Mock P2 for "Examplain" Hydrochloride
- Draft Discussion Paper-

Overall Objective

*The overall objective of this 'Mock P2' Draft Discussion Paper is to facilitate a scientific and regulatory dialogue between the Industry Association, EFPIA and Regulatory Authorities on the presentation of enhanced product and process understanding in regulatory dossiers, as suggested by **ICH Q8** guideline, Pharmaceutical Development (Step 2) and how this could provide "…opportunities…to develop more flexible regulatory approaches"(ICH Q8).*

*In addition, the document attempts to illustrate how the principles of Quality Risk Management as outlined in **ICH Q9**, Quality Risk Management (Step 2) are applied during the development process and how these principles could be presented in a P.2. section of the CTD format.*

The discussion paper serves as a draft of current industry thinking and to promote discussion and learning between companies, and between EFPIA and Regulatory Authority reviewers and inspectors.

This document is not intended to be taken as the standard for future applications.

Key Aspects

This draft discussion paper attempts to illustrate the following key aspects relating to ICH Q8 and Q9 principles

- *Enhanced Process Understanding/Quality by Design*
  - *To exemplify how modern in- or at-line analytical technologies can assist with process understanding*
  - *To illustrate the type and extent of information that would constitute "…other pharmaceutical development studies that lead to an enhanced knowledge of product performance…" (ICH Q8)*
  - *To illustrate the use of Design of Experiments (DOE) in process development*
  - *To exemplify how multivariate models can be generated and used for prediction*

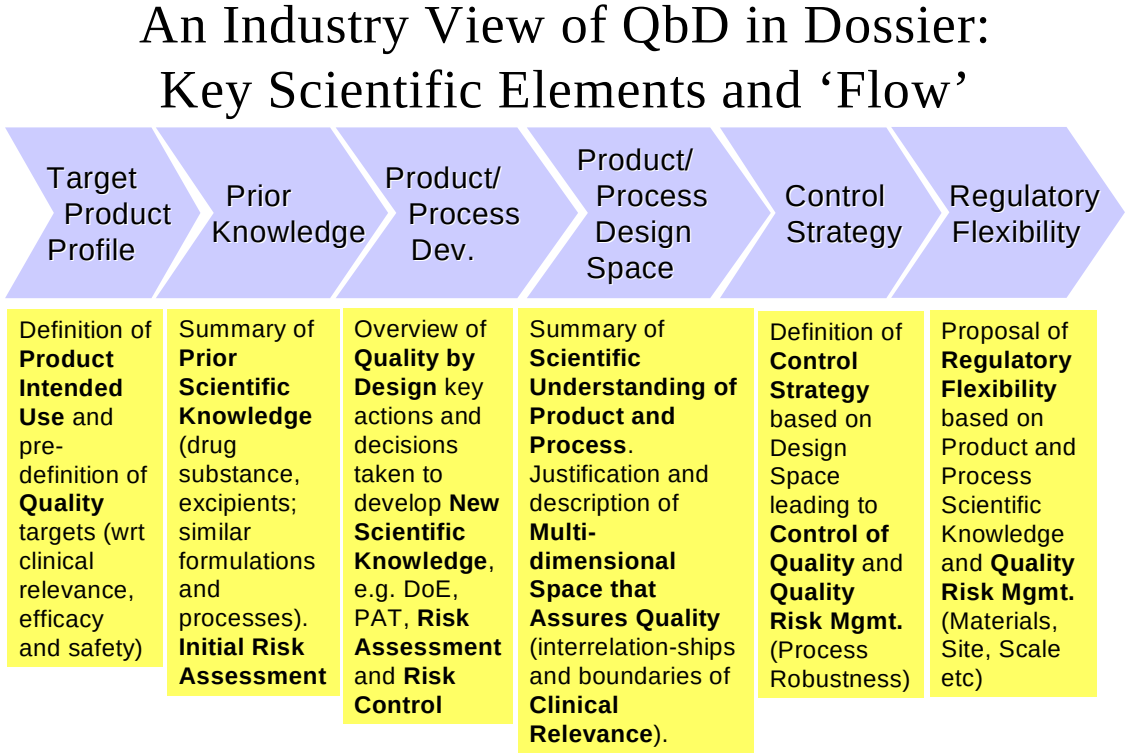
- *Design Space*
  - *How it is established through scientific understanding, including use of multivariant models*
  - *How it could be represented in regulatory submissions*
  - *How it could be linked to process control strategies*

- *Quality Risk Management*
  - *Approach to risk assessment throughout the development process*
  - *Approach to risk management in the design of the control strategy*
  - *Presentation of risk management in a regulatory submission*

'Mock P.2' – Roadmap

This document is not a complete P2 Pharmaceutical Development section. Some sections of the manufacturing process design are only briefly described, and some sections not described at all, which may give rise to perception of incoherence of the technical arguments in parts. The focus has been on those section which are key to the scope of the proposed discussion.

The main purpose is to exemplify some fundamental principles and key concepts using a conventional, wet granulated tablet formulation of a relatively low dose, highly soluble, highly permeable (Biopharmaceutics Classification System Class I) drug substance, which has some potential for degradation. The flow of the discussion is presented in the chart (below) summarising the goals of the development (Target Product Profile) through the development process itself, generation of the proposed design space and associated control strategy, and finally proposed regulatory flexibility.



Moisture content after fluidised bed drying has been identified as a critical attribute, and fluidised bed drying is the critical manufacturing step.

Studies to produce 'design space' for wet granulation and fluidised bed drying are described in detail.

The description of other unit operations and the impact of all unit operations on some quality attributes have not been described.

Additionally and deliberately not all data and risk management steps are presented. These data and records of risk management process would be available at a site for inspection if so desired.

The 'Mock' P.2 is complemented by a 'Mock' P.3.3 excerpt outlining the process control strategy proposed for routine manufacture. It is designed based on the process understanding and risk assessment data generated during the development process.

Section numbering as given in ICH M4Q, The Common Technical Document for the Registration of Pharmaceuticals for Human Use: Quality is followed as far as possible but perhaps not completely accurately.

Science and Risk Based Regulatory Approach - Discussion Points

ICH Q8 (step 2) outlines that demonstration of a high level of formulation and process understanding can provide for maximum regulatory flexibility in the areas of:

- *risk-based regulatory decisions (reviews and inspections)*
- *manufacturing process improvements within the design space described in the dossier without further regulatory review*
- *"real time" quality control, leading to a reduction of end-product release testing*

In this context, the EFPIA PAT Topic Group is seeking feedback and discussion on the following proposals for regulatory flexibility based on the design space, knowledge and understanding exemplified for the granulation and fluid bed drying operations in the 'Examplain' Mock P.2: and summarized as follows:

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	Area for Regulatory Flexibility	***Position Statement***	***Rationale***
1	*Continuous Improvement*	*It is proposed to make manufacturing changes within design space*	*Full understanding of process and use of ICH Q8.*
2	*Real Time Release (RTR)*	*It is proposed that no conventional end product tests be performed routinely*	*RTR is justified based on an extended process control and monitoring scheme which includes traditional and advanced controls and has been designed based on the process understanding and application of risk assessment.*
3	*Process Validation*	*It is proposed that the conventional 3-batch validation is replaced by continuous process verification*	*Assurance is given that each process step (exemplified for granulation and drying) is routinely and reproducibly producing suitable material for the next processing step.*
4	*Changes to Scale and Site*	*It is proposed that changes to scale and site be made without Authority approval, provided the process continues to operate within the design space*	*Process understanding and risk assessment have resulted in the establishment of a 'design space' for fluid bed drying that is transferable to and reproduced for different processing equipment, representing different processing scales, potentially on different sites, and which is linked to the routine control strategy.*

