roller pressure. This is shown by the half normal plot and ANOVA data provided in **Figure 17.**

Figure 17: Half-normal Plot and ANOVA for Effects on Ribbon Density

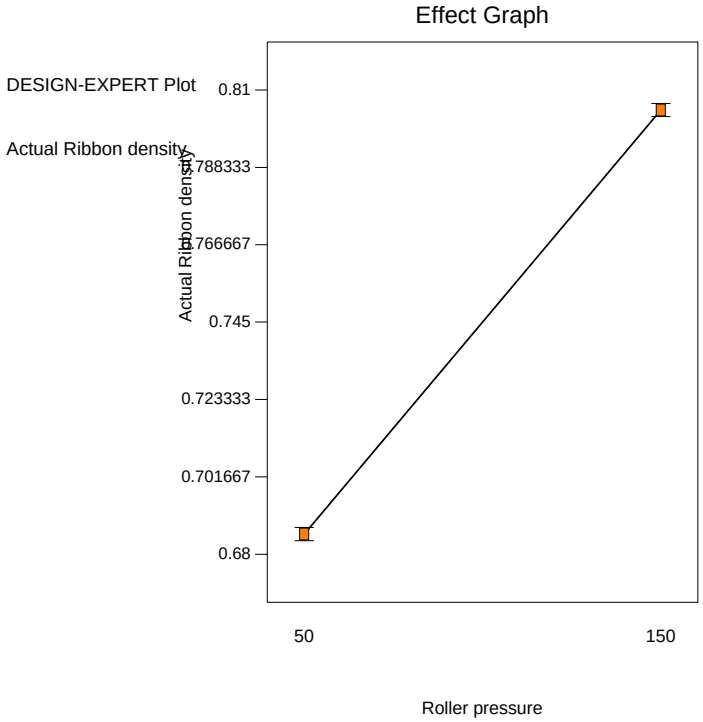


Factor	Coefficient Estimate	DF	Standard Error	t for H_0 Coeff=0	Prob > |t|	VIF
Intercept	0.74	1	9.057E-04			
D-Roller pressur	0.059	1	9.057E-04	65.56	< 0.0001	1.00

This figure shows the dominating effect of roller pressure on ribbon density with little or no effect of the other factors investigated. The relationship between roller pressure and ribbon density is presented in **Figure 18**. Some further work was required to investigate

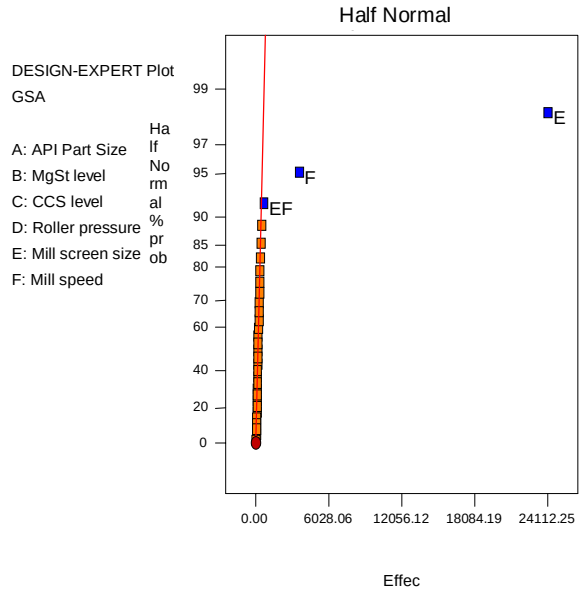
more central data points and to determine if any curvature existed in this relationship. This was part of a second design of experiments (DoE-2).

Figure 18: Relationship between Roller Pressure and Ribbon Density



Two significant factors were shown to affect granule surface area (GSA) and these were also found to interact to a minor extent. These factors were mill screen size and mill speed. The half normal probability plot and ANOVA in **Figure 19** shows that mill screen size had, by far, the most significant impact on GSA with a minor effect imparted by mill speed and the interaction between screen size and mill speed.

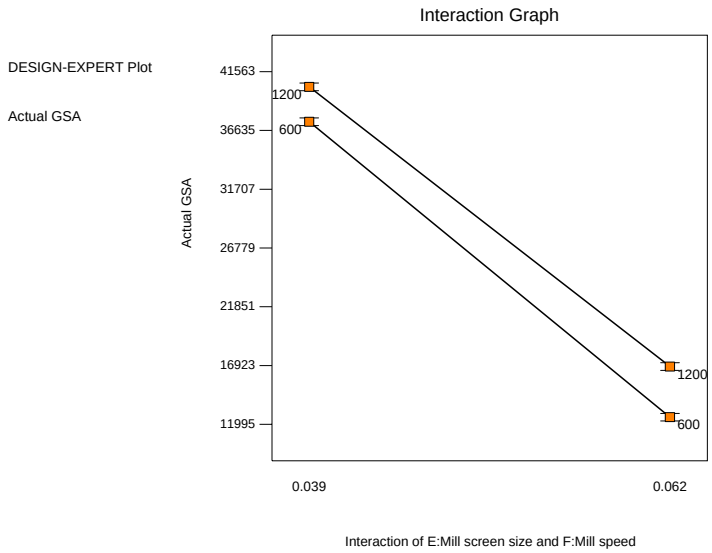
Figure 19: Half-normal Plot and ANOVA for Effects on GSA



Factor	Coefficient Estimate	DF	Standard Error	t for H0 Coeff=0	Prob > |t|	VIF
Intercept	26765.38	1	110.04			
E-Mill screen siz	-12056.12	1	110.04	-109.57	< 0.0001	1.00
F-Mill speed	1789.94	1	110.04	16.27	< 0.0001	1.00
EF	328.69	1	110.04	2.99	0.0058	1.00

The relative effects of mill screen size and mill speed on GSA are more clearly illustrated in **Figure 20**. This further highlights the dominating effect of screen size.

Figure 20: The Effects of Mill Screen Size and Mill Speed (600 or 1200 rpm) on GSA

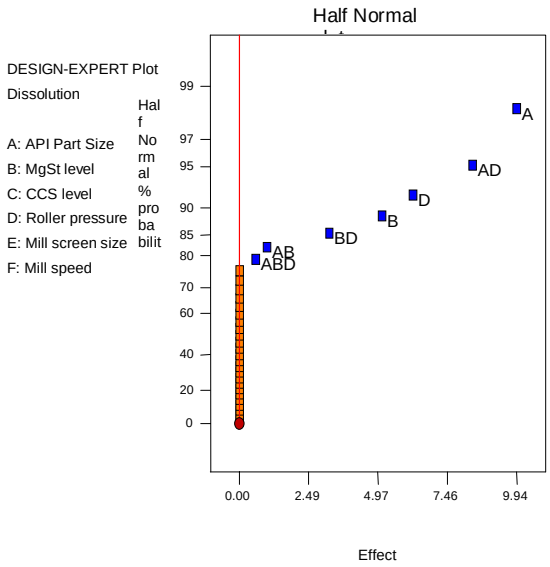


It was also demonstrated that varying the formulation and process factors had no impact on granule uniformity of content. Furthermore, assay of the granule sieve fractions showed that the API is distributed evenly from the fine to coarse fraction further reducing the risk of downstream product segregation leading to unacceptable tablet uniformity of content.

Significant Factors for Final Product Attributes

Hardness and dissolution were the only product attributes affected by the factors investigated. No significant cause and effect relationships were identified for the other final product attributes, i.e., tablet weight, friability and uniformity of content.
Three significant factors were identified for dissolution including a number of interactions. These were API particle size, magnesium stearate level and roller pressure. The half normal probability plot and ANOVA in **Figure 21** show that, in terms of single factor effects, acetriptan particle size had the most significant effect. This was followed by roller pressure and then the magnesium stearate level. Varying levels of croscarmellose sodium were shown to have no significant effect.

Figure 21: Half-normal plot and ANOVA for effects on tablet dissolution



Factor	Coefficient Estimate	DF	Standard Error	t for H_0 Coeff=0	Prob > |t|	VIF
Intercept	86.99	1	0.000			
A-API Part Size	-4.97	1	0.000	-7978.72	< 0.0001	1.00
B-MgSt level	-2.56	1	0.000	-7978.72	< 0.0001	1.00
D-Roller pressur	-3.11	1	0.000	-7978.72	< 0.0001	1.00
AB	-0.50	1	0.000	-7978.72	< 0.0001	1.00
AD	4.18	1	0.000	7978.72	< 0.0001	1.00
BD	-1.61	1	0.000	-7978.72	< 0.0001	1.00
ABD	-0.29	1	0.000	-7978.72	< 0.0001	1.00

4.3.E DoE-2: Roller compaction response surface

The three factors found to have a significant effect on tablet dissolution by the screening DoE (API particle size, roller pressure and magnesium stearate level) were further investigated in a response surface DoE (12 experiments) in an attempt to better understand the inter-relationships between these factors. This would allow the potential for appropriate control of dissolution performance.

This second DoE used the following ranges:

Acetriptan particle size	d_{90} 10-40 micron
Magnesium Stearate level	1-2% intragranular, 0.25% extragranular
Roller pressure	50 –150bar

Contour plots for API particle size and roller pressure versus dissolution rate (at different magnesium stearate levels) are included in **Figure 22**, **Figure 23**, and **Figure 24.** The results confirmed that all parameters investigated had an impact on dissolution rate, and

that particle size had the most significant effect followed by roller pressure and then magnesium stearate. The contour plots also demonstrate the interaction between the parameters investigated. For example, if a minimum of 90% dissolution at 30 minutes was required then this could be achieved by controlling API particle size alone; or through a combination of particle size, roller pressure and/or magnesium stearate level. Therefore by application of the understanding gained from DoE-2, it would be possible to assure dissolution performance by control of input material attributes and process parameters.

Figure 22: Contour plot for API particle size and roller pressure versus tablet dissolution (% at 30 mins) with a 1% magnesium stearate level

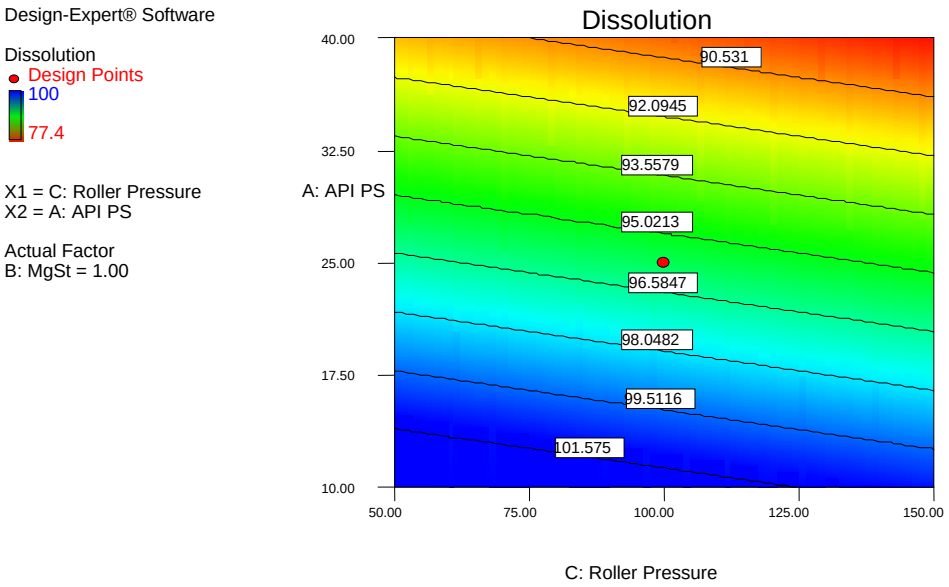


Figure 23: Contour plot for API particle size and roller pressure versus tablet dissolution (% at 30 min) with a 1.5% magnesium stearate level