5	*Confirmatory Stability Studies*	*It is proposed not to conduct confirmatory stability studies:* *a) after changes of equipment, scale or site provided the process continues to operate within the design space* *b) for cGMP maintenance purposes* *c) after drug substance manufacturing changes, provided the drug substance has been characterized adequately and complies with the established quality criteria* *Instead, use of product development and process understanding knowledge, linked with risk assessment, will be used to decide what studies to conduct*	*The proposal is based on in-depth scientific understanding of how rate of production of des-ethyl examplain is related to moisture content of tablets at time of manufacture, underpinned by knowledge of water uptake and degradation rates, control of storage of bulk product prior to packing, design of the packaging, long-term stability data on pilot batches and long term data on the first 3 production batches.*

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3.2.P.2 Pharmaceutical Development

INTRODUCTION

Examplain hydrochloride is being developed for the treatment of acute anxiety following regulatory submissions. The proposed commercial formulation for examplain hydrochloride is an uncoated immediate release tablet. A single strength (20 mg as free base) is proposed for commercialisation.

Tablet formulations, of strengths 1, 10 and 20 mg, were initially developed for clinical trials. The low bulk density of the drug substance precluded a directly compressible formulation and consequently a non-complex, high shear wet granulation process followed by compression has been developed. Film coating is not required to improve subjective properties of the tablet, or to provide any additional protection of the product.

Extensive development and process qualification studies have been carried out to evaluate the significance of changing process parameters on the quality and performance of the tablet formulation. These are described in detail in 3.2.P.2.2.1 *Formulation Development* and 3.2.P.2.3 *Manufacturing Process Development*.

The development of the examplain hydrochloride, 20 mg tablet and the associated manufacturing process used prior knowledge from previous products and process development projects. This comprised prior knowledge on the variability with respect to physicochemical and functional properties in all excipients used in the formulation design. In addition, complementary mechanistic understanding of the manufacturing process was obtained through application of PAT (process analytical technology) during process development. A risk analysis (Failure Mode and Effect Analysis, FMEA), in accordance with ICH Q9, was used to establish those process parameters that are likely to have the greatest impact on product quality. Appropriate multivariate experimental plans were designed based on the prior knowledge and the risk analysis.

Processing experience has been gained by manufacturing three batches, at a scale of 25 kg (10% proposed commercial scale), in Tabs'R'Us commercial production site in *Pilltown*. All batches met the predetermined acceptance criteria.

Data from stability studies performed in accordance with ICH guidelines show good stability of the product at intermediate and long-term storage conditions.

The proposed commercial packaging for examplain hydrochloride tablets is clear Aclar UltRx 2000 unit dose blisters. Further information on the packaging is provided in 3.2.P.2.4 *Container Closure System*.

A target product profile for an examplain hydrochloride tablet, 20 mg is given in (Table 1)

Table 1. Target product profile for examplain hydrochloride tablets

Description	Round normal convex uncoated tablet
Identification	Positive for examplain hydrochloride
Assay	20 mg ± 5% examplain free base at time of manufacture
Degradation products	Less than 2% des-ethyl examplain at end of shelf life
Dissolution	Immediate release
Uniformity of dosage units	Meets pharmacopoeial acceptance criteria
Microbiological limits	Meets pharmacopoeial acceptance criteria

This target product profile summarises the quality attributes of the product required to meet the needs for safety and efficacy of the patient. Safety is assured primarily by ensuring that the degradation product, des-ethyl examplain, is less than 2% at the end of shelf life. This limit has been qualified in toxicological studies (reference to Safety section of application) up to a level of 10%. Additionally, application of limits for assay and uniformity of dosage units assure excess drug substance is not administered. The pharmacopoeial ranges for acceptable uniformity of content are much less than that seen for variability of plasma levels seen in patients in Phase 2 and Phase 3 clinical studies, (see Clinical section of this application). Safety is not compromised by administration of a tablet at the highest content allowed by the pharmacopoeial limit since higher doses were administered without safety findings in earlier Phase 1 and Phase 2 clinical studies. Meeting globally-agreed limits for any microbiological contamination, and application of appropriate GMP standards during manufacture assure microbiological quality of this orally administered drug.

Efficacy is assured for this BCS Class I drug substance by application of a dissolution test during development. There is extensive biopharmaceutical literature, which led to the FDA Guidance for Industry-'Biowaver Guidance', CDER 2000, and this work concludes that in vivo availability in patients can be assured by studying in vitro release over the physiological pH range and typically looking for equal to or greater than 85% of drug substance released in 30 minutes. Similar to the safety justification, efficacy is assured by application of a lower limit for uniformity of dosage units.

3.2.P.2.1 Components of the Drug Product

3.2.P.2.1.1 Drug Substance

<This section outlines properties of the drug substance with the potential to influence the manufacture or performance of the drug product.>

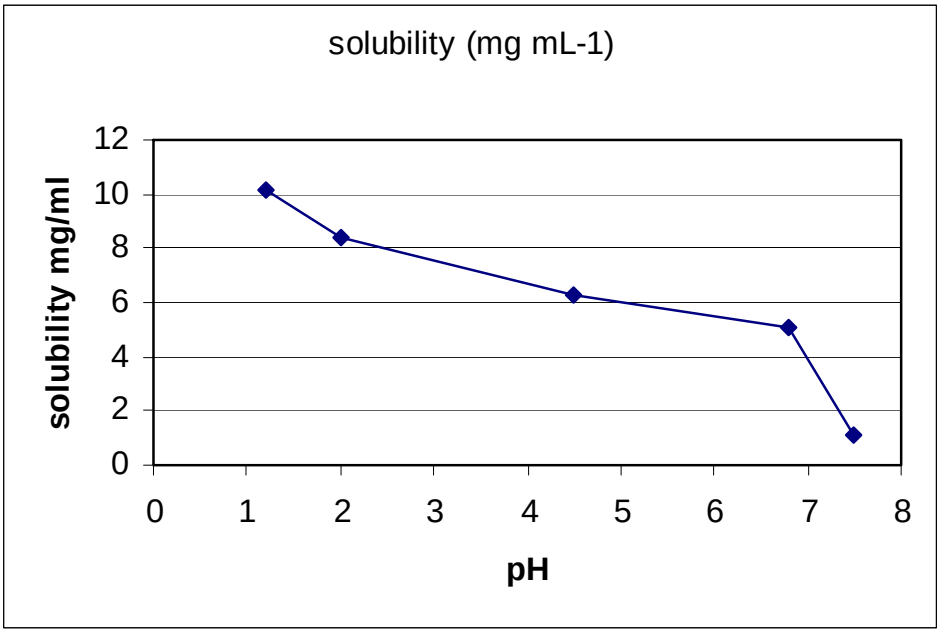
Salt Selection

Examplain free base and a range of salts with pharmaceutically acceptable counterions (including acetate, bromide, chloride and tartrate) were studied to determine the optimum form for development. The hydrochloride salt was selected as it is anhydrous and crystalline with a high melting point and low hygroscopicity. It is also highly water soluble, crystallised with high chemical purity and demonstrated good stability in the solid state.

Solubility

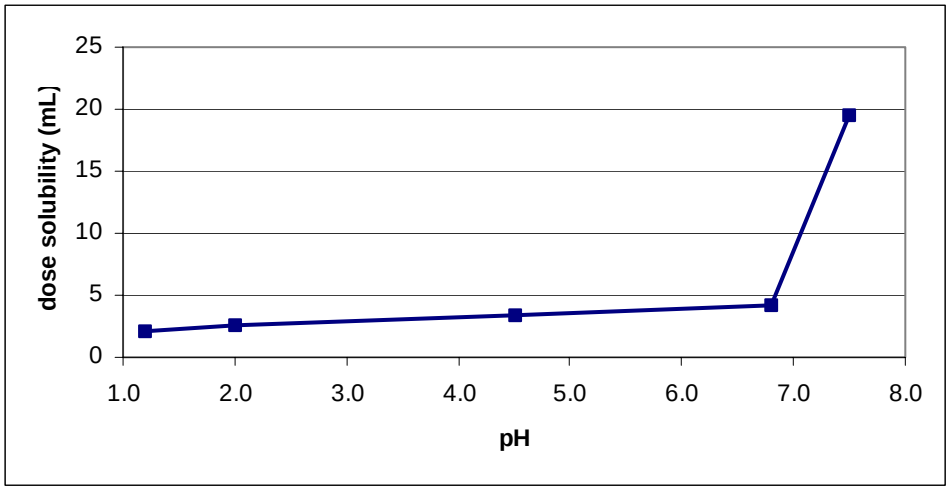
The aqueous solubility of examplain hydrochloride is approximately 5 mg mL^{-1} at 37ºC. The solubility of examplain hydrochloride has also been studied in various aqueous buffer systems across the pH range 1.2-7.5, as shown in Figure 1. As expected, due to the basic nature of examplain (pKa = 10.1 in aqueous solution at 25ºC), the solubility is greatest at low pH values and begins to drop as the pH rises.

Figure 1 - Solubility of examplain hydrochloride in aqueous buffers



(Figure 2) shows the pH dependence of the dose solubility volume of examplain hydrochloride, that is the volume of medium required to dissolve a unit dose (20 mgA[1]). It can be clearly seen that the unit dose is soluble in volume of much less than 250 mL across the physiological pH range, and so examplain hydrochloride can be considered a high solubility compound in the Biopharmaceutics Classification System (BCS).

Figure 2 – Dose solubility plot for examplain hydrochloride in aqueous buffers at 37°C



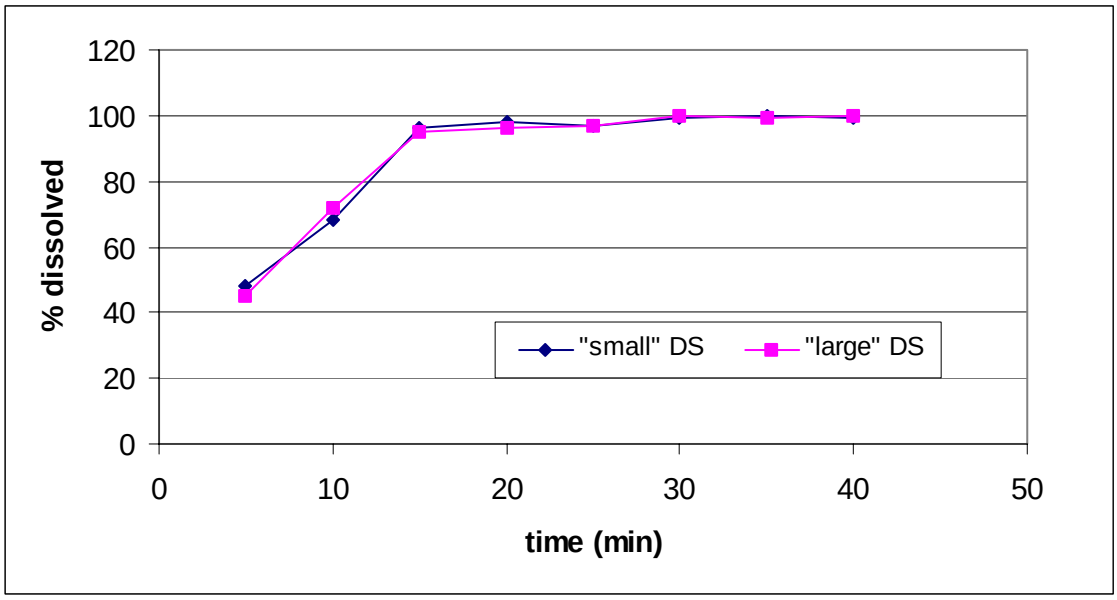
Particle Size

The influence of the particle size distribution of examplain hydrochloride on the processing attributes, homogeneity and *in vitro* dissolution of the tablet have been examined. Examplain hydrochloride drug substance has been produced with a wide range of particle sizes during development and scale-up. The drug substance particle size has been shown to have no significant effect on processing, granule homogeneity or tablet content uniformity (see 3.2.P.2.3 *Manufacturing Process Development*). Tablets manufactured from drug substance with small (d90 < 15 µm, d10 < 5 µm) and large (d90 < 180 µm, d10 < 30 µm) particles showed essentially equivalent dissolution performance (Figure 3)

[1] mgA = mg Active = mg expressed as free base

Figure 3 - Dissolution profiles for examplain hydrochloride tablets made from drug substance with different particle size distributions (pH 6.8, 50 rpm, paddles)

[DS = Drug substance]



Solid State Properties

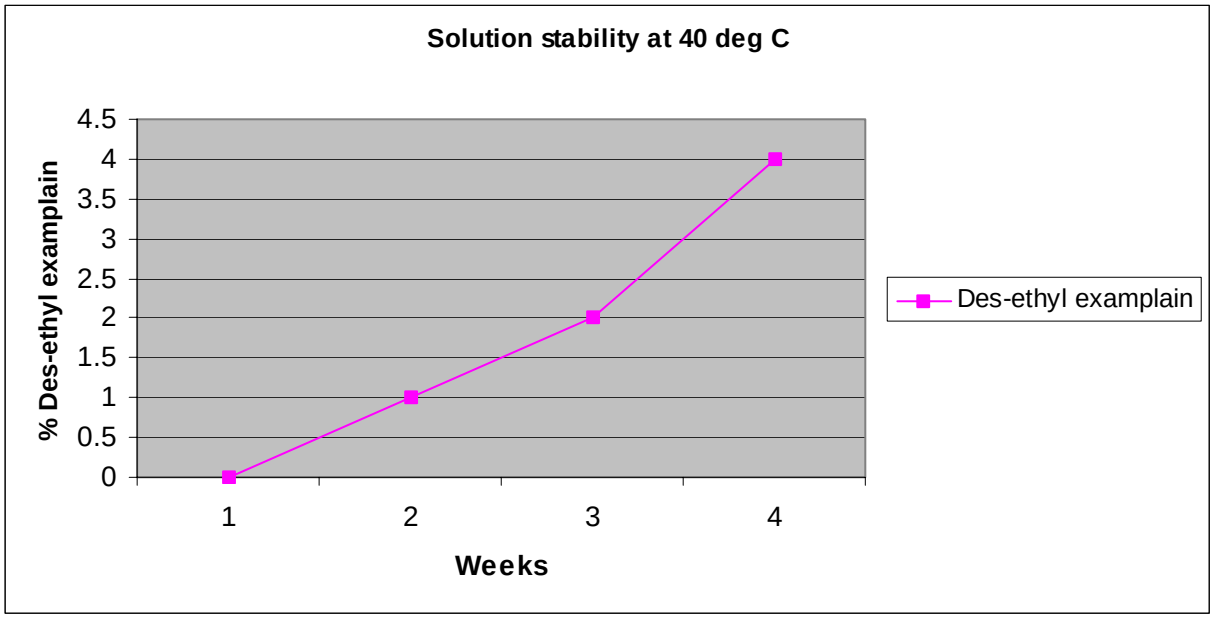
After extensive screening of a wide variety of solvents and conditions, only a single anhydrous solid form of examplain hydrochloride has been identified. The material is a highly crystalline, non-hygroscopic, high melting solid. Characterisation of this material is described in 3.2.S.1.3 *General Properties*. No evidence has been found for any hydrates or solvates of examplain hydrochloride.