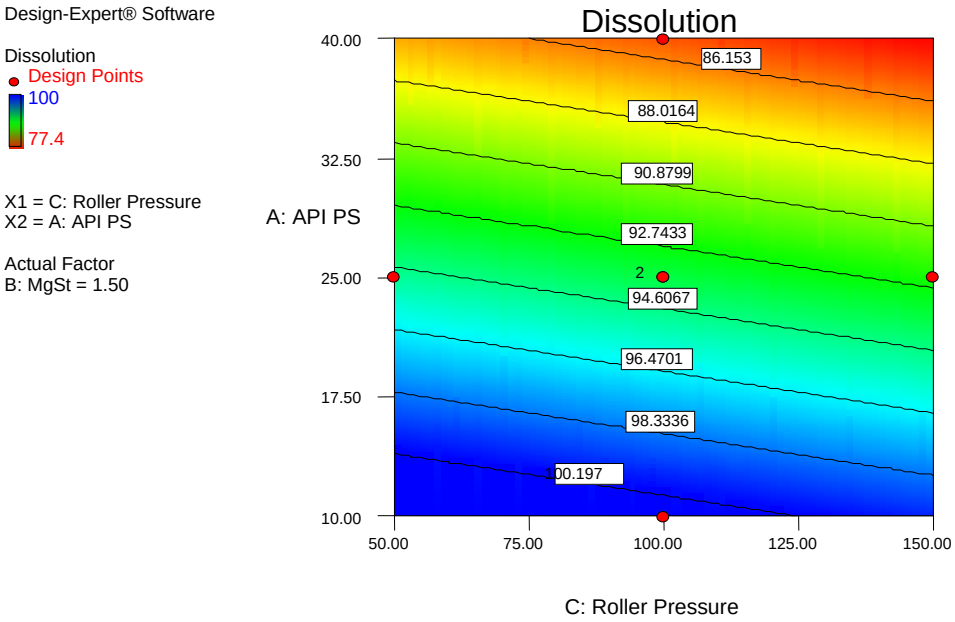
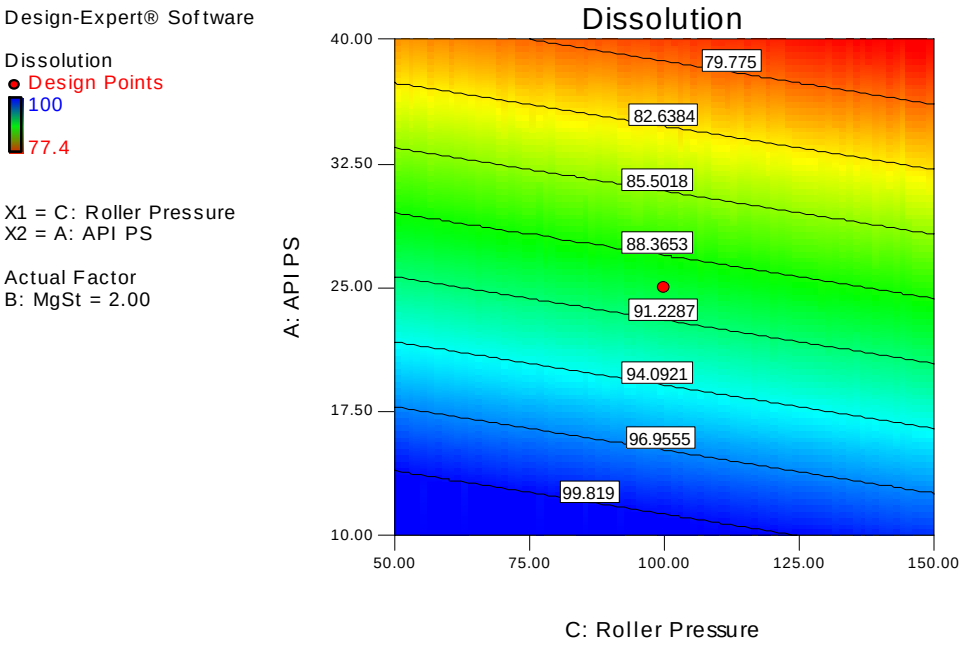
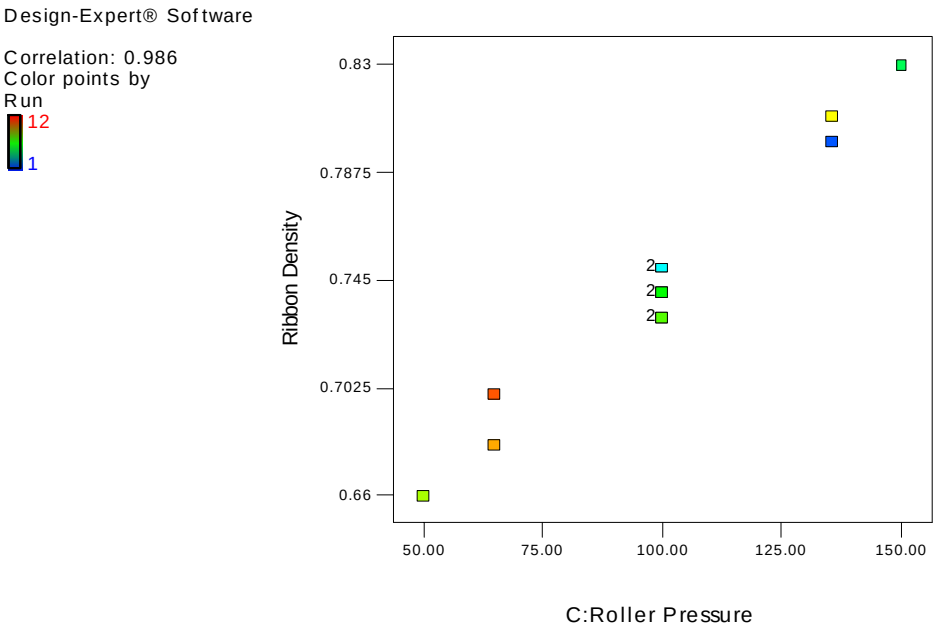


Figure 24: Contour plot for API particle size and roller pressure versus tablet dissolution (% at 30 min) with a 2% magnesium stearate level



In addition this work confirmed a linear relationship between roller pressure and ribbon density i.e. no curvature exists (see **Figure 25**). Based on this linear relationship and the observed relationship between roller pressure and tablet dissolution rate it can be concluded that a relationship between ribbon density and tablet dissolution rate also exists. The establishment of this relationship is significant, as it enables an intermediate material attribute (ribbon density) to be used as a control to assure dissolution performance.

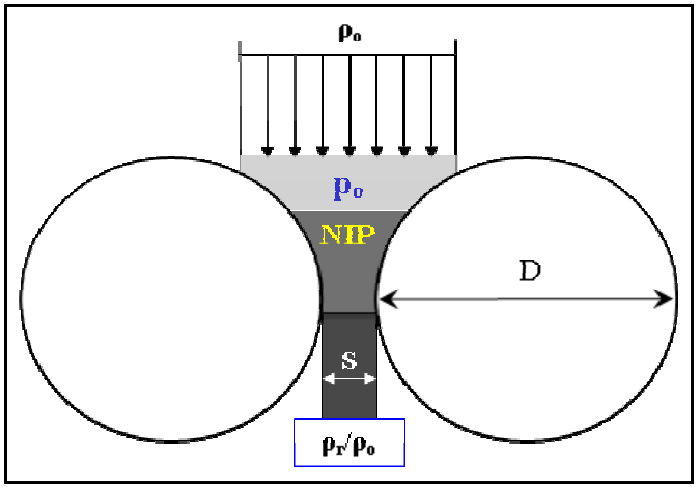
Figure 25: Confirmed Linear Relationship between Roller Pressure and Ribbon Density



Impact of Scale

As shown above, the roller pressure (compaction force) and material mechanical (yield) properties impact the results of roller compaction (i.e., ribbon density). Johansen (J. App. Mech. p.842, Dec. 1965), identified several dimensionless groups for roller compaction and these are given below in **Figure 26**.

Figure 26: Description of Parameters associated with Roller Compactor



Ω = roll speed [1/T]
D = roll diameter [L]
s = roll gap width [L]
p_o = feed pressure [$F/L^2 = M/LT^2$]
E = Young's modulus [$F/L^2 = M/LT^2$]
σ_y = yield stress [$F/L^2 = M/LT^2$]
ν = Poisson's ratio [-]
ε_o = initial porosity [-]
μ_{pr} = friction between powder/roll [-]
μ_{pp} = internal powder friction [-]
ρ_o = initial bulk density [M/L^3]
ρ_r = ribbon bulk density [M/L^3]

where the square brackets […] indicate the dimensions of a parameter, T refers to time, L is length, M is mass, and F is force (= ML/T^2).

The dimensional relation between the ribbon bulk density and the other parameters may be written as:

$$\rho_r = fcn_1\left(D, \Omega, s, p_0, E, \sigma_y, \nu, \varepsilon_0, \rho_0, \mu_{pr}, \mu_{pp}\right) \quad (1)$$

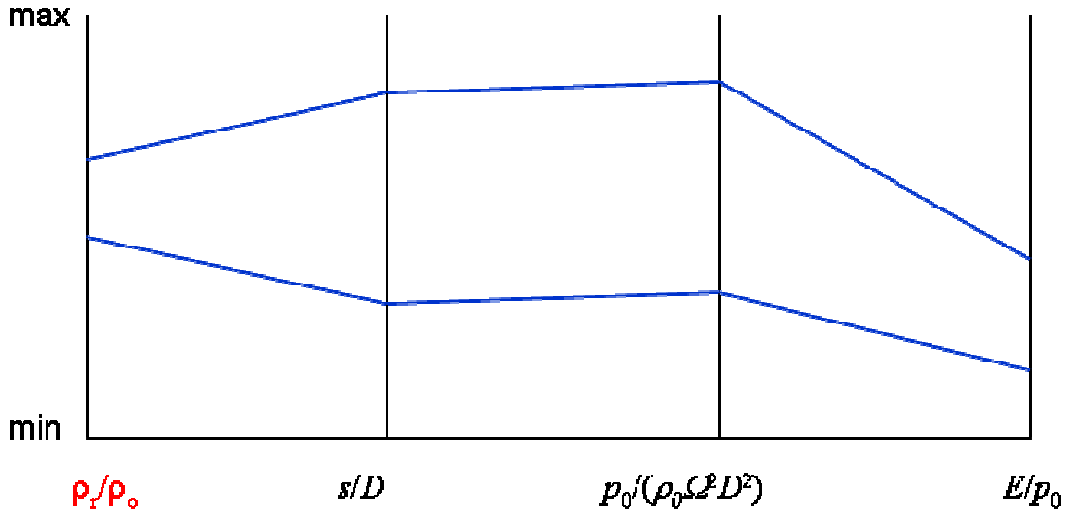
In dimensionless form, Eqn. (1) may be written as:

$$\frac{\rho_r}{\rho_0} = fcn_2\left(\frac{s}{D}, \frac{p_0}{\rho_0 \Omega^2 D^2}, \frac{E}{p_0}, \frac{\sigma_y}{E}, \nu, \varepsilon_0, \mu_{pr}, \mu_{pp}\right) \quad (2)$$

The dimensionless parameters in Eqn. (2) serve to establish truly scale and equipment independent metrics. Using the *relative density* of the ribbon (ρ_r/ρ_o) as the response, the range of s/D, $p_0/(\rho_0\Omega^2D^2)$, and E/p_0 were selected to give an acceptable ribbon density.

Such a scale independent relationship is illustrated in parallel coordinates as shown below in **Figure 27**.

Figure 27: Scale independent Relationship Illustration



This process understanding establishes the independence of site, scale, and equipment.

4.3.F Roller Compaction and Milling Conclusions

The conclusions from this work were:

1. All dissolution values were in the range 75-100% at 30 minutes. However, a later in-vivo study showed that a target value for dissolution of 80% was required.

2. Dissolution was only affected by acetriptan particle size, magnesium stearate level & roller pressure. This included a number of interaction terms.

3. Ribbon density was directly affected by roller pressure. This is a linear relationship and is independent of the other factors that were investigated. A relationship between ribbon density and tablet dissolution rate was also concluded

4. All ribbon densities were in the range 0.68 – 0.81.

5. Dissolution can be controlled by placing boundaries on acetriptan particle size, ribbon density and magnesium stearate level.

6. No significant cause and effect relationships were identified between the factors investigated and the remaining final product attributes, i.e. tablet weight, hardness, friability, and uniformity of content.

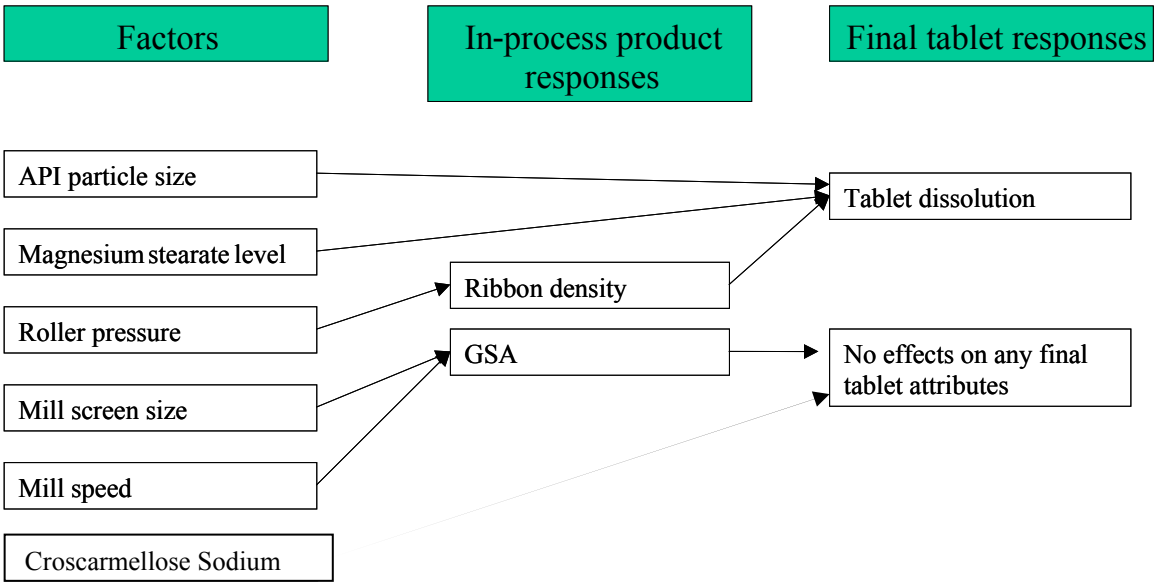
7. Granule Surface Area (GSA) was only affected by mill screen size and mill speed. Screen size was shown to be the dominating factor with mill speed imparting a minor effect. However, there was no impact of the milling parameters (and consequently GSA) on final product attributes within the ranges studied.

8. Varying the input factors had no impact on granule uniformity of content.

9. Assay of the granule sieve fractions showed that the acetriptan is distributed evenly from the fine to coarse fraction.

The knowledge gained from the process development work is summarized in a cause and effect diagram, presented in **Figure 28**.

Figure 28: Roller Compaction: Summary of Cause and Effect Relationships identified from Process Development Studies



Ribbon density is proposed to be measured in-line by NIR as part of the control strategy. This is described further below.

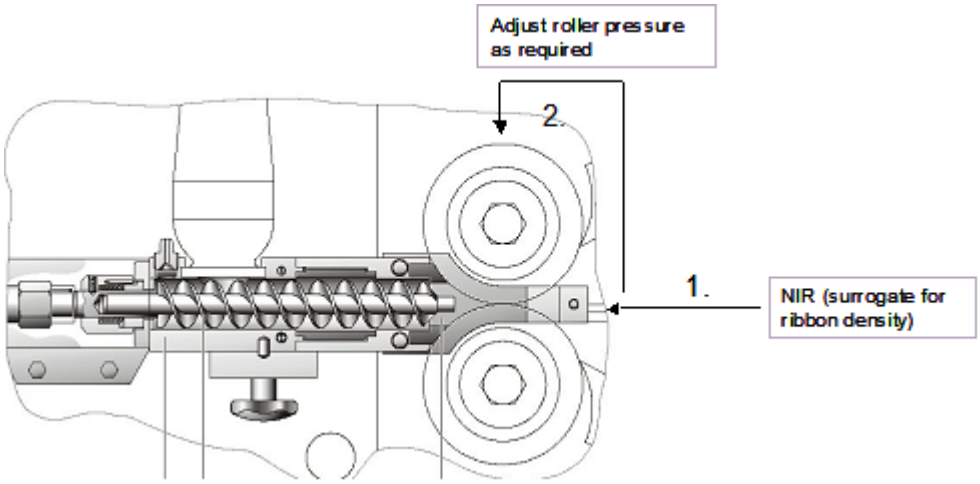
The intent of the control strategy for roller compaction is to maintain the ribbon density within the required range to ensure drug product of appropriate product quality can be produced. To maintain a ribbon density of 0.68 to 0.81 during routine operation, a real time NIR in-process control will be employed. This will be based on two elements:

1. NIR will be used as a real time surrogate measure for ribbon density to detect any variability

2. The cause and effect understanding, generated during process development, will be used to react to any variability and correct it.

This is represented schematically in **Figure 29**.

Figure 29: NIR in-process control feedback loop



The surrogate NIR measure for ribbon density was established through extensive calibration work to ensure that a robust in-process control model was established.