Due to the needle-like morphology of the examplain hydrochloride crystals, the bulk density of the solid is low (<0.2 g cm^{-3}). A wet granulation process was selected to densify and promote powder flow. Examplain hydrochloride has only one polymorphic form.

Chemical Stability

As described in section 3.2.S.7 *Stability*, examplain hydrochloride drug substance exhibits good chemical stability in the solid state when protected from extremes of temperature and humidity. Under stressed conditions in aqueous solution, examplain hydrochloride undergoes hydrolytic cleavage of the ethyl ester moiety to des-ethyl examplain (Figure 4). This is also the major metabolite of examplain hydrochloride in man, and has been qualified in toxicology studies up to a level of 10%.

Figure 4– Aqueous solution stability data for examplain hydrochloride showing increase of des-ethyl examplain degradation product over time



Excipient Compatibility

Compatibility of examplain hydrochloride with a range of excipients suitable for wet granulation was assessed using binary mixtures under stress conditions (50ºC/20% RH and 50ºC/80% RH) for periods up to one week. No evidence was seen for degradation of drug substance in the presence of microcrystalline cellulose, mannitol, dibasic calcium phosphate, povidone K-30, hydroxypropylmethyl cellulose, croscarmellose sodium or magnesium stearate. Examplain hydrochloride was shown to be incompatible with lactose, as expected due to the ability of the primary amine in the drug substance to undergo a Maillard reaction.

3.2.P.2.1.2 Excipients

The excipients below are used to produce the proposed commercial tablet formulation:

Mannitol

Mannitol is added as a diluent. A concentration of 40% w/w of the excipient was selected: this level is pharmaceutically precedented. Also, development studies have shown it to provide appropriate tablet properties in combination with microcrystalline cellulose e.g. hardness, dissolution. Mannitol is non-hygroscopic at relative humidities less than 75%.

Microcrystalline cellulose (MCC)

MCC is added as a diluent. A concentration of 39% w/w of the excipient was selected: this level is precedented and also development studies have shown it to provide appropriate tablet properties in combination with mannitol e.g. hardness, dissolution.

Povidone

Povidone K-30 is added as a binder at a pharmaceutically precedented level of 5% w/w. It is added as a 25% w/w aqueous solution during granulation. Previous experience has demonstrated the suitability in essentially similar formulations.

Croscarmellose sodium

The croscarmellose sodium is added as a disintegrant at a pharmaceutically precedented level. A total concentration of 3% w/w is used to impart rapid disintegration. Half of the disintegrant is added intra-granularly and half added extra-granularly.

Magnesium stearate

The magnesium stearate is used as a tablet lubricant at a level of 2% w/w. This level is higher than typical but is necessary for lubrication of this mannitol-based formulation.

3.2.P.2.2 Drug Product

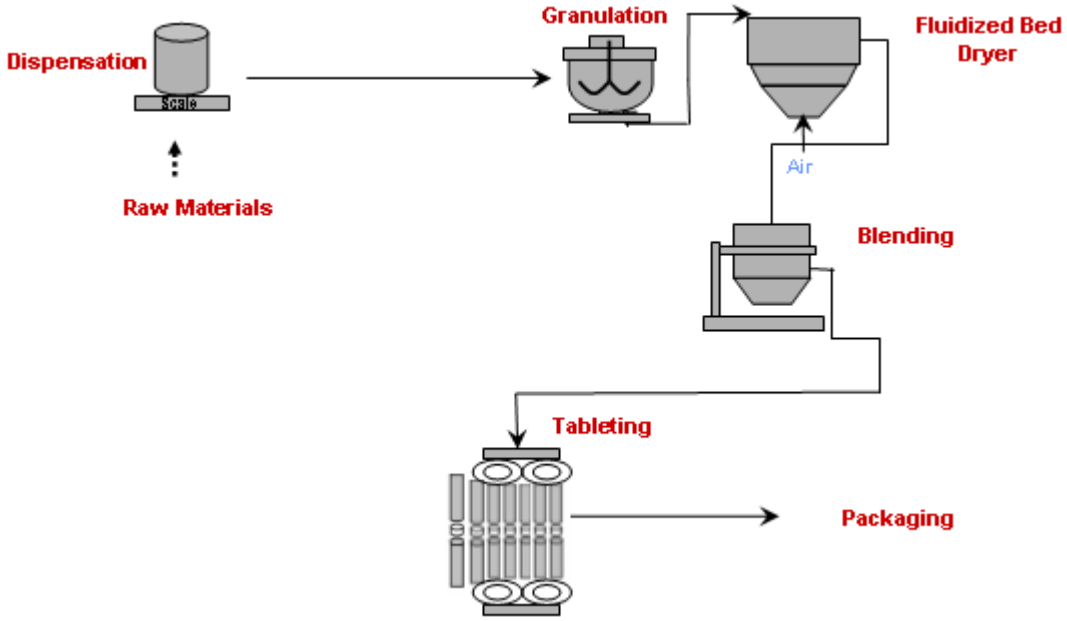
Initial Quality Risk Management for Examplain

Based on the target product profile (Table 1), initial evaluation of

- physical and chemical properties of the drug substance and other components
- scientific knowledge
- prior knowledge from previous products and process development projects,

the following manufacturing process (Figure 5) was suggested.

Figure 5– Unit operations of the proposed Manufacturing Process

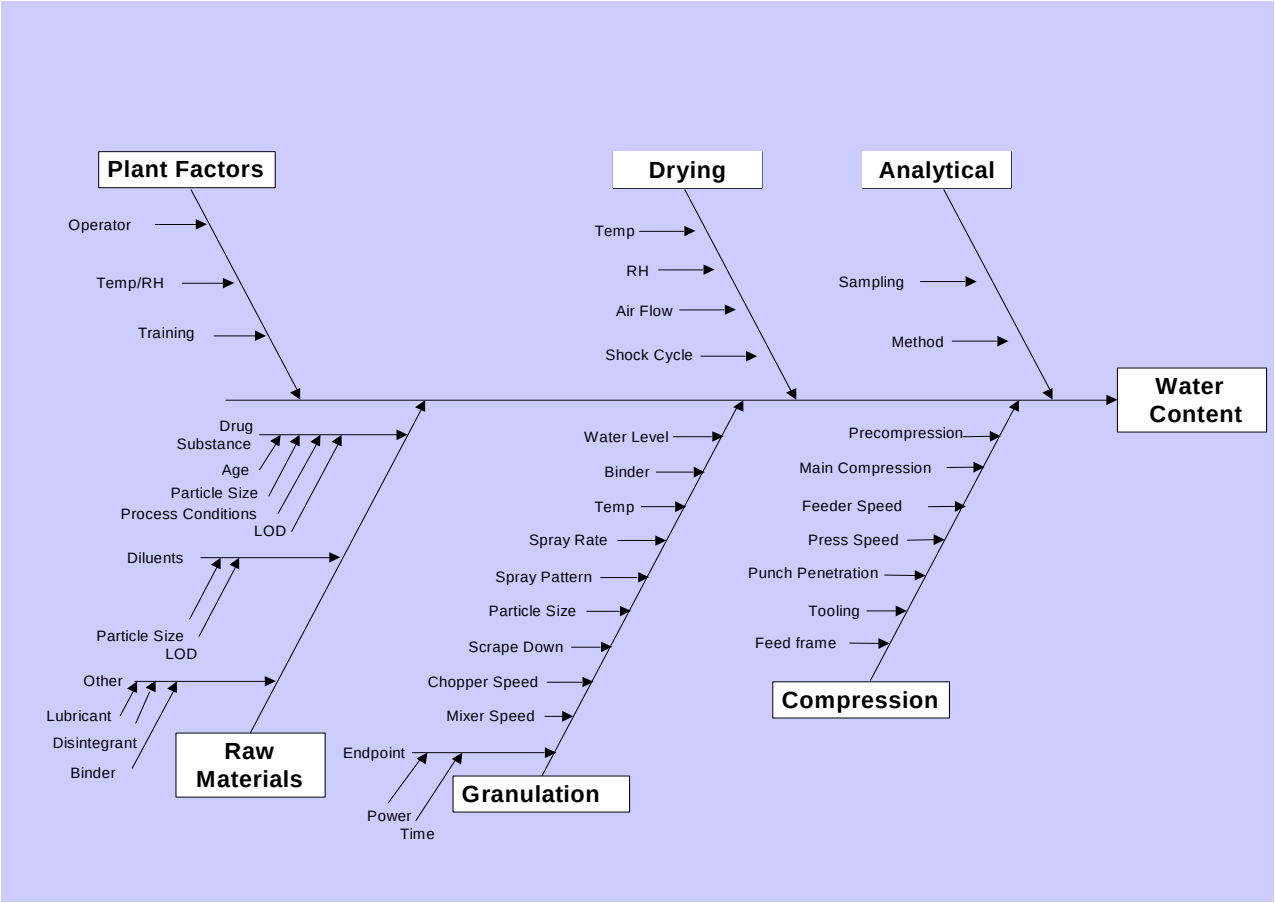


The low bulk density of the drug substance and early formulation development studies led to selection of a high shear wet granulation process.

The same information that has led to the proposed manufacturing process was used for an **initial** risk assessment. This initial assessment lead to an action plan for investigations of the formulation and the process. The risk assessment is repeated and another action plan produced leading to more studies and increased understanding, with a subsequent reduction of risks. The goal was to reduce all risks identified by formulation development and process understanding to acceptably-low levels and control any significant risks remaining with the proposed control strategy (see section 3.3).

For the proposed manufacturing process for examplain hydrochloride tablets the parameters that may effect quality as described in the target product profile and the specification are evaluated in the cause and effect diagram (Ishikawa)(Figure 6)

Figure 6 – Ishikawa (fishbone) diagram for commercial manufacturing process



The initial risk identification was based on the evaluation of all the factors as shown in (Figure 6), prior knowledge and experience with very similar products, similar formulations and preformulation studies. This risk identification lead to a formal **initial** risk analysis, which is presented in (Table 2)

Table 2. Initial classification of importance of unit operation to have an impact on quality

Unit operations Quality attributes	Dispensing (Raw Material Properties)	Granulation	Drying	Blending (Magnesium Stearate)	Tableting	Packaging
Dissolution			Prior knowledge			Prior knowledge
Disintegration			Prior knowledge			Prior knowledge
Hardness	Prior knowledge	Prior knowledge	Prior knowledge			Prior knowledge
Assay	Prior knowledge	Prior knowledge	Prior knowledge	Prior knowledge		Prior knowledge
Content uniformity	Prior knowledge					Prior knowledge
Degradation	Prior knowledge			Prior knowledge	Prior knowledge	Prior knowledge
Stability	Prior knowledge	Prior knowledge		Prior knowledge	Prior knowledge	Prior knowledge
Appearance	Prior knowledge	Prior knowledge		Prior knowledge		Prior knowledge
Identification		Prior knowledge	Prior knowledge	Prior knowledge	Prior knowledge	Prior knowledge
Water	Prior knowledge	Prior knowledge		Prior knowledge	Prior knowledge	Prior knowledge
Microbiology			Prior knowledge	Prior knowledge	Prior knowledge	Prior knowledge

Influence:
high
low

Time elements related to storage and transportation are included as a part of the unit operation.

All unit operations in (Table 2)are assessed for their importance in terms of impact on quality attributes of the finished product (essentially the target product profile).Those with a possibility of having an impact on quality are coloured dark blue.Those with low possibility of having an impact on quality based on the prior knowledge are coded in light blue. The goal of the development summarised in the following sections is to reduce the number of dark blue sections and control the remaining risk to an acceptable level (see Control Strategy 3.3).

As a conclusion from this initial risk evaluation the following interactions and parameters require experimental investigation to define the criticality of them:

- raw material variability for dissolution/disintegration and microbiology
- impact of granulation on dissolution/disintegration, homogeneity and degradation
- drying on content uniformity, degradation, stability, appearance, water content and microbiology
- blending on content uniformity, dissolution/disintegration and hardness
- tableting on dissolution/disintegration, content uniformity, hardness, assay, and appearance

Normally all these attributes and parameters would be discussed intensively in the Formulation development (see 3.2.P.2.2.1) and the Manufacturing Process Development (see 3.2.P.2.3) sections, however, for the purpose of this mock submission the unit operations of granulation and fluid bed drying are discussed in detail as they exemplify concepts for discussion.