The milling studies showed acceptable process performance and generated GSA between 12,000 to 41,000 $cm^2/100g$. No routine control strategy will be employed at the milling stage; however, some controls will be applied as part of change management. For the initial process, mill screen size and speed will be selected to ensure that GSA will remain within the proven ranges. If a change to the mill is made e.g. scale-up or down, then the impact on granule surface area will be assessed across the pre-defined ribbon density range. Changes to the mill screen or impeller speed may be required at this stage to ensure that granules manufactured during future routine operation fall within the proven GSA ranges across the defined ribbon density.

4.3 G Second Risk Assessment for Compaction and Milling (QRA-2)

Following completion of process development studies (DoE-1 and DoE-2), a greater understanding of the risks to drug product quality associated with the roller compaction and milling stages has been developed. Cause and effect relationships have been identified that link input materials, process parameters and attributes of in-process materials to drug product quality.

Understanding of these cause and effect relationships has led to identification of the target output attributes and a control strategy for the roller compaction and milling stages to ensure that product of requisite quality is consistently manufactured. As a consequence of these controls, the probability of failure modes being realized has been lowered and the risks reduced.

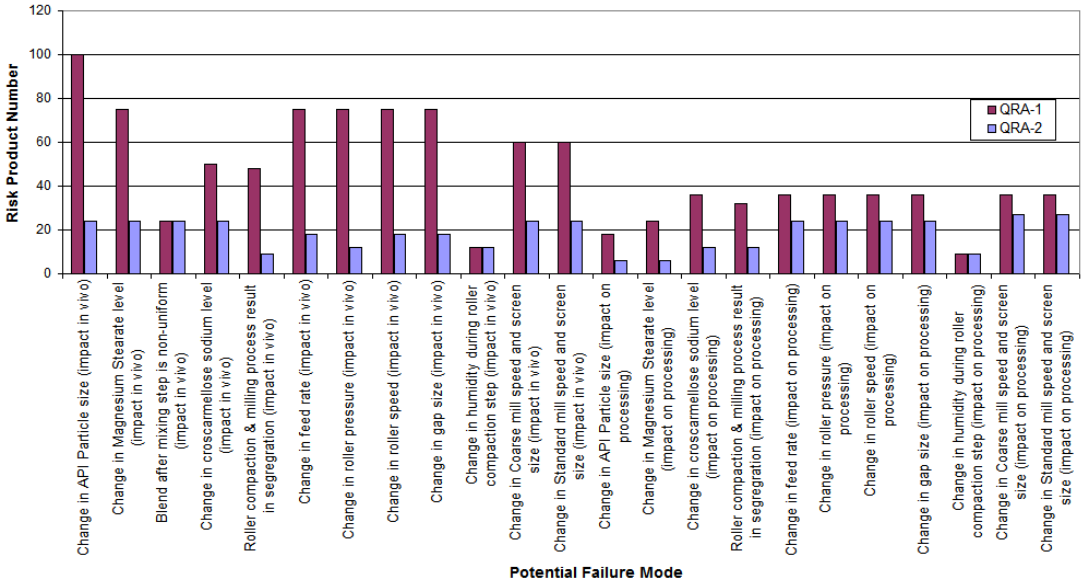
In addition, these experimental studies have also allowed for the development of more appropriate tests to measure key in-process parameters and potential critical quality attributes. Therefore, earlier detection becomes possible and the detectability score for

failure modes is improved, thus leading to a reduction in the level of risk. With the use of more appropriate tests to enable earlier detection, the severity of a failure mode may be lowered and again, the level of risk is reduced. Key tests and acceptance criteria that have been identified include:

- NIR for ribbon density
- Discriminatory dissolution Q=80%

With the increased understanding gained from these experimental studies and the establishment of appropriate controls, a re-evaluation of the initial quality risk assessment was undertaken (QRA-2). This is summarized in **Figure 30** which includes the initial risk priority numbers for QRA-1.

Figure 30: Final Risk Assessment (QRA-2) for the Roller Compaction and Milling Stages



From this risk assessment, it can be seen that the level of risk has been reduced for both failure effects that could impact *in vivo* performance, and failure effects that could impact upon processing and product physical quality.

For the failure effects associated with formulation variables (acetriptan particle size, magnesium stearate level, croscarmellose sodium level) the level of risk has been reduced on the basis of knowledge and understanding gained from the experimental studies and the controls applied.

In summary, by a process of risk assessment, risk evaluation and subsequent risk control, identification of the target output attributes and control strategy for the roller compaction

and milling stages of the ACE tablets drug product process have been demonstrated that minimize the risks to drug product quality associated with these processing stages.

4.4 Process Optimization – Lubrication Unit Operation

4.4 A Lubrication Blending

Following the roller compaction and milling, the milled granulation is blended with extragranular excipients in a second blending operation. The granules are mixed with 0.25% magnesium stearate (as lubricant) and 5% talc (as glidant). Since NIR monitoring of the blend is not capable of fully measuring the lubrication process (i.e. over-lubrication), a traditional method (fixed blending range based on a number of revolutions) is used to establish the end-point of blending. Based on the development data, the blending parameter targets listed in **Table 13** are acceptable for the proposed commercial scale lubrication blending process. Because studies have shown that wide variations in both blending time and blender fill volume have negligible impact on any CQA, this unit operation is considered robust and has no critical process parameters.

Table 13: Process Parameter Targets for Lubrication

Process Parameter	Proposed process target
Revolutions	75
Fill volume	53%

Development and scaling of the lubrication blending process was performed at the 1 kg lab scale with a 5 L capacity diffusive blender and at the 50 kg pilot plant scale with a 200 L capacity diffusive blender. Charging approximately half of the granulation, sequentially charging the extragranular excipients, and then charging the remaining granulation accomplished loading in all cases.

An initial risk assessment was conducted for this blending step. The cause and effect matrix analysis shown in **Table 14** indicated that the potential effect of lubrication on the release of drug from the dosage form as measured by dissolution and appearance required additional investigation.

Table 14: Cause and Effect Matrix Risk Analysis for Lubrication

Critical Quality Attribute	Identity	Content Uniformity	Assay	Dissolution	Impurities	Appearance
Preliminary Risk Assessment	**Low**	**Low**	**Low**	**High**	**Low**	**Low**

Low Risk: Based on scientific understanding or prior knowledge

Potential Higher Risk

Although dissolution is a critical quality attribute, a statistically significant dependence ($p < 0.10$) of dissolution on blending parameters was not observed at the lab scale. Also, a dependence of compressing performance on blender rotational speed was not observed at the lab scale; and because free flowing materials are reported in the literature to mix at a rate independent of blender rotational speed, the blender rotational speed was not considered an important parameter upon scale up. Total number of revolutions and fill volume are known to influence mixing uniformity and rate of mixing (respectively) in a blending operation, therefore these parameters were retained for study in blending development at the pilot scale. The metric by which sufficient mixing was confirmed was by the level of tablet picking or sticking.

To investigate the impact of fill volume and number of revolutions on compressed tablet appearance, a full factorial 2-factor 3-level DoE was performed at the pilot scale using the acceptable quality limits (AQL) for visual inspection of 1250 tablets as the response variable. The granules used in this study contained 2% magnesium stearate to represent a worst case scenario for potential over-lubrication. Tablets were inspected for each condition and acceptable limits were defined by the quality system. Because the relationships between the DoE factors and degree of mixing are already qualitatively described in mixing theory, the DoE was performed in order to define process targets and demonstrate product robustness around the proposed targets. The results are shown in **Table 15** and in all cases acceptable tablets were produced.

Table 15: DoE Results: AQL Observations as a Response to Fill Ratio and Number of Revolutions (<25 cosmetic observations acceptable)

	N_{rev}=50	N_{rev}=75	N_{rev}=100
Fill=40%	3	3	1
Fill=50%	8	6	2
Fill=60%	19	15	5

To confirm the lab scale results showing that tablet hardness and release rate are not a function of blending parameters, tablet hardness and dissolution were also investigated as a response to the DoE factors at the pilot scale and the results are shown in **Figure 31** and **Figure 32.** The results confirm that tablet hardness and dissolution are indeed independent of blend parameters and that there is no risk in over-blending over the ranges studied. While the main effects plot did exhibit an apparent relationship between drug release and fill level, it was not a statistically significant effect.

Figure 31: Effect of Blending Parameters on Tablet Hardness

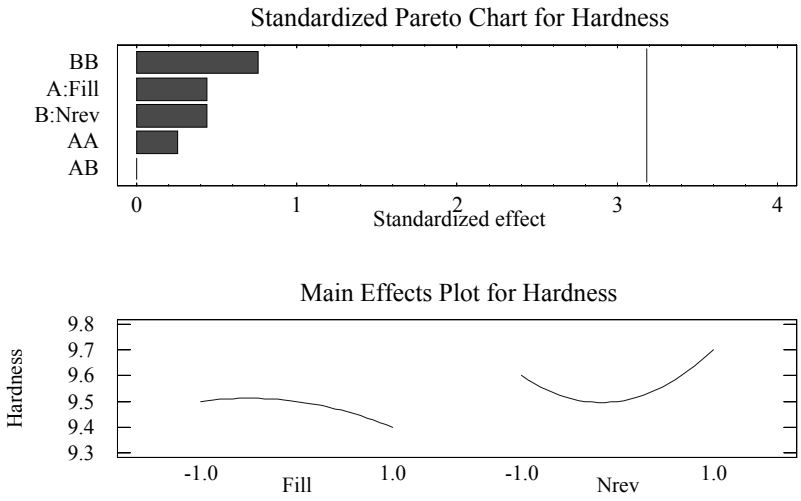
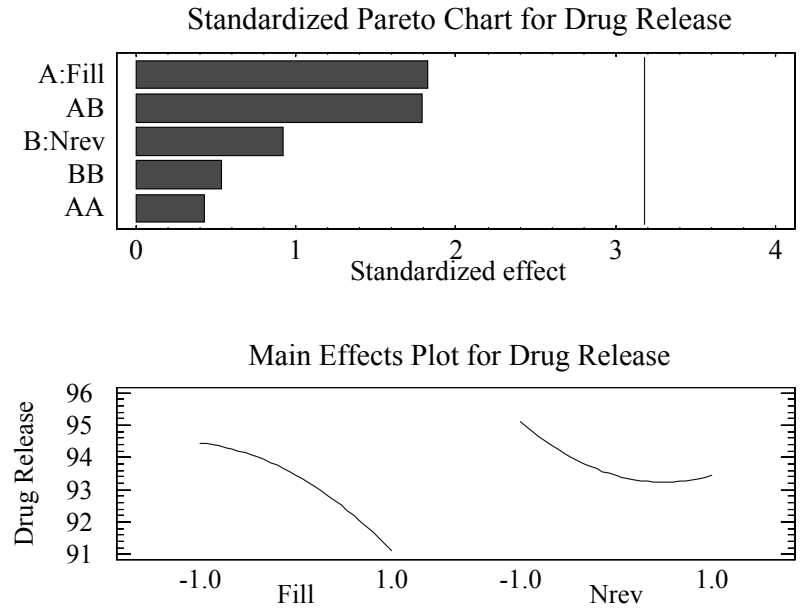


Figure 32: Effect of Blending Parameters on Drug Release at 30min



It should be noted that when the blending was completed using a very high number of revolutions (N_{rev} = 150) a reduction in dissolution rate was observed. Although the tablets still met the dissolution acceptance criteria this indicated that blending for an extreme number of revolutions could affect wettability and should be avoided. In addition, evaluation of compression data indicated that higher compressing forces were required to produce tablets of the desired hardness when materials were blended for extended times.

NIR measurements cannot predict over-lubrication, therefore an endpoint based on number of revolutions is recommended.

A re-examination of the risk associated with this unit operation demonstrated that all risks are low based on the experimental work described. This is reflected in **Table 16**.

Table 16: Cause and Effect Matrix Risk Analysis for Lubrication

Critical Quality Attribute	Identity	Content Uniformity	Assay	Dissolution	Impurities	Appearance
Final Risk Assessment	**Low**	**Low**	**Low**	**Low**	**Low**	**Low**

Low Risk
High Risk

The blending process will be scaled to commercial size based on classical scale-up rules for free flowing materials[1]. **Table 13** lists the commercial target lubrication parameters based on keeping the number of revolutions invariant to scale. A summary of target lubrication parameters across scales is given in **Table 17**.

Table 17: Summary of Scale Up Lubrication Parameters

Scale	Amount (kg)	Blender Capacity (L)	Blending Speed (rpm)	Blending Time (min)	N_{rev}	Volume Fill Ratio
Laboratory	1	5	9	8	72	40%
Pilot	50	200	5	15	75	50%
Commercial	400	1500	3	25	75	53%

As long as diffusive blending is employed, it is proposed that changes to site, scale and/or target process parameters can be made within the company's quality system due to the proven robustness of the system and negligible impact on CQAs,

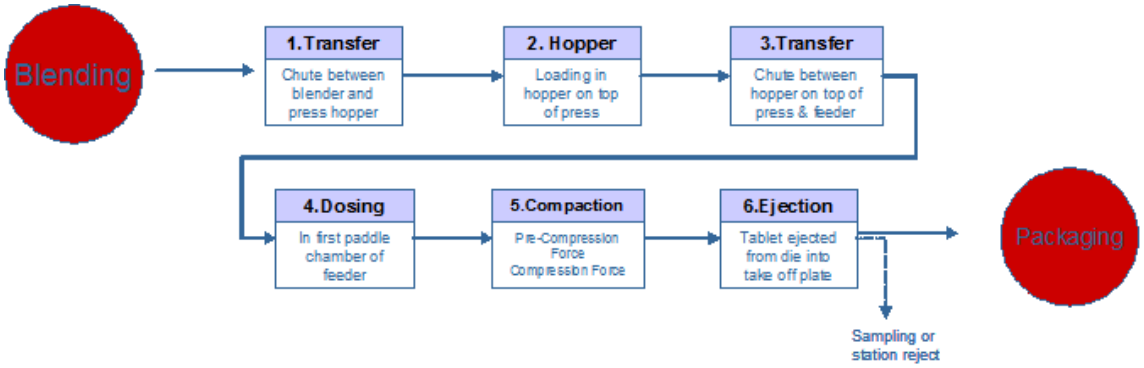
4.5 Process Optimization – Tablet Compression Unit Operation

4.5.A Introduction

Following blending with extragranular excipients, the manufacturing process utilizes a compression step to produce tablets that meet the requirements of the Critical Quality Attributes. The ACE compression manufacturing process flow is provided in **Figure 33**.