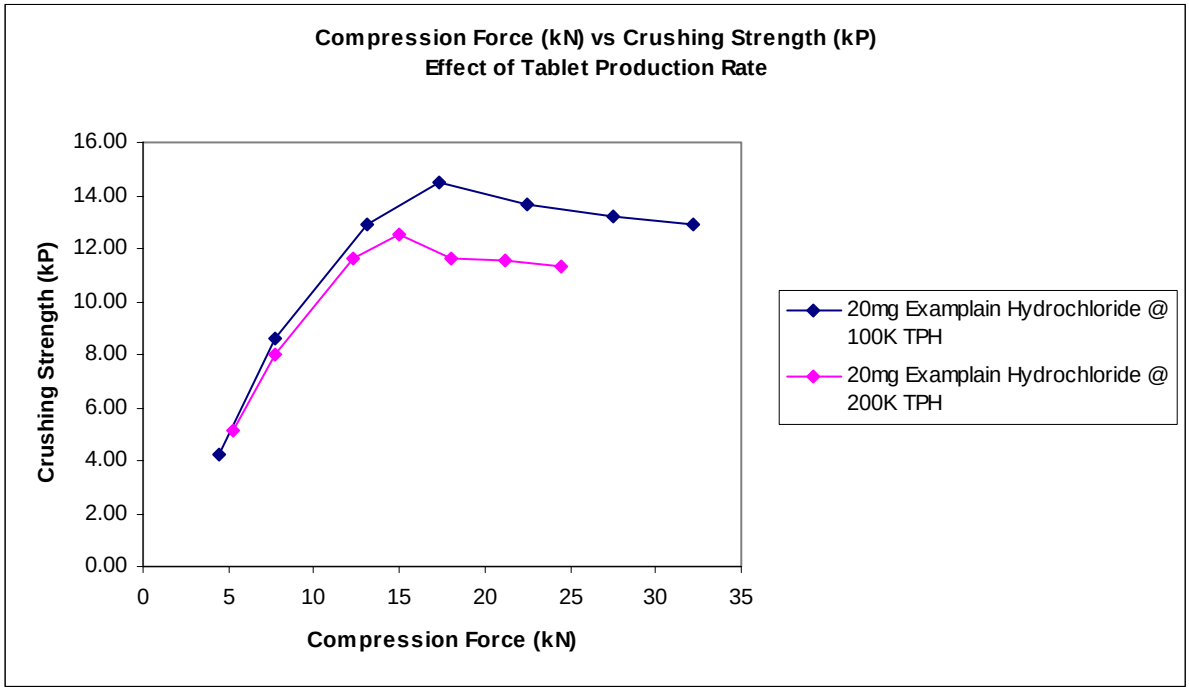
3.2.P.2.2.1 Formulation Development

The development of the proposed commercial formulation is described in this section. The qualitative and quantitative compositions of the proposed commercial formulation and the formulations used in clinical development are presented in Attachment A.

In early clinical trials, tablet formulations of 1, 10 and 20mg were used but only one strength, 20mg, is proposed for commercialisation.

Examplain hydrochloride is a primary amine and undergoes a Maillard reaction with lactose. Consequently, mannitol was chosen as the diluent at pharmaceutically precedented levels. The low bulk density of the drug substance precluded a directly compressible formulation and a high shear wet granulation process was developed using povidone K30 as the binder. Mannitol is well precedented as a diluent for wet granulation formulations. Microcrystalline cellulose was chosen as the other diluent as it exhibits appropriate compression properties in combination with mannitol (see Figure 7).

Figure 7– Compression profiles for examplain hydrochloride tablets made at different tableting speeds



(TPH = tablets per hour)

Magnesium stearate is included as the lubricant as precedented for mannitol based formulations (Handbook of Pharmaceutical Excipients p376 4th Edition (2003), Pharmaceutical Press, edited by R C Rowe, P J Sheskey and P J Weller). In the range of 1% to 3% no significant effects on compression or dissolution at this level have been demonstrated (see Figure 8and Figure 9).
Hardness above or equal 4 kp produces acceptable tablets.

Figure 8 – Compression profiles for examplain hydrochloride tablets made with different lubricant levels

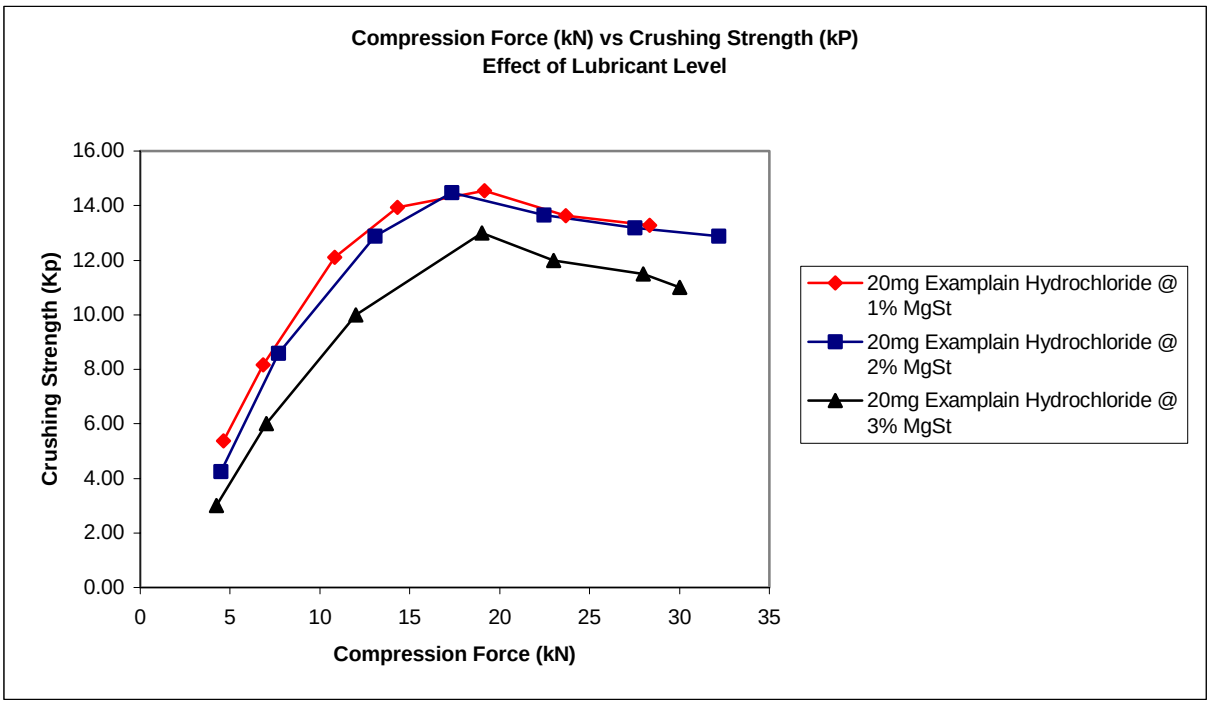
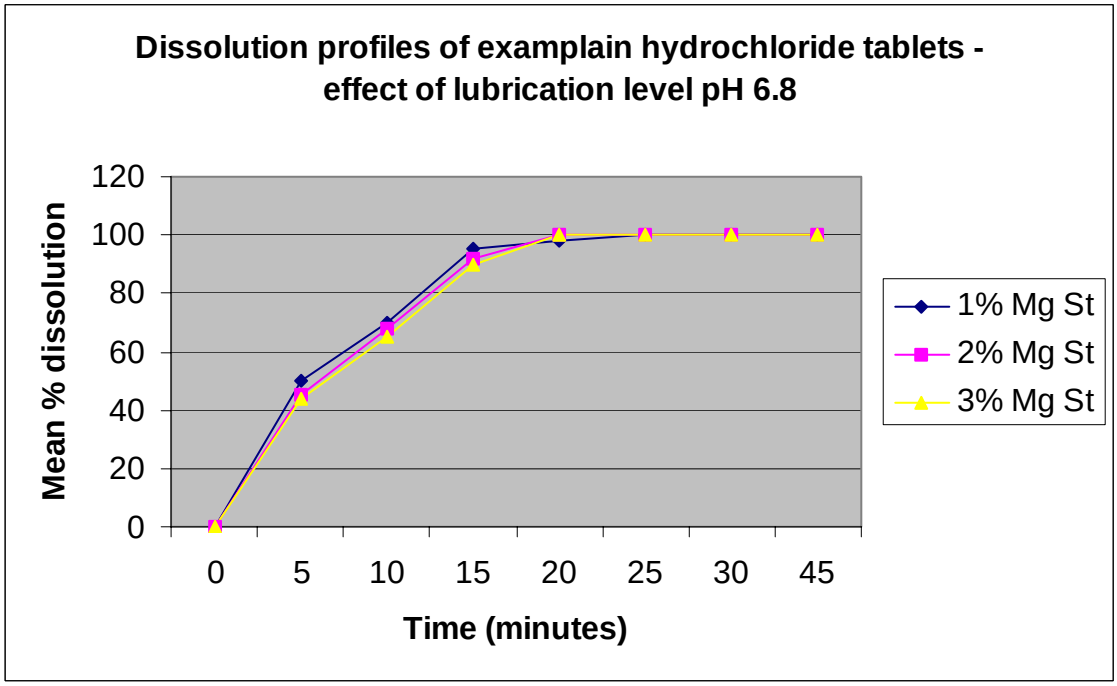