[1] Pharmaceutical Process Scale-up, edited by Michael Levin, Chapter: Batch Size Increase in Dry Blending and Mixing, A.W. Alexander, F.J. Muzzio pp. 115-132 Marcel Dekker, NY (2002) ISBN: 0-8247-0625-0

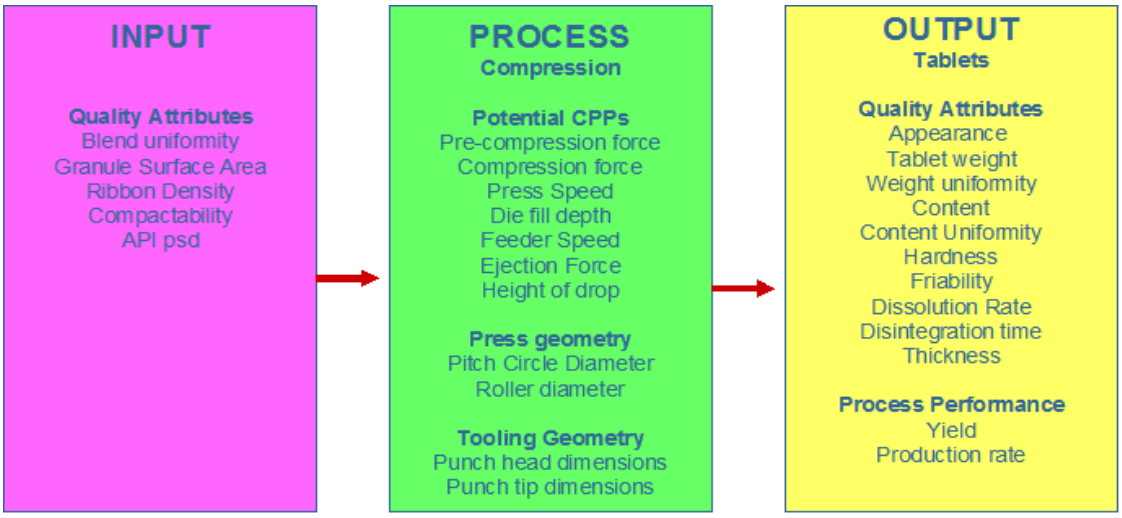
Figure 33: ACE Tablet Compression Process Flow



All variables relevant to the compression process were identified using an IPO (Input, Process, Output) diagram (**Figure 34**). A parameter/attribute matrix of all potentially significant parameters for compression was developed. Based on prior knowledge and process experience, the variables most likely to influence the quality of the drug product were identified. The effect of lubrication blending on tablet hardness and tablet appearance had been investigated previously and is described in the aforementioned lubrication section;, therefore they will not be considered further here.

A risk assessment was then undertaken using FMEA, to establish those variables that are likely to pose the greatest risk to the quality of the product and be associated with a drug product CQA. A summary of the highest potential risks identified by the FMEA is provided in **Table 18**. The variables identified as a result of the FMEA as highest potential risk to quality and requiring further evaluation are given in **Table 20**.

1542 **Figure 34: IPO Diagram for ACE Compression Step**



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1545 **Table 18: Summary of High Potential Risks from ACE Compression Step FMEA**

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Potential Risks	DP potential CQA impacted	RPN	Comments	Recommended Actions
Pre Compression/ Compression force too high	Dissolution Hardness (if a CQA)	High	High hardness is known to impact disintegration and dissolution	Investigate impact of pre-compression and compression forces
Pre Compression/ Compression force too low	Dissolution Hardness (if a CQA) Appearance	High	Decreased compaction leading to softer tablet	Investigate impact of pre-compression and compression force
Decrease in the blend bulk density	Dissolution Content Uniformity	High	Ribbon density too low	Assess impact of blend made from different ribbon densities
Increase in the blend bulk density	Dissolution Content Uniformity	High	Ribbon density too high	Assess impact of blend made from different ribbon densities
Feeder speed too high	Hardness Tablet Weigh variation	High	Variation in die fill due to high speed	Optimise feeder speed and feeder fill
Press speed too high	Dissolution Hardness (if a CQA) Tablet weight Appearance	High	Tablet hardness too low Capping of tablets	Feeder speed and press speed must be optimised to achieve correct weight
Non uniform tablet weight	Content Uniformity	High	Impacted by weight control throughout the compression run	Assess continuity of 6 batches of tablets produced at scale, across batch and compare

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Table 19: **Potentially Important Compression Process Variables and Quality Attributes**

Input Material Attributes	Compression Process Parameters	Tablet Quality Attributes
Blend uniformity Granule surface area Ribbon density Acetriptan particle size	Pre-Compression force Compression force Press speed Feeder speed Feeder fill depth	Appearance Tablet weight Weight uniformity Content Uniformity Hardness Friability Dissolution rate Disintegration time

A series of multivariate analyses, including DoE, was undertaken to investigate the relationship between the input attributes, compression process parameters and output attributes.

Initially a screening DoE (DoE 1) was undertaken to provide an assessment of the impact of the compression process parameters on the tablet quality attributes. The screening study confirmed that feeder speed and feeder fill have no impact on quality over the ranges investigated; therefore, feeder speed and feeder fill depth were eliminated for further studies.

A detailed statistical design of experiments (DoE 2) was then performed to investigate more fully the remaining compression process parameters and identify the target ranges. The DoE looked at the impact of pre-compression force, compression force and press speed on tablet hardness, friability, disintegration time, weight and dissolution. DoE 2 identified output attributes which were then used in a third DoE (DoE 3) to investigate the impact of the ranges of input material attributes identified from the previous unit operations.

4.5.B Compression DoE 2

Although pre-compression force and compression force are listed as process parameters, they are actually dependant on equipment operating variables and the properties of the blend being compressed. Pre-compression force and compression force are a direct function of the distance between upper and lower punch faces, as long as all other factors such as tablet weight and other machine parameters are kept constant. Under these conditions the pre-compression and compression force can be increased by decreasing the distance between punches. The DoE was performed on a rotary tablet press on one batch of blend (prepared with acetriptan particle size of d_{90} = 35micron and with 1.5% magnesium stearate), made from ribbon with relative density in the middle of the target, with tablet weight set at 200mg , press speed varied and all other machine parameters kept constant, in order to allow evaluation of pre-compression and compression force as process parameters.

A central composite design was used comprising 17 runs consisting of three centre points, eight factorial points and six star or alpha points. The upper and lower levels of each variable were chosen to bracket the expected target tableting process parameters. The process parameter ranges investigated are given in **Table 20.**

Table 20: **Process parameters ranges investigated in compression DoE 2**

Compression Process Parameters	Lower	Upper
Pre-Compression Force (kN)	0.3	2.9
Compression Force (kN)	7.4	12.9
Press Speed (tablets per hour)	26000	94000

Results of Compression DoE 2

An ANOVA was used to evaluate whether the factors had a statistically significant effect on each response. Significant factors were selected using stepwise regression, and were included in the model if their p-value was less than 0.05. None of the factors had a statistically significant response for friability, therefore friability will be considered insignificant within the ranges studied. Each of the other responses is discussed below.

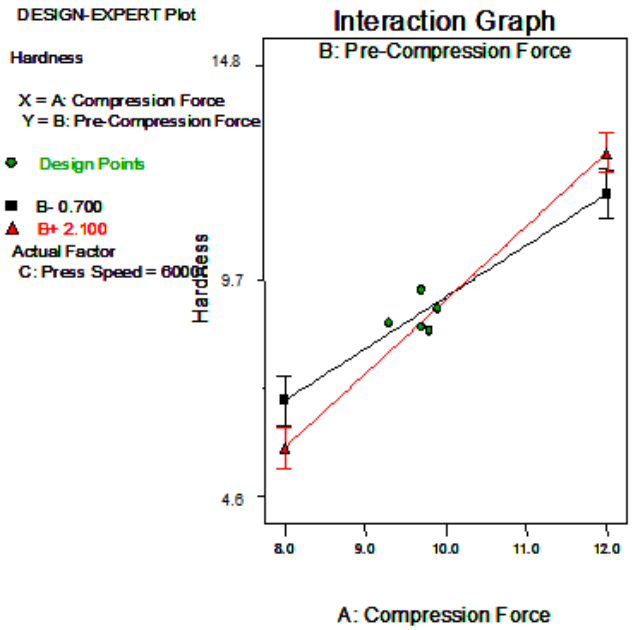
Hardness

The summary of fit and analysis of variance results show that a very good model was obtained for hardness. Compression force is the most important factor impacting tablet hardness, indicated by a high sum of squares value (**Table 21**). Pre-compression force on its own does not have a significant effect on tablet hardness; however the interaction of compression force and pre-compression force is statistically significant. The interaction of press speed and compression force and the squared term for press speed are the other significant factors. The sums of squares for all significant terms, except compression force, are relatively small indicating that they are not major contributors to the model. Although these terms are statistically significant and are included in the model to provide the best fit, from a practical perspective, compression force is the only factor that impacts hardness significantly. The effect of compression force on hardness is shown in **Figure 35**. As expected, an increase in compression force produces harder tablets. The slight interaction of compression force and pre-compression force is also shown in **Figure 35**. At low compression forces, tablet hardness is reduced slightly as pre-compression force is increased. This relationship is reversed at high compression forces.

Table 21: Effect tests for Hardness

Source	DF	Sum of Squares	F Ratio	Prob>F
A:Compression Force	1	142.5	475.4	<0.0001
B:Pre-Compression Force	1	0.016	0.054	0.82
C:Press speed	1	0.299	1.00	0.34
A:Compression Force* B:Pre-Compression Force	1	2.323	7.75	0.019
A :Compression Force*C:Press Speed	1	5.154	17.2	0.0020
C:Press Speed*C:Press Speed	1	3.007	10.03	0.0100

Figure 35: Effect of Compression Force on Tablet Hardness



Dissolution

A very good model was obtained for the relationship between compression force and dissolution at 15 minutes. Compression force and the squared term for compression force are the important factors (**Table 22**). There is a significant decrease in dissolution as compression force is increased (**Figure 36**). Dissolution decreases from 88% at a compression force of 8 kN to 64% at a compression force of 12 kN. As discussed in the previous section, an increase in compression force increases tablet hardness. Harder tablets would be expected to show slower dissolution and a plot of dissolution at the 15 minute time point versus tablet hardness (**Figure 37**) shows that this is indeed the case.

A similar model was obtained for dissolution at the 30 minute time point (**Table 23**). Dissolution drops from 95% at a compression force of 8 kN to 85% at a compression force of 12 kN (**Figure 38**). As seen with the 15 minute dissolution time point, a very good correlation is obtained between tablet hardness and dissolution at 30 minutes (**Figure 39**).

Since dissolution is a critical quality attribute, compression force is a potential critical process parameter because of its significant effect on dissolution. Because of the good correlation between tablet hardness and dissolution, tablet hardness is considered a surrogate for dissolution. Therefore controlling tablet hardness will control dissolution (assuming the API particle size, ribbon density and magnesium stearate levels are appropriately controlled). Models developed as a result of the compression DoEs have been used to set appropriate in-process measurement limits for tablet hardness, to ensure that appropriate dissolution is obtained. Dissolution testing on final product will not be undertaken routinely.

Table 22: Effect tests for 15min Dissolution

Source	DF	Sum of Squares	F Ratio	Prob>F
A:Compression Force	1	1399.5	170.4	<0.0001
A:Compression Force* A:Compression Force	1	126.2	15.4	0.0015

Figure 36: Effect of Compression Force on Tablet Dissolution at 15min

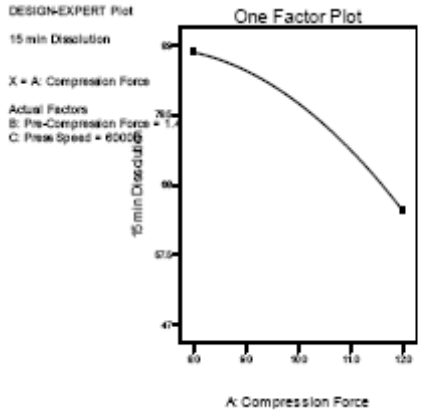


Figure 37: Correlation between Tablet Hardness and Dissolution at 15 Minutes

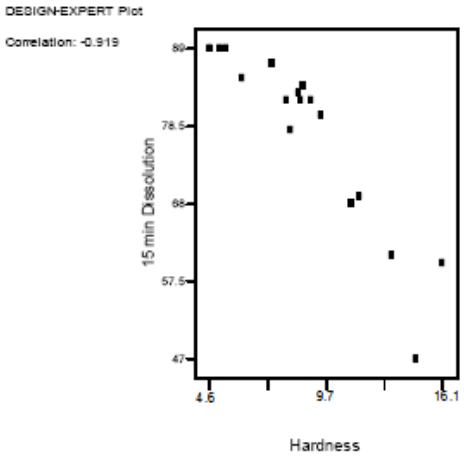


Table 23: Effect tests for 30min Dissolution

Source	DF	Sum of Squares	F Ratio	Prob>F
A:Compression Force	1	246.4	78.1	<0.0001
A:Compression Force* A:Compression Force	1	84.7	26.8	0.0001

Figure 38: Effect of Compression Force on Tablet Dissolution at 30min

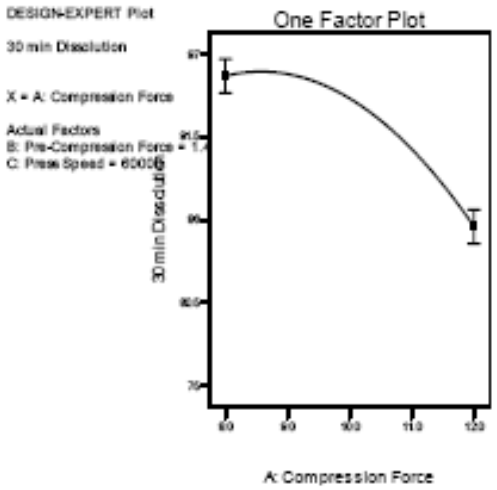
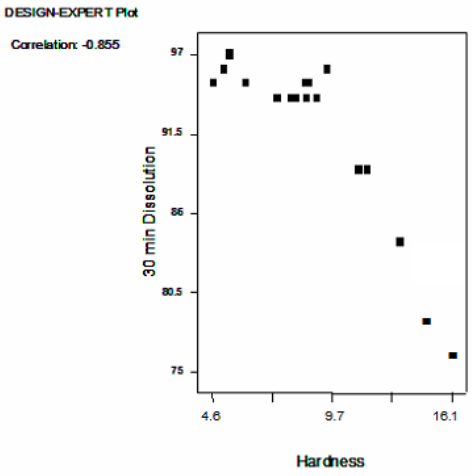


Figure 39: Correlation between Tablet Hardness and Dissolution at 30 Minutes



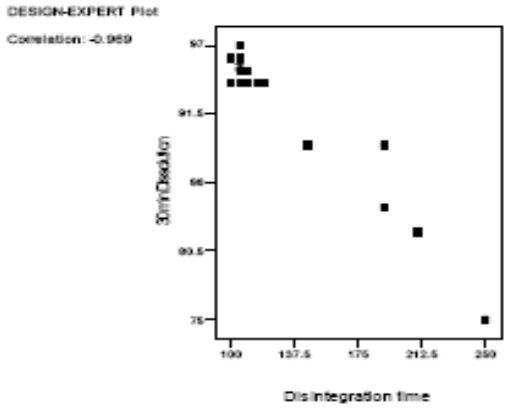
Disintegration Time

A very good model was obtained for disintegration time. As seen with the previous responses, the main factor impacting disintegration time is compression force (**Table 24**). Disintegration time is highly correlated with dissolution at 30min (**Figure 40**).

Table 24: Effect tests for Disintegration Time

Source	DF	Sum of Squares	F Ratio	Prob>F
A:Compression Force	1	14462.2	215	<0.0001
B:Pre-Compression Force	1	47.6	0.71	0.42
C:Press speed	1	431.5	6.42	0.0278
A:Compression Force* A:Compression Force	1	5638.2	83.84	<0.0001
A :Compression Force*B:Pre-Compression Force	1	565.2	8.40	0.0145

Figure 40: **Correlation between Disintegration Time and Dissolution at 30min**



Conclusion from Compression DoE 2

Based on process understanding and risk assessment (utilizing FMEA), compression was determined to be a critical step in the manufacture of ACE tablets. Compression force was identified as a potential critical process parameter, because of its significant impact on the critical quality attribute of dissolution if not adequately controlled. Pre-compression force and press speed are included in some of the models to get a better statistical fit, however their contributions are not significant within the ranges studied.

The compression force required to obtain a particular tablet hardness can be influenced by a number of factors including properties of the blend and equipment parameters, therefore the compression force required to produce tablets with the required hardness could vary from batch to batch and from machine to machine. The equipment parameters are established by controlling the target output attributes for compression, the output attributes are monitored and controlled by in-process measurements,

The results of the compression DoE were used to define the process output attributes for compression presented in **Table 25**. The lower limit of the hardness is based on handling studies. The upper hardness limit is based on achieving acceptable dissolution. For tablets

with 12kP hardness, the compression DoE model predicts tablet dissolution of at least 80% at the 30 minute time point.

During batch set-up the compression force is set at a value that produces tablets which exhibit the target attributes as indicated by the in process measurements. Once the appropriate compression force is established, it is controlled within specified limits by a feedback control loop.

Table 25: Output Attributes for Compression Unit Operation

Process Measurement	Target Properties
Mean core weight 20 cores	194-206mg
Individual core weights	190-210mg
Crushing strength (Hardness) 5 cores	5-12kP

4.5.C Compression DoE 3

DOE 2 established the target attributes (**Table 25** above) which describe the desired output from the compression process. As the compression process is the final unit operation following a number of other process steps, the input to the compression process will have inherent variability, Therefore the impact of process input variables on the output from the compression step was investigated in order to ensure that the tablets produced from the variable inputs met the target ranges for the tablet CQAs.

A DoE study was undertaken to assess the impact of variable inputs on the compression process. The upper and lower level of each variable were chosen to bracket the expected range of process inputs (identified from optimization of the formulation and previous process stages) and target tableting process parameters . The input variables and process parameter ranges investigated are given in **Table 26**. The experiments were performed on a rotary tablet press.

Table 26: Input variables and process parameter ranges investigated

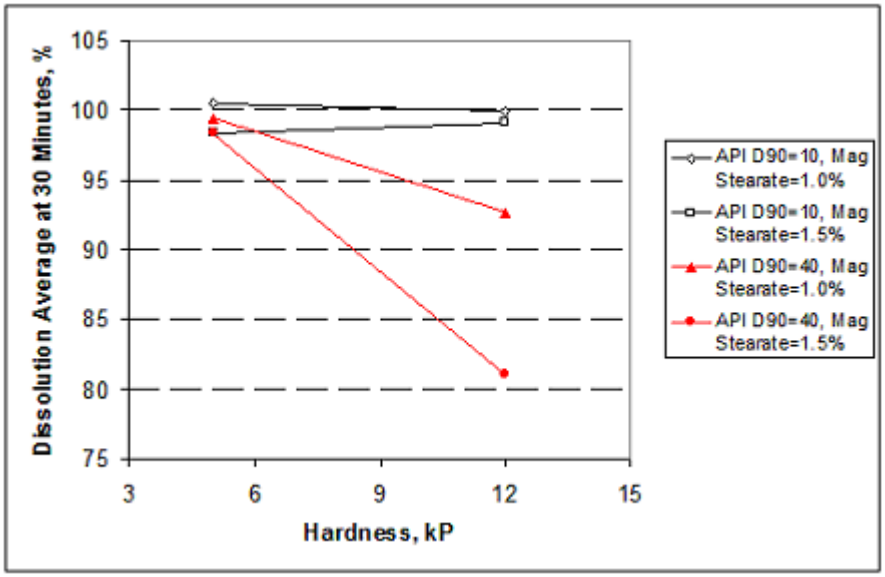
Input Variable and Compression Process Parameters	Lower	Upper
Magnesium Stearate level	1%	2%
Acetriptan particle size (d_{90} - micron)	10	40
Relative ribbon density	0.68	0.81
Granule GSA (cm^2/100g)	12,000	41,000
Hardness (kN)	5	12
Press Speed (tablets per hour)	26000	94000
Pre-Compression force (kN)	0.3	2.9
Compression Force (kN)	as required to achieve hardness limits	

All of these variations reflect the likely variability of inputs which will be experienced during routine manufacture of ACE tablets. The impact of the variable inputs and process parameters on tablet weight, friability, disintegration time, and dissolution was determined.

All tablets produced met the acceptable ranges for the critical product attributes defined in the target product profile. In the target product profile a dissolution limit of not less than 75% in 30 minutes was required. In light of subsequent in vivo data, it is now known that a specification of not less than 80% in 30 minutes is required for dissolution (see Section 4.6, The *in vivo* investigation). From the experiments conducted, and in line with predictions from previous experiments, a reduction in dissolution rate was observed as the acetriptan particle size increased. At high acetriptan particle size and high magnesium stearate level, the dissolution data did not meet the criterion for dissolution of not less than 80% at 30 minutes, confirming the formulation component levels established previously .

Some example plots of dissolution versus hardness are shown in **Figure 41**. The plots show that tablets made from acetriptan with low particle size (d_{90} = 10 micron) show almost constant dissolution across the range of acceptable hardness. For tablets made from acetriptan with larger particle size (d_{90} = 40 micron), the plots show that dissolution reduces with increased hardness but still lies within the acceptable ranges.

Figure 41: Example Plots of Dissolution versus Hardness for Different Tablet Variants



Therefore, it can be concluded that the design space encompasses all the ranges explored in **Table 26**, however the amount of magnesium stearate must be limited (1-1.75% instead of 1-2%) in tablets with high acetriptan d_{90} particle size (35-40 micron).

Additionally it is concluded that, batches of ribbon which exhibit densities towards the lower end of the acceptable specification range require pre-compression forces and compression forces towards the upper end of the ranges described in **Table 27**.

These findings led to definition of example operating conditions described in **Table 27**, which sit within the input variables and process parameter ranges given in **Table 26**. These are operating conditions for the rotary tablet press used in this study which, when complied with, result in the process operating successfully and tablets which meet the required process output for compression are produced.

Table 27: **Example compression process operating conditions**

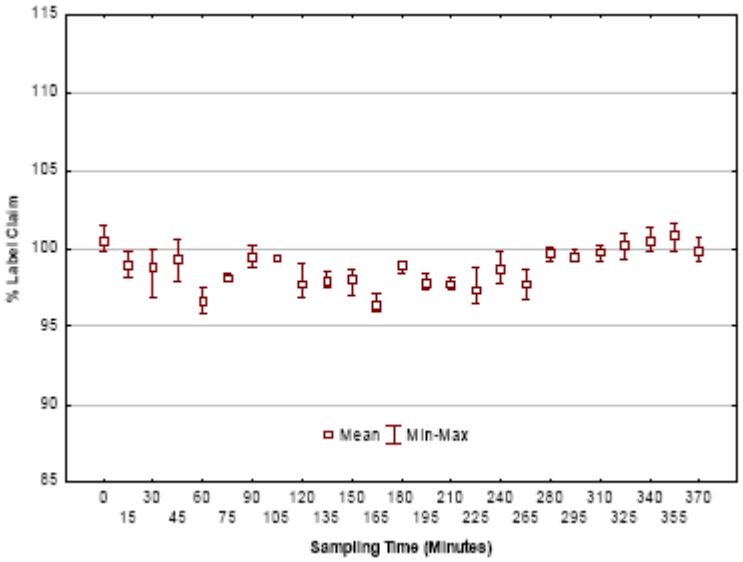
Compression Process Parameters	Relative ribbon density 0.68 to 0.75	Relative ribbon density 0.75 to 0.81
Pre-Compression Force (kN)	1.0 – 2.9	0.3 – 2.0
Compression Force (kN)	9.0 – 13.5	6.8 – 11.0
Press speed (tph)	30000 - 90000	30000 - 90000
Feeder Speed (rpm)	10 - 18	10 - 18

Content Uniformity

The impact of blend uniformity on content uniformity has already been discussed. To ensure content uniformity of the tablets is maintained by control of the tablet weight throughout the duration of the compression process, tablet samples were collected at approximately 15 minute intervals during the compression of six batches of ACE tablets at pilot scale. Samples were taken from a total of 25 sample points for each batch and three tablets from each sample point were analyzed. Data for one batch of tablets is shown in **Figure 42**. The data shows excellent content uniformity that exceeds the current harmonized content uniformity monograph and no trends are observed during the compression run.

The data from the other 5 batches were very similar with the RSD of all individual results being ≤ 1.9% for all six batches.

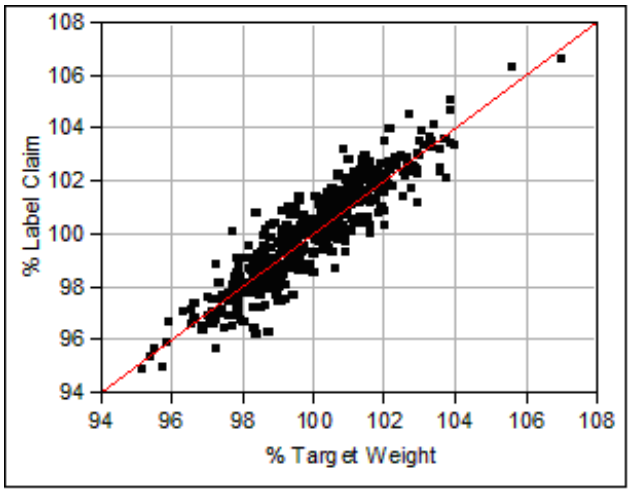
Figure 42: **Tablet Content Uniformity: data plot for one of six tablet batches**



From the data above a plot of %Target Weight versus % Label Claim was produced (**Figure 43**). The plot shows that % target weight correlates with % label claim and indicates that weight can be used as a predictive surrogate for content uniformity.

This work gives additional confidence that tablet content uniformity is being adequately controlled during manufacture of ACE tablets.

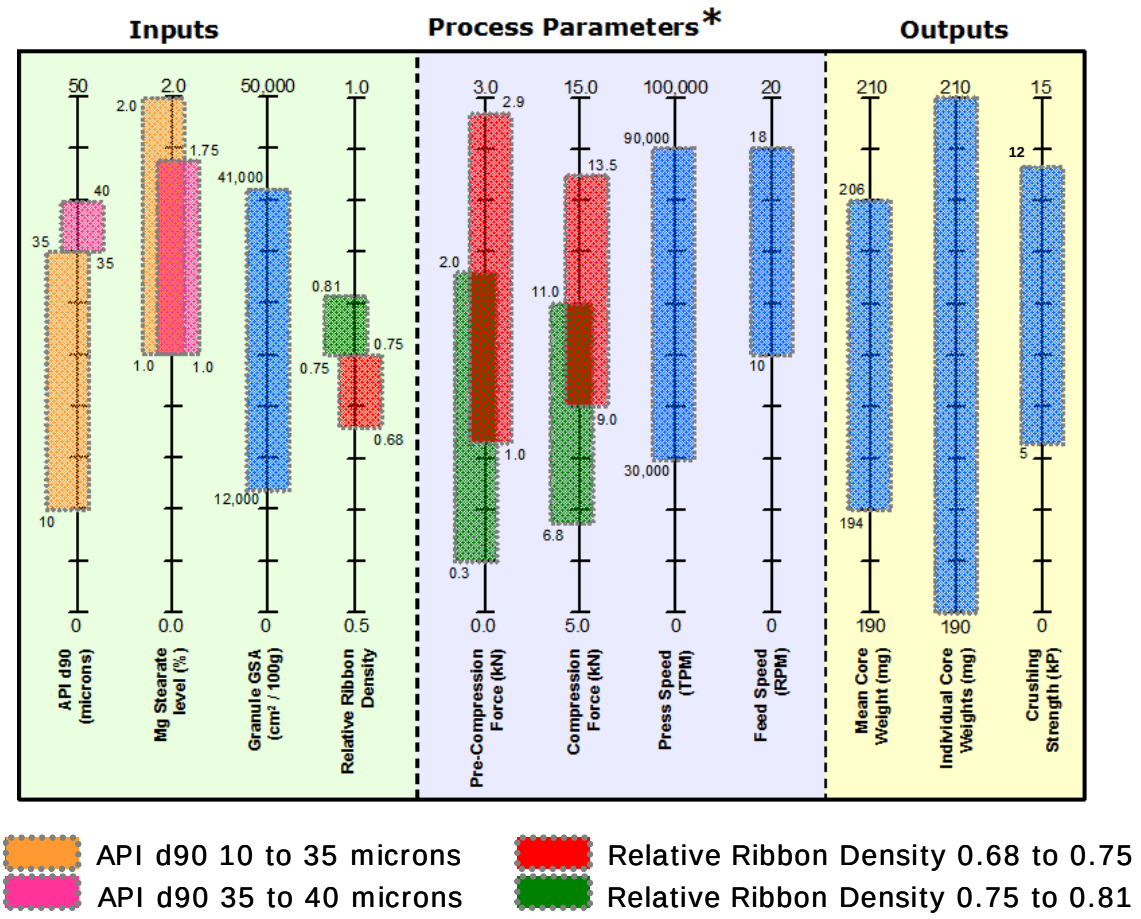
Figure 43: Plot of %Target Weight versus % label Claim



Operating Ranges for Compression

Based on the understanding of compression, appropriate process operating conditions will be determined to accommodate different types of rotary tablet press. These conditions may be different to those exemplified in **Table 27**, but will result in tablets which meet the output attributes for compression given in **Table 25**. The proven acceptable ranges for compression are represented in **Figure 44** below.