Figure 9 – Dissolution profiles for examplain hydrochloride tablets made with different lubricant levels



The effects of varying excipient quantities on disintegration and dissolution for this finalised formulation were assessed by development studies, that product quality and

performance is unaffected by small changes. Tablets from these studies also gave acceptable assay values and uniformity of content, and good appearance.

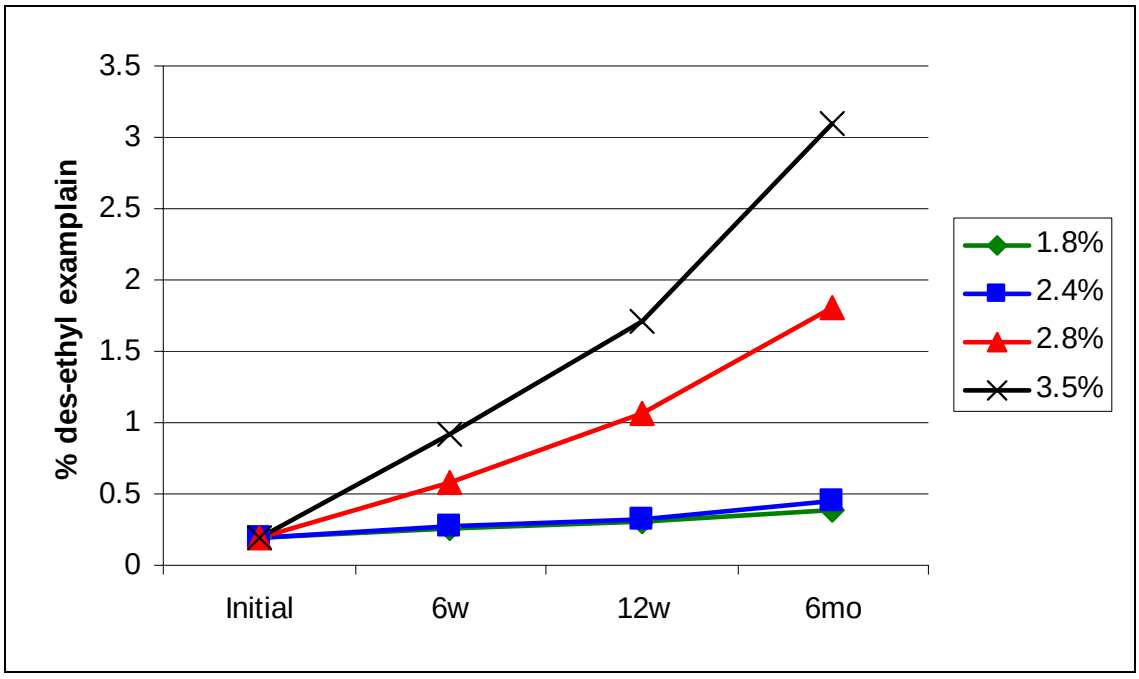
Risk factors identified from the initial risk assessment are partially mitigated by design of the formulation, for example wet granulation assures that active ingredient homogeneity and compressibility, and the impact of raw material variability are reduced compared with a direct compression formulation and process.

In conclusion, a formulation has been developed which is suitable to progress into process development, particularly examining the impact of granulation and drying on content uniformity and stability. Risks associated with the impact of all unit operations on dissolution, disintegration, hardness, assay, and appearance have been significantly reduced.

Early studies were performed to examine the impact of water content on stability of this formulation.

Pre-formulation stability studies have demonstrated that examplain hydrochloride undergoes hydrolytic cleavage of the ethyl ester moiety to form des-ethyl examplain (see section 3.2.P.2.1.1). Development studies have been undertaken to examine the relationship of tablet water content to stability of packaged tablets stored at 40°C/75% (Figure 10).

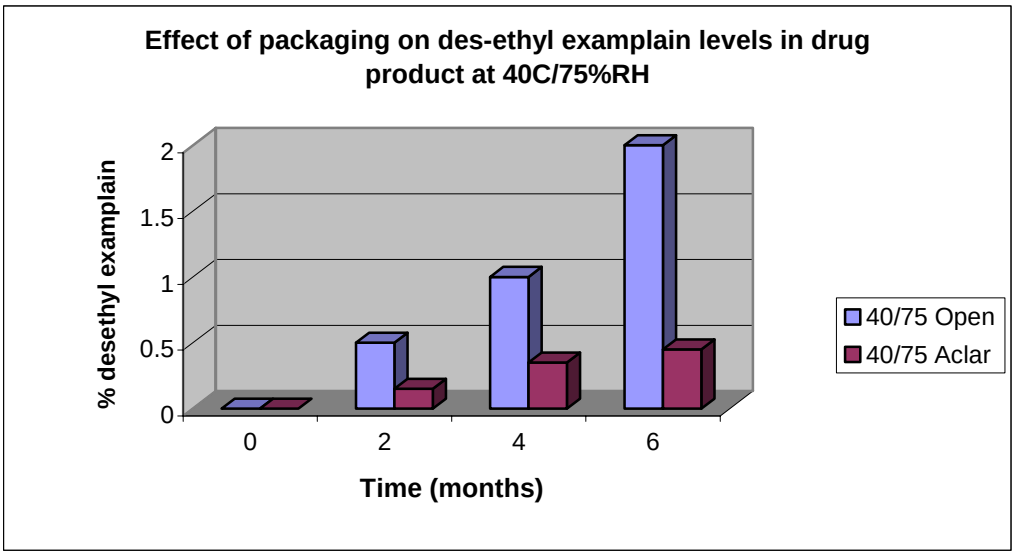
Figure 10 – Impact of tablet water content on formation of des-ethyl examplain on storage of tablets in Aclar blisters at 40ºC / 75% RH



These studies show that a maximum water content of 2%w/w in tablets produces acceptably stable drug product.