Figure 44: Representation of Proven Acceptable Ranges for Compression



* Appropriate process parameters will be determined to accommodate different types of rotary tablet press

Control Strategy for Compression

The control strategy for compression is to maintain the tablet attributes within the required ranges listed in **Table 25**. The target compression force required to produce tablets with acceptable quality attributes is established using the in process measurements at the beginning of the run. The compression force is measured throughout the run and compared to the target compression force. Deviations from the target compression force result in tablet weight corrections by adjusting the fill depth. Upper and lower limits of compression force are set and any tablet that registers a compression force outside these limits is automatically rejected by the tablet press.

Quality Risk Management

In order to confirm sufficiently that the control strategy defined for compression reduces the risk of producing poor quality product and to assess whether any of the process parameters are Critical Process Parameters, the risk assessment (FMEA) was repeated. **Table 28** below shows the FMEA updated for the high risk attributes and parameters

identified previously, based on the process understanding gained and control strategy defined. For all the parameters and attributes identified the risk to product quality is now low, therefore the process parameters are not considered to be Critical Process Parameters and the input material attributes are not Critical Quality Attributes, though the parameters and attributes still must be controlled.

Table 28: **Updated Compaction FMEA**

Potential Risks	DP potential CQA impacted	RPN	Recommended Actions	Comments
Pre Compression/ Compression force too high	Dissolution Hardness (if a CQA)	Low	Compression force is set based on in process measurements and then controlled by feedback control loop	Likelihood of compression force being set too high is low, and will be monitored throughout the run to maintain desired level. Occurrence and detection reduced so not critical
Pre Compression/ Compression force too low	Dissolution Hardness (if a CQA) Appearance	Low	Compression force is set based on in process measurements and then controlled by feedback control loop	Likelihood of compression force being set too low is low, and will be monitored throughout the run to maintain desired level. Occurrence and detection reduced so not critical
Decrease in the blend bulk density	Dissolution Content Uniformity	Low	Ribbon density measured and controlled during roller compaction, compression process can cope with extremes of ribbon density	Likelihood of blend with low bulk density is minimal. Not critical.
Increase in the blend bulk density	Dissolution Content Uniformity	Low	Ribbon density measured and controlled during roller compaction, compression process can cope with extremes of ribbon density	Likelihood of blend with high bulk density is minimal. Not critical.
Feeder speed too high	Hardness Tablet Weight variation	Low	PAR of feeder speed identified. Tablet weight monitored throughout the run.	Tablets not meeting weights requirements are automatically rejected. Not critical.
Press speed too high	Dissolution Hardness (if a CQA) Tablet weight Appearance	Low	PAR of press speed identified.	Tablet hardness too low Capping of tablets
Non uniform tablet weight	Content Uniformity	Low	Tablet weight is monitored throughout the compression run and out of range tablets are rejected	Six batches of tablets produced at scale showed acceptable RSD for tablet content uniformity.

4.6 The In vivo investigation

4.6.A Rationale for study ACEPK0015

Prior knowledge of the properties of acetriptan and the drug product manufacturing coupled with quality risk assessment identified drug substance, formulation and process attributes that could be critical to the final quality and performance of the product. These attributes were:

1. API particle size
2. Ribbon density
3. Levels of magnesium stearate (lubricant)

In order to understand the potential clinical relevance of these attributes, an *in vivo* clinical pharmacokinetics study (ACEPK0015) was conducted with five tablet variants that were manufactured using a range of parameters representative of these critical quality attributes. The selection of these variants was based on prior product knowledge, a number of detailed quality risk assessments, and screening using the dissolution method.

The second aim of this investigation was to establish a relationship between *in vitro* dissolution and clinical bioavailability, with the possibility of establishing an *in vitro in vivo* correlation (IVIVC). The dissolution method is believed to be capable of mechanistically differentiating between tablets manufactured using extremes of process and formulation parameters. However, by following the IVIVC approach, it is envisaged that this dissolution test would be used as a surrogate to pharmacokinetic studies in assuring clinical quality of ACE tablets.

4.6.B Clinical pharmacokinetic study (ACEPK0015)

The variants dosed in the clinical pharmacokinetics study ACEPK0015 encompassed a range of processing and formulation parameters and were selected with the objective of achieving the greatest mechanistic understanding of the *in vivo* performance of the ACE tablets. These variants were:

A. Standard clinical ACE tablet: standard conditions and API D_{90} = 10 µm
B. Standard clinical ACE tablet: standard conditions and API D_{90}= 40 µm
C. Standard clinical ACE tablet: Process variant: highest ribbon density = 0.81
D. Formulation variant: API D_{90} = 10 µm, 2.25% MgSt, ribbon density = 0.81, 3% CCS
E. Worst-case variant: API D_{90} = 40 µm, 2.25% MgSt, ribbon density = 0.81, 3% CCS

These tablet variants were selected based on the understanding of the mechanism of dissolution retardation and represent the upper limit of the formulation and process parameters, and hence the worst-case scenario in terms of impact of dissolution and

bioavailability. Variant B was manufactured using the upper-limit drug substance particle size of 40 µm, and the knowledge that a larger particle size could affect in-vivo performance. Variant C was manufactured from granules manufactured using the upper limit ribbon density of 0.81, based on the knowledge that increasing the ribbon density will reduce the dissolution rate. Variant D was selected because of the reduced level of disintegrant, ribbon density of 0.81 and increased lubricant levels could impact in vivo performance. Finally, variant E represents the combination of all the particle size, formulation and process limits that demonstrates the edge of knowledge of the ACE drug substance and product. All five, tablet variants were compressed to a hardness of 12 kP.

The clinical pharmacokinetic study was conducted in a complete crossover design; 12 subjects were enrolled in the study whereby each subject received all five, tablet variants and a non-precipitating co-solvent based oral solution. The oral solution was dosed as a reference to allow the calculation of the *in vivo* dissolution/absorption vs. time profiles of acetriptan by deconvolution, and to investigate any potential *in vitro-in vivo* correlation (IVIVC). The quantitative and qualitative composition of variants A, B and C is identical. The composition of the 5 tablets is summarised in **Table 29**.

Table 29: Composition of ACE 20mg Tablets used in Study ACECPK00015

Variant	A, B, C	D, E	
Formulation Component	**Mg/tablet (w/w%)**	**Mg/tablet (w/w%)**	**Function**
Acetriptan	20 (10%)	20 (10%)	Drug substance
Microcrystalline cellulose	80 (40%)	80 (40%)	Diluent
Croscarmellose Sodium	8 (4%)	6 (3%)	Disintegrant
Magnesium stearate			Lubricant
intragranular	2 (1%)	4 (2%)	
extragranular	0.5 (0.25%)	0.5 (0.25%)	
Lactose monohydrate	79.5 (39.75%)	79.5 (39.75%)	Diluent
Talc	10 (5%)	10 (5%)	Glidant
Core tablet weight	200 mg	200 mg	

4.6.C Results

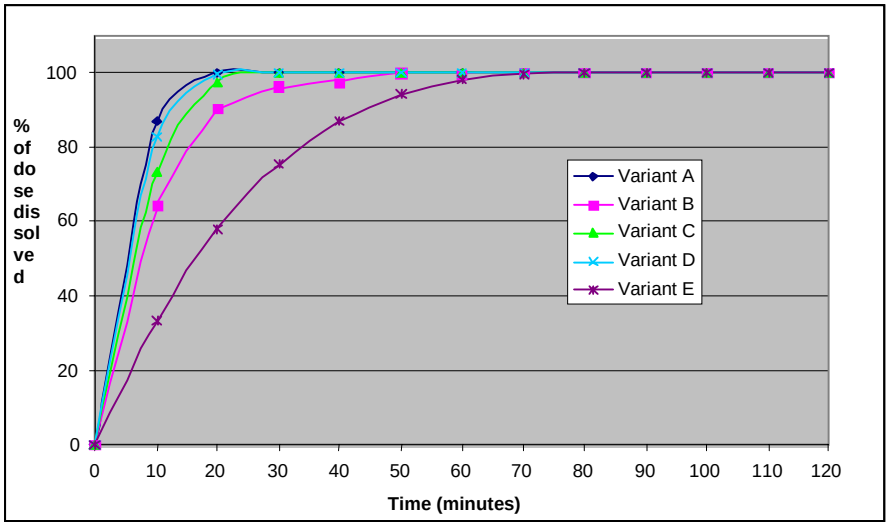
In vitro dissolution

Prior to study ACEPK0015, the *in vitro* performance of variants A-E was evaluated using the previously described 1.0% SLS dissolution method, with sampling at 10-minute

intervals. This dissolution method was shown to discriminate between the various tablet variants produced.

The dissolution experiments (**Figure 45**) demonstrate that the dissolution method is capable of differentiating between different variants manufactured using a wide range of parameters that are thought to impact *in vitro* dissolution of ACE tablets by a variety of mechanisms. As such, the dissolution method can be used to monitor changes to potential critical product attributes.

Figure 45: Average dissolution of all 5 tablet variants in the 1% SLS method



In vivo investigation (ACEPK0015)

Twelve healthy subjects from a single centre completed all 6 dosing periods. The pharmacokinetics results ($AUC_{0-\infty}$, C_{max}, $t_{max,}$ and $t_{1/2}$) are summarized in **Table 30**.

Table 30: Mean Pharmacokinetic Parameters for the ACE Tablet Variants ($AUC_{0-\infty}$, C_{max}, t_{max} and $t_{1/2}$) all represented as Geometric Mean Values

Dosing period	N	$AUC_{(0-\infty)}$ (µg.h/mL) Geomean (%CV)	Rel AUC	C_{max} (µg/mL) Geomean (%CV)	Rel C_{max}	t_{max} (hr) Median	$T_{1/2}$ (hr) Geomean (%CV)
Oral Solution (reference)	12	8.659 (22.30)	--	0.2504 (29.37)	--	1.33	24.01 (18.36)
Variant A	12	8.450 (17.56)	0.97	0.2414 (18.36)	0.96	1.37	23.98 (26.99)
Variant B	12	8.077 (22.62)	0.93	0.2299 (24.74)	0.92	1.55	25.59 (19.66)
Variant C	12	8.359 (23.02)	0.96	0.2320 (15.77)	0.93	1.67	23.12 (22.75)
Variant D	12	8.256 (25.67)	0.95	0.2379 (15.55)	0.95	1.68	24.98 (22.62)
Variant E	12	7.010 (20.71)	0.90	0.2153 (28.3)	0.86	2.50	21.50 (24.54)

Following a single oral dose of 20 mg of ACE oral solution, C_{max} was achieved at a median of 1.33 hours, with similar values observed for variants A to D. Statistical evaluation of these data using from study ACEPK0015 the T-test at 95% CI ($p<0.05$) demonstrate the following key observations:

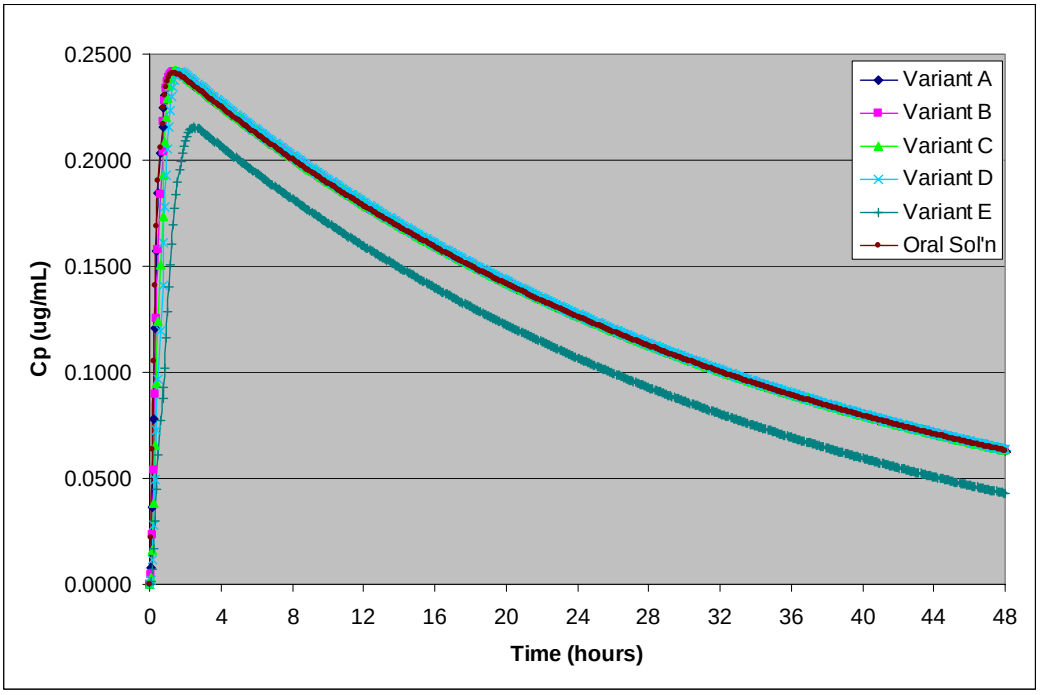
1. C_{max} and AUC values for variants A to D and the oral solution were similar
2. C_{max}, AUC and T_{max} of tablet variants A to D were similar
3. C_{max}, AUC and T_{max} for variant E was different from all other variants and its pharmacokinetic properties are considered unacceptable for this indication.

4.6.D Exploration of an *in vitro-in vivo* correlation for ACE tablets

These observations support the findings in the formulation study, which demonstrated an interaction between acetriptan particle size and magnesium stearate levels. At a hardness of 12 kP, variant E gave unacceptable *in vivo* performance in that its T_{max} was longer than the target product profile. The remaining 4 variants have very similar *in vivo* performance.

Based on the evidence provided in this section, the development of an IVIVC was not attempted. In terms of *in vitro* dissolution, variant E had an average dissolution rate of 75.22% in 30 minutes, and hence the specification requirement of dissolution rate of Q = 80% in 30 minutes for all units was set to ensure the suitability of ACE tablets.

Figure 46: Average plasma concentration-time profiles (0 to 48 hrs) for 20 mg ACE IR variants and oral solution (geomean, n=12)



In summary, the *in vitro* dissolution test was able to differentiate between various processing and formulation parameters. Therefore, the revised dissolution specification of Q = 80% provides a threshold to discriminate between suitable and unsuitable variants.

4.7 Summary Control Strategy for the ACE Tablets Manufacturing Process

4.7.A Overview

ACE tablets will routinely be the subject of 'Real Time Release' wherein the final product quality is ensured though operation within the approved design space. The control strategy presented in this section will ensure that input attributes and process parameters are maintained within the approved design space and hence that the product meets specification without recourse to end product testing. The finished product specification is given in Section 8 and final product would meet this specification if tested. Only in the case of instrument failure will reversion to end product testing supported by a statistically appropriate sampling plan occur.

The development activities have led to an enhanced level of formulation and process understanding of critical operations. An initial assessment of each unit operation was made using tools such as IPO and Fishbone diagrams, to identify potential variables that could impact product quality. A risk assessment was undertaken to identify the variables that should be studied further, to fully understand their impact on product quality. Multivariate analysis was used to understand the relationship between the variables and the drug product quality attributes. A control strategy was then defined to ensure that the output of the unit operation met the requirements of onward processing steps and the drug product CQAs. The initial overall risk assessment updated in line with the process understanding obtained is given in **Table 31**.

Table 31: Overall Risk Assessment Updated in line with Process Understanding Developed

	Variables and Unit Operations					
DP CQAs	**Formulation Composition**	**Blending**	**Roller Compaction**	**Milling**	**Lubrication**	**Compresssion**
Appearance	Low	Low	Low	Low	No. of revolutions	Control of tablet hardness
Identity	Low	Low	Low	Low	Low	Low
Assay	Low	Low	Low	Low	Low	In line control of tablet weight and tablet weight uniformity
Impurities	Excipient Compatability	Low	Low	Low	Low	Low
Content Uniformity	Choice and level of Excipients and excipient particle size	Blend uniformity controlled by NIR	No issue within the ranges studied	Granule SA controlled	Low	In line control of tablet weight and tablet weight uniformity
Dissolution	API particle size, choice and level of excipients	Low	Ribbon Density controlled by NIR	Granule SA controlled	No. of revolutions	Control of tablet hardness

Low risk based on prior knowledge
Control Strategy applied to high risk to mitigate risk
High risk

Table 32 summarizes the overall design space for ACE tablets. The first part of the table illustrates that formulation component adjustment may be made to account for the particle size distribution of the ingoing API. The design space elements for the blending and roller compaction are based largely on ensuring that the output material attributes are within pre-defined ranges of blend uniformity and relative ribbon density. There are no design space elements proposed for the lubrication step as it has been shown to be non-critical. The compaction process can accommodate the range of input variables from the previous

unit ops and the compaction process parameters are adjusted to ensure the output material attributes of hardness and weight meet the pre-defined ranges.

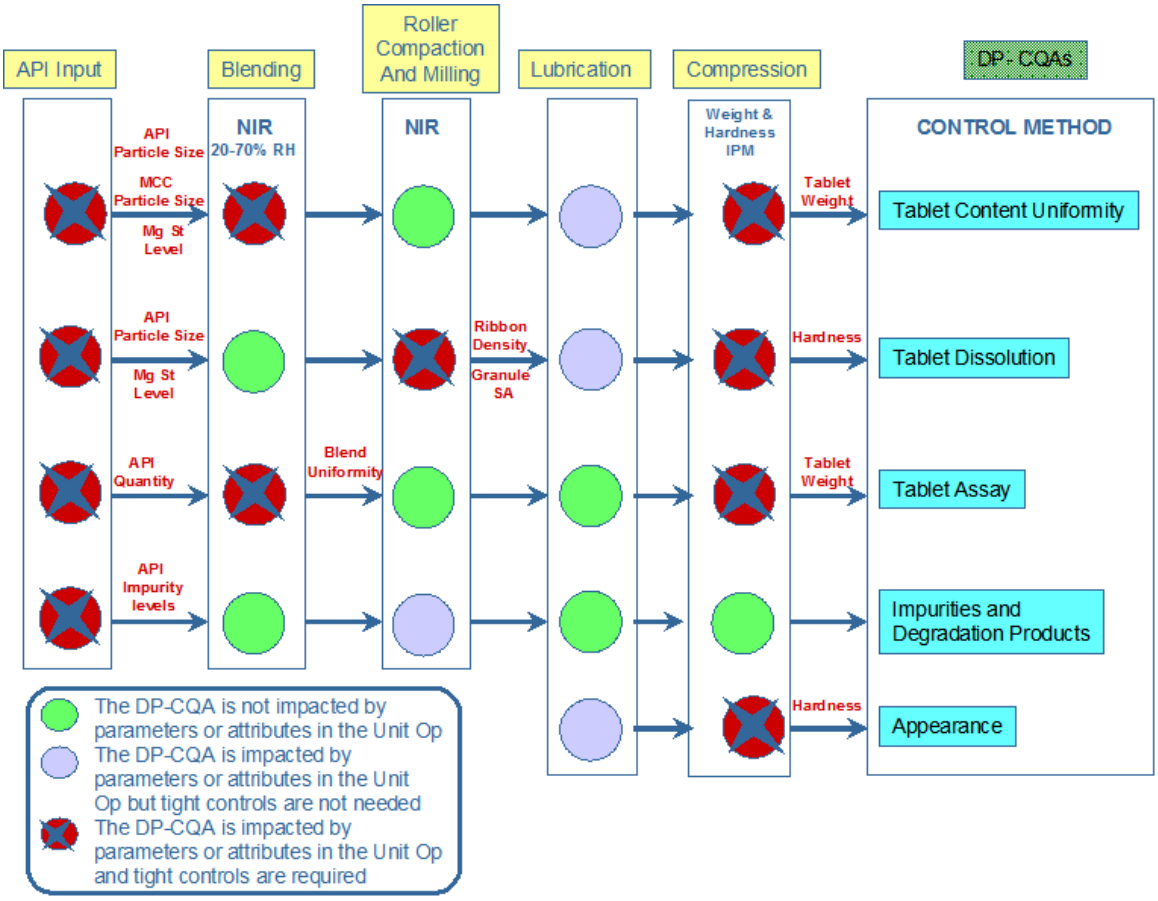
Table 32: Summary of overall Design Space for ACE tablets

Formulation, blending, compaction and milling parameters		
Acetriptan particle size	d_{90} 10-35 microns	d_{90} 35-40 microns
Acetriptan concentration	10%	10%
Microcrystalline cellulose (MCC)	40% (intragranular)	40% (intragranular)
MCC particle size (d_{50})	30 - 90 micron	30-90 micron
Croscarmellose level	3-4%	3-4%
Lactose monohydrate	38.75 - 40.75%*	39.00 – 40.75%*
Lactose particle size (d_{50})	70 – 100 micron	70 – 100 micron
Talc	5%	5%
Mg Stearate level	1-2% (intragranular) 0.25% (extragranular)	1-1.75% (intragranular) 0.25% (extragranular)
Blender	Any diffusive blender	Any diffusive blender
Humidity	20-70% RH	20-70% RH
Relative ribbon density	0.68-0,81	0.68-0.81
Granule GSA (cm^2/100g)	12,000-41,000	12,000-41,000
Hardness (kN)	5 -12	5-12
Mean core weight 20 cores	194-206mg	194-206mg
Individual core weights	190-210mg	190-210mg
Scale	Any	Any
Site	Any certified site using equipment of same principles	Any certified site using equipment of same principles
*Quantity adjusted to compensate for amount of croscarmellose sodium and/or magnesium stearate used in order to ensure 200mg overall tablet weight.		

The control strategy is designed to ensure that the manufacturing process operates reproducibly within the above design space. **Figure 47** provides a high level overview of

the control strategy developed for ACE tablets. The diagram shows which unit operations impact each drug product CQA, the control points, control method and the intermediate quality attributes controlled.

Figure 47: Control Strategy for CQAs for ACE Tablets



4.7.B Unit Operation Control Strategy

An overview of the control strategy for each critical unit operation is described below. The control strategy for each unit operation assumes that the control strategy for all previous unit operations has been followed.

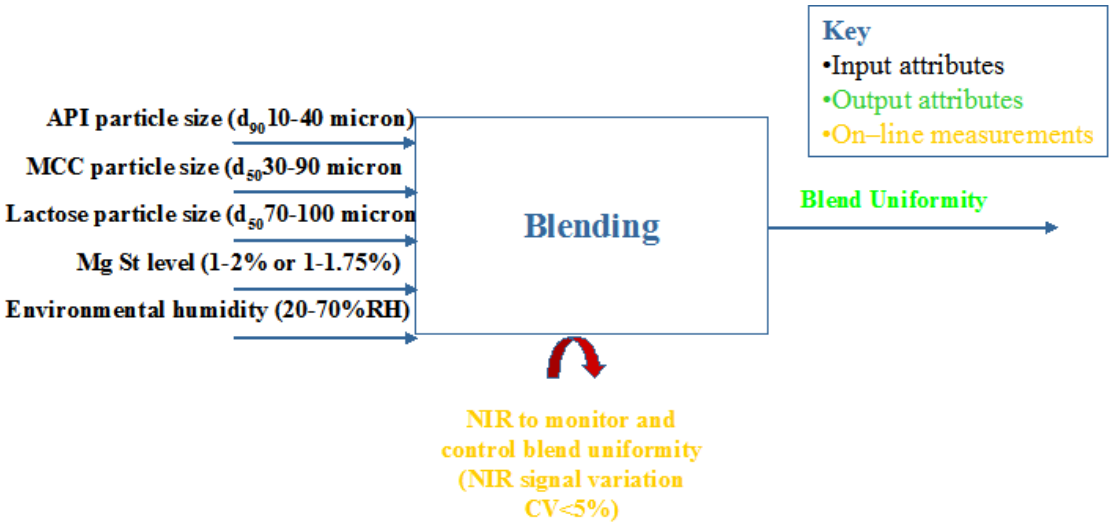
Blending

The control strategy for blending is summarized in **Figure 48** below. The parameters that can significantly affect the blending process are environmental humidity, particle sizes of the API, microcrystalline cellulose and lactose and magnesium stearate level. It is proposed that NIR be used for routine determination of the endpoint of the blending process. Because NIR monitoring of the blend uniformity ensures that adequate mixing is performed, it obviates the need to specify any of the input process parameters such as

rotation speed, time, scale, excipient sources, environmental humidity or equipment (provided a diffusive blender is employed). The blend operation will be terminated when blend uniformity is first achieved, as indicated by NIR, to avoid segregation.

However, in the event of the NIR instrument failing, where acetriptan of a previously used particle size is employed, the input parameters recorded in previous batches will be used for blending. Release of the finished batch will then require appropriate sampling followed by end product testing according to the approved specification.

Figure 48: **Control Strategy for Blending**

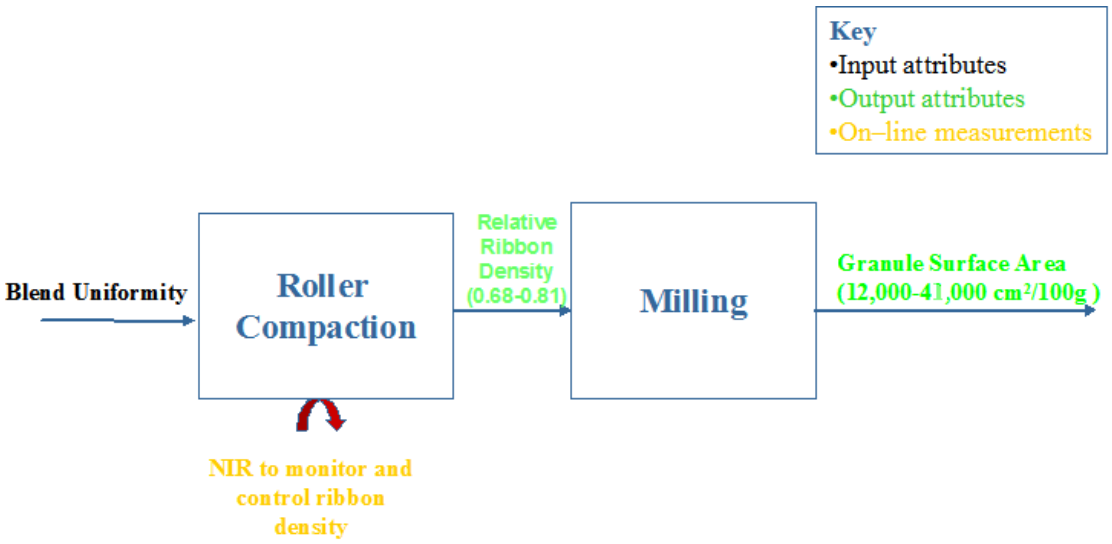


Roller Compaction and Milling

The control strategy for roller compact is summarized in **Figure 49** below. The control strategy is based on producing ribbon with relative density 0.68 to 0.81, in order to deliver acceptable tablet attributes of hardness and dissolution. NIR is used as a real time surrogate measure for ribbon density to detect any variability, with manual or automated intervention as required to alter the process to achieve the required ribbon density.

For milling the mill screen size and speed will be selected to ensure that the Granule Surface Area remains within the proven ranges (12,000-42, 000 cm^2/100g).

Figure 49: Control Strategy for Roller Compaction



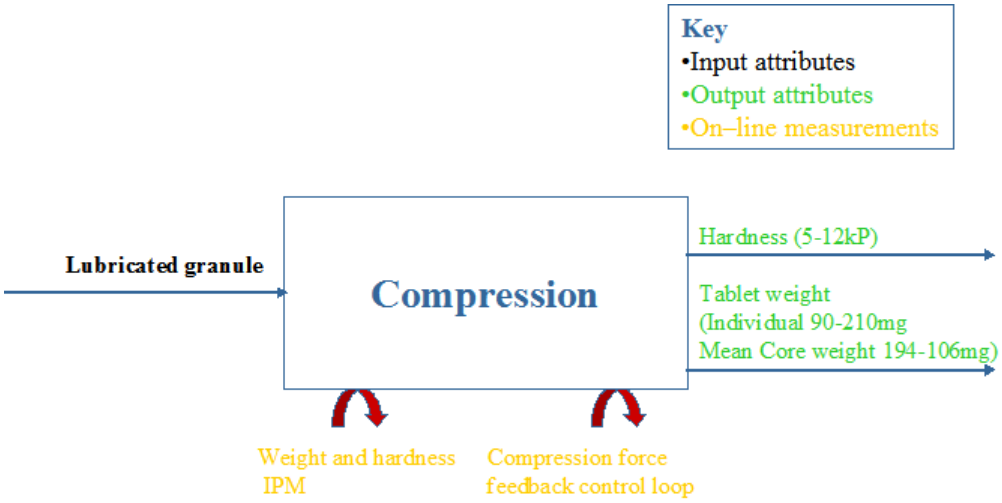
Lubrication

Since NIR on the blender is not capable of fully measuring the lubrication process (i.e. over-lubrication), a traditional method (fixed blending range based on a number of revolutions) is used to establish the end-point of blending.

Tablet Compression

The control strategy for compression is summarized in **Figure 50**. The control strategy for compression is to maintain the tablet attributes of hardness and tablet weight within the required ranges. The target compression force required to produce tablets with acceptable quality attributes is established using the in process measurements at the beginning of the run. The compression force is measured throughout the run and compared to the target compression force. Deviations from the target compression force result in tablet weight corrections by adjusting the fill depth. Upper and lower limits of compression force are set and any tablet that registers a compression force outside these limits is automatically rejected by the tablet press.

Figure 50: Control Strategy for Compression



4.7.C Control of Drug Product Critical Quality Attributes

The control strategy for each drug product critical quality attribute is detailed below.

Appearance

Tablet appearance is impacted primarily by the compression process. The compression process is controlled by maintaining the tablet hardness and weight within the specified limits. This is achieved through control of compression force and weight throughout the compression run using a feedback control loop.

Identity

Controlled at the synthesis stage, see section S.2., and by GMP.

Assay

Tablet assay is impacted by the amount of acetriptan that is added at the mixing and blending stage and the tablet weight following compression.

The quantity of acetriptan added is adjusted based on the acetriptan assay, acetriptan assay is controlled by the acetriptan syntheses and the control strategy is described in section S.2.

Tablet weight and weight uniformity are controlled on-line during the compression process by a feedback control loop.

Impurities (Degradation Products)

The impurities resulting from synthesis are controlled during the acetriptan synthesis and the control strategy is described in section S.2.

The levels of individual and total known and potential degradation products were monitored throughout process development. No increase in degradation products was observed in ACE tablets, in comparison to the input acetriptan. Based on the evidence of stability during manufacturing, testing for degradation products will not be performed at release.

Tablet Content Uniformity

The attributes that must be controlled to control the tablet content uniformity are API particle size, microcrystalline cellulose particle size, lactose particle size and magnesium stearate level, blend uniformity following blending and tablet weight and tablet weight uniformity on compression.

Acetriptan particle size is controlled within specified limits, the control strategy for API particle size is discussed in section S.2.

Microcrystalline cellulose particle size is controlled by the microcrystalline cellulose specification.

Lactose particle size is controlled by the lactose specification.

The intra-granular magnesium stearate level is defined based on the acetriptan particle size.

Tablet Content Uniformity is impacted by the mixing and blending step prior to roller compaction. Based on process understanding and risk assessment, the attribute that influences content uniformity has been identified as blend content uniformity. Uniformity of the blend and blending end-point is monitored and controlled by NIR. The blend operation will be terminated when blend uniformity is first achieved, as indicated by NIR, to avoid segregation.

Content uniformity is also impacted by the weight and weight uniformity of the tablets produced following compression. Tablet weight and weight uniformity are controlled on-line during the compression process by a feedback control loop.

Dissolution

The attributes that can impact dissolution have been identified as acetriptan particle size, magnesium stearate level, ribbon density following roller compaction and tablet hardness on compression.

Acetriptan particle size is controlled within specified limits, the control strategy for particle size is discussed in section S.2.

The roller compaction process is controlled by monitoring and controlling the ribbon density using NIR.

The compression process is controlled by maintaining the tablet hardness within the specified limits. This is achieved through control of compression force throughout the compression run using a feedback control loop.

Microbiology

No testing of ACE tablets is deemed to be necessary (see Section 5).

4.7.D Control Strategy Conclusion

Assuming the control strategy, as outlined above, is followed the tablets will be released without recourse to end product testing (Real Time Release).

In the case of failure of any of the on-line monitoring systems, process conditions previously demonstrated to provide satisfactory performance will be used, and a statistically appropriate sampling plan coupled with additional testing will be utilized to ensure the quality of the batch is acceptable..

5. Container Closure System

ACE tablets are packaged into 30cc HDPE bottles containing cotton wadding and a heat-induction seal, closed with polypropylene caps (10 tablets per bottle) and Aclar blisters with push-through foil lidding (20g/cm^2), 6 tablets per blister, and contained within a cardboard carton. Stability data can attest to the suitability of these container closure systems.

6. Microbiological Attributes.

Water activity for ACE tablets was measured on three primary stability batches and all results were below 0.4. A water activity of greater than 0.9 is required for the survival of most pathogenic bacteria and a water activity of greater than 0.6 is the physiological minimum required for the proliferation of any known microorganisms (Baird, R.M., ed., *Microbiological Quality assurance in Cosmetics, Toiletries and Non-Sterile Pharmaceuticals.* Bristol. PA. 121-123)

The excipients used in the manufacture of ACE tablets are tested for microbial growth according to the USP.

Microbiological testing will not be routinely undertaken for ACE tablets due to the extremely low water activity of the product and controls on the incoming raw materials. However, microbiological acceptance criteria are included on the specification for ACE tablets and the tablets would meet this specification requirement, if tested.

7. Summary of the Manufacturing Procedure

7.1 Manufacturing Formula for ACE 20 mg Tablets

The manufacturing formula for ACE 20 mg tablets is presented in **Table 33**. This is reflective of a nominal 100 kg scale. Because roller compaction, milling and compressing are continuous unit operations, batch size is related to the time the equipment is in operation and therefore, a wide range of batch sizes can be made without a change in scale of the equipment. In addition, the design space is presented as scale independent where possible. Although the blending and lubrication unit operations are not continuous, and therefore, different scales of equipment might be used for different batch sizes, the scientific understanding presented, shows that ,provided the defined control strategies are in place, changes to scale should be considered as movement within the design space. Therefore, variation in the scale of product manufacture is considered acceptable, provided that, the operation is conducted within the company's quality systems and the manufacturing control strategy is utilized.

Table 33: Manufacturing Formula for ACE 20 mg Tablets

Ingredients	Quantity per 100 (kg)
Active Substance	
ACE	10.0
Intragranular Excipients	
Microcrystalline Cellulose	40.0
Lactose Monohydrate	38.75-40.75*
Croscarmellose Sodium	3-4
Magnesium Stearate	1-2
Extragranular Excipients	
Magnesium Stearate	0.25
Talc	5.0
Total	100.0

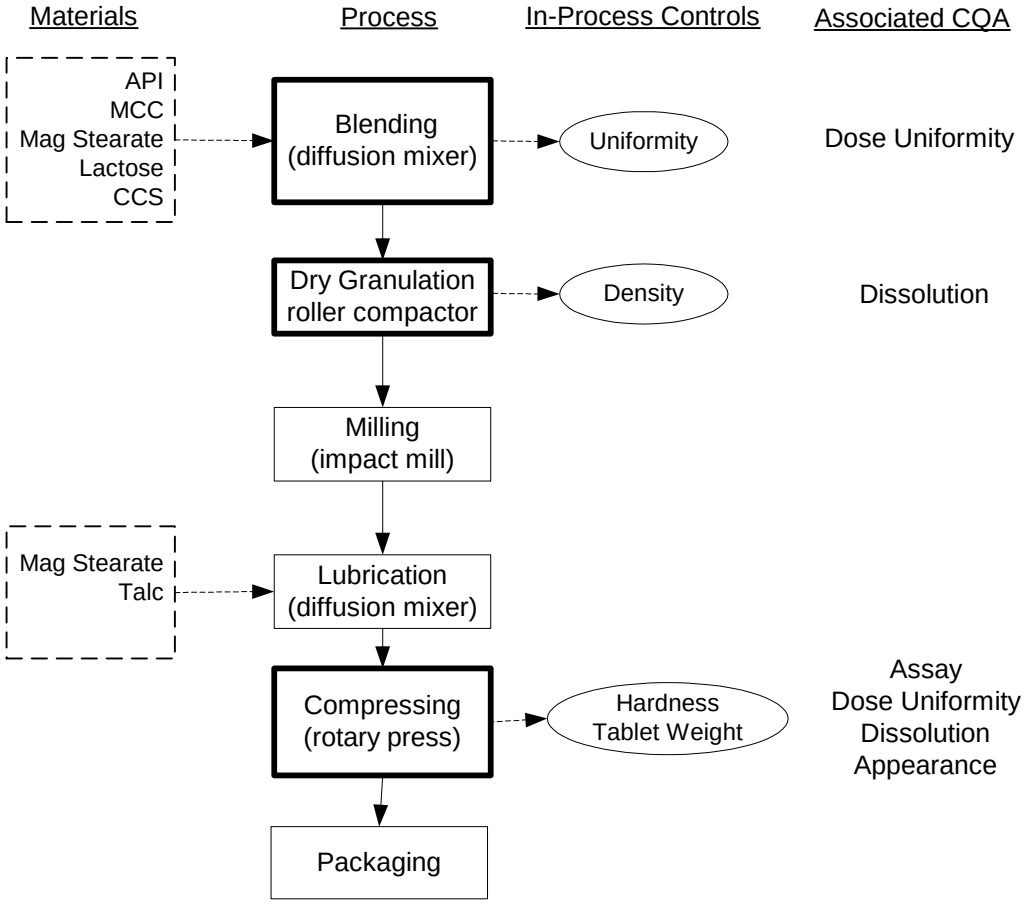
* Quantity adjusted to compensate for amount of croscarmellose sodium and/or magnesium stearate used in order to maintain the same total quantity of material.

7.2 Description of Manufacturing Process and Process Controls for ACE, IR Tablets

Introduction

The following section will describe the manufacturing process for ACE tablets. Each tablet contains 20 mg of Drug Substance (Acetriptan).

7.2.A Process Flow Diagram



Unit operations with bold borders impact critical quality attributes.

7.3 Description of Manufacturing Process

The manufacturing process for ACE tablets can be divided up into 6 separate manufacturing steps. These are: (1) Blending, (2) Dry Granulation, (3) Milling, (4) Lubrication, (5) Compression, and (6) Packaging. The critical steps are blending, dry granulation and compressing. The enhanced process understanding has enabled a design space to be built around these processes and gain operational flexibility in order to facilitate continuous improvement.

Blending

The purpose of the blending step is to produce a homogenous powder mixture of drug substance and excipients that is fed into the downstream dry granulation process. Drug substance and excipients are charged into a diffusion mixer. There is not a specified order of addition. The mixture is blended until homogeneity is obtained and then is stopped to ensure no de-mixing occurs. The environment should be maintained between 20% and 70% relative humidity. Homogeneity will be verified by utilizing an on line spectroscopic technique. The endpoint of the online technique will be a %CV of NMT 5 with a moving window size of NLT 10 revolutions.

Dry Granulation

The purpose of the dry granulation unit operation is to provide material that is suitable for the subsequent compressing operation. Dry granulation is achieved using a roller compactor that produces ribbons of material that are subsequently milled to the desired particle size for compaction. As discussed in Section 4.3, ribbon density is the important attribute of the material during this step. Ribbon density will be maintained within the range of 0.68-0.81. Density is monitored on-line by NIR and is controlled by adjusting the roller pressure.

Milling

The purpose of the milling step is to produce a powder with acceptable flow properties for downstream processing. The ribbon is fed to an impact mill with a screw feeder and is milled through a screen to ensure a granule surface area within the range 12,000 to 41,000 $cm^2/100g$.

Lubrication

The purpose of the lubrication step is to ensure the milled material runs smoothly on the compression machine. There is not a specified order of addition for the talc or magnesium stearate. The product is blended using a diffusion mixer for a targeted number of revolutions (e.g. 75 revolutions)

Compression

The lubricated product is compressed into tablets with a target weight of 200 mg and average hardness between 5-12 kP. After tablets with target weight and hardness are obtained as part of the compressing machine set-up, the distance between the upper and lower punches is fixed and this sets the target compression force. The compression force is measured throughout the compression run and compared to the target compression force and tablet weight for the batch. Deviations from the target weight are corrected by adjusting the fill depth.

7.4 Primary packaging

The tablets are packaged into HDPE bottles with polypropylene caps and Aclar blisters with push-through foil lidding.

8. Control of Critical Steps and Intermediates for ACE Tablets

This section describes the control measurement conducted for each of the identified critical unit operations, the general test methodology and the acceptance criteria. The justification for the information provided in this section is contained in Section 3. Table 34 lists the critical process steps and critical intermediates identified and the controls that are used to mitigate risk to product quality. Should future knowledge indicate that changes are required to these controls, then they will be the subject of an appropriate regulatory filing. The controls of all other steps may be adjusted to ensure that the unit operations produce appropriate output(s): these adjustments will be managed within the company's quality system.

Table 34. Critical Process Steps and associated Intermediates

Unit Operation	Intermediate Attributes	Measurement Methodology	Acceptance Criteria
Blending	Homogeneity	Spectrometric	%CV NMT 5
Granulation	Density	Spectrometric	0.68-0.81 g/cm^3
Tablet Compression	Tablet Hardness Weight	5-tablet measurement On-line Weight Control	5-12 kP Mean of 20 Tablets within 194-206mg

8.1 Control of Drug Product

8.1.A Specification for ACE 20 mg Tablets

The specification for ACE 20 mg tablets is presented in Table 35. The specification relates to the criteria that the product will meet if sampled from the field and then tested. Tablets will not be specifically tested against this specification at the time of manufacture except in the case of failure of the on-line NIR used to measure blend uniformity. The manufacturing control strategy together with the knowledge of how the product changes upon storage ensures that the tablets will meet these criteria through the proposed shelf life.

2281 **Table 35. Specification for ACE 20 mg Tablets**

Test	Acceptance Criteria	Analytical Procedure
Description	White to off-white, round unilaterally convex tablets embossed with ACE and 20	Visual inspection
Identification: Acetriptan free base	Concordant with reference standard.	IR
Content: Acetriptan free base	90.0% – 110.0%	HPLC
Impurities ACE12345 Any other degradation product Total degradation products	 Not more than 0.5% Not more than 0.2% Not more than 2.0%	HPLC
Uniformity of Dosage Unit	Content Uniformity per JP	JP
Resistance to Crushing	5-12kP	Ph Eur
Dissolution	Q = 80% in 30 minutes per USP Acceptance Table 1	USP App 2, HPLC
Microbial Quality: Bacteria Fungi Escherichia coli	Category 3A Not more than 10^3/g Not more than 10^2/g None/g	Ph. Eur.

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