Further preformulation studies showed that use of Aclar unit dose blisters with an aluminium foil backing improved stability compared with unpacked tablets after storage at 40°C/75% RH for 6 months (Figure 11). The batch of tablets contained 2.4% moisture content.

Figure 11– Stability data for examplain hydrochloride showing the effect of packaging on increase of des-ethyl examplain over time in the formulated tablet



From these formulation development studies a formulation and associated primary pack have been designed and the process has been selected to provide an immediate release tablet that reduces the previously identified risk factors, e.g. dissolution and appearance.

Furthermore development studies have demonstrated that water content in tablets at time of manufacture is critical for quality and requires further study during process development.

3.2.P.2.2.2 Overages

There are no overages used in the manufacturing of examplain hydrochloride tablets.

3.2.P.2.2.3 Physicochemical and Biological Properties

Summary of pharmacokinetic studies:

- single dose PK study
- multiple dose PK study
- fed-fasted PK study
- 1, 10 and 20mg PK study

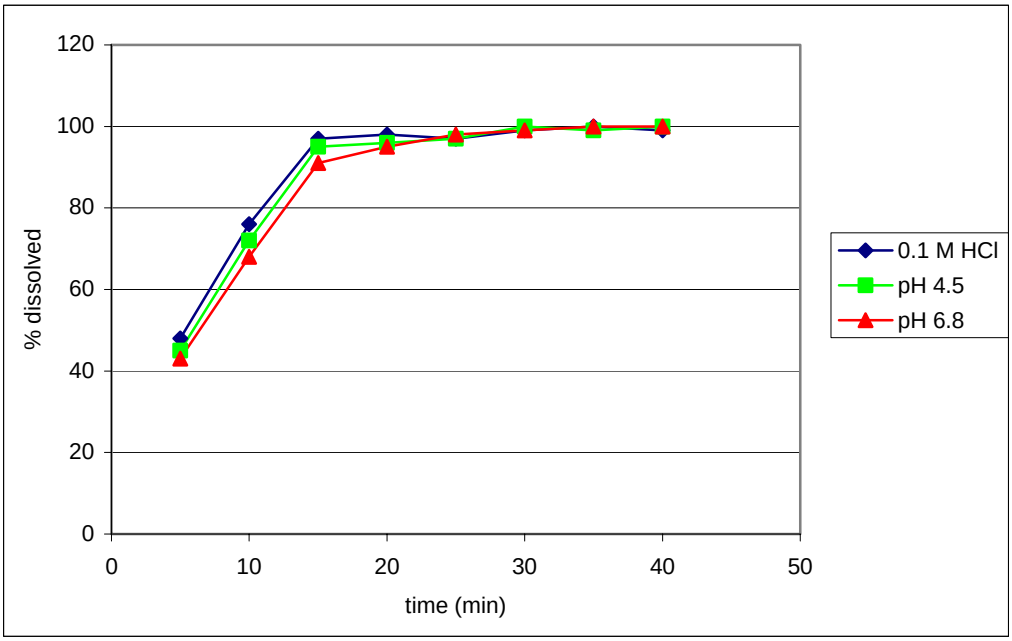
Examplain hydrochloride is a non-hygroscopic white to off-white powder, and has a molecular weight of 536.5 (the free base has a molecular weight of 500). Examplain, the free base, has a pKa of 10.1 in aqueous solution at 25ºC. Examplain hydrochloride demonstrates solubility in excess of 1.0 mg mL^{-1} across the pH range 1.2-7.5 (see section 3.2.P.2.1.1.). It has a high trans-membrane absorptive permeability value of 30cm/s x 10^{-6} per hour (stirred) in a Caco-2 model of human intestinal absorption and is rapidly absorbed following oral administration (T_{max} is 2 hours), with oral bioavailability estimated to be 95% in man. Given the solubility, in vitro permeability and pharmacokinetic information examplain can be considered as a BCS Class 1 high solubility, high permeability compound. The absolute bioavailability of examplain hydrochloride drug product, 20 mg tablet formulation was obtained from a comparison with an intravenous formulation. In addition, a blood level study in man has shown that bioavailability achieved with the 20 mg clinical trial formulation is at least as good as that given by an oral solution. This study also demonstrated that food has no effect on bioavailability.

Dissolution and Disintegration

Absorption and bioavailability of examplain hydrochloride 20 mg tablet is not affected by drug dissolution as verified by the similar bioavailability for the tablet as with the oral solution. Therefore maintaining the rapid dissolution characteristics of the tablet during formulation and process development should guarantee consistent bioavailability.
A dissolution test was therefore developed as an indicator of the performance of examplain hydrochloride drug product tablets and used during the formulation and process development programme.

The dissolution characteristics of the examplain hydrochloride 20 mg tablet in three different dissolution media are shown in (Figure 12).

Figure 12– Dissolution for Examplain hydrochloride 20 mg tablet at different pH values



The detailed discussion to justify omission of the dissolution test from the finished product specification is given section P5.4.

The compendial test was used for disintegration time in water (37^{o}C). The disintegration test was used throughout the development programme to monitor the performance of the examplain hydrochloride tablet manufacturing process. Details of the respective unit operations with impact on disintegration are described in 3.2.P.2.3.

The details of the strategy to control disintegration and hence dissolution is described in 3.2.P.3.

Conclusions from formulation development studies are:

-a suitable formulation and primary package have been developed for further process development work.
-a suitable dissolution test has been developed, which is an excellent surrogate for in vivo absorption.
-risks associated with in vitro dissolution have been reduced to the level where consideration can be given to using disintegration as a surrogate for dissolution
-water content in tablets is a critical to quality attribute and requires further study during process development
-insufficient data have been generated for content uniformity, however, the formulation and process appear satisfactory to warrant extensive process development studies.

3.2.P.2.3 Manufacturing Process Development

From the initial risk evaluation and formulation development studies described in section 3.2.P.2.2, above, a formulation and associated wet granulation process were proposed (Appendix Table 7, Figure 5).

The process consists of an initial mixing step of the drug substance, the diluents (mannitol and microcrystalline cellulose) and the intra-granular disintegrant in the high shear granulator. The blend is granulated with an aqueous solution of povidone. The wet mass is transferred to a fluid bed drier and dried to a water content between 1.5 and 2% w/w. The granules produced are then blended with the extra granular quantity of croscarmellose sodium and lubricated with the magnesium stearate. The final blend is tableted.

Further studies were conducted during manufacturing process development to understand better and mitigate all identified remaining high risk factors.

Detailed description is given of studies to understand and mitigate risk factors in unit operations of granulation and fluidised bed drying. In each case there is a risk assessment, action plan with development, usually DOE, studies, an assessment of the results leading to a proposed design space and then control strategy.

3.2.P.2.3.1 Unit operations in the manufacture of examplain hydrochloride tablets

3.2.P.2.3.1.1 Mixing

3.2.P.2.3.1.2 Wet Granulation

All parameters relevant to wet granulation were identified from the Ishikawa diagram (Figure 6) and were introduced into a detailed risk assessment (FMEA), in accordance with ICH Q9, to establish those process parameters that are likely to have the greatest impact on the quality of the product and be associated with a critical to quality attribute, water content (Figure 13), and hence were incorporated in Design of Experiments (DOE) studies

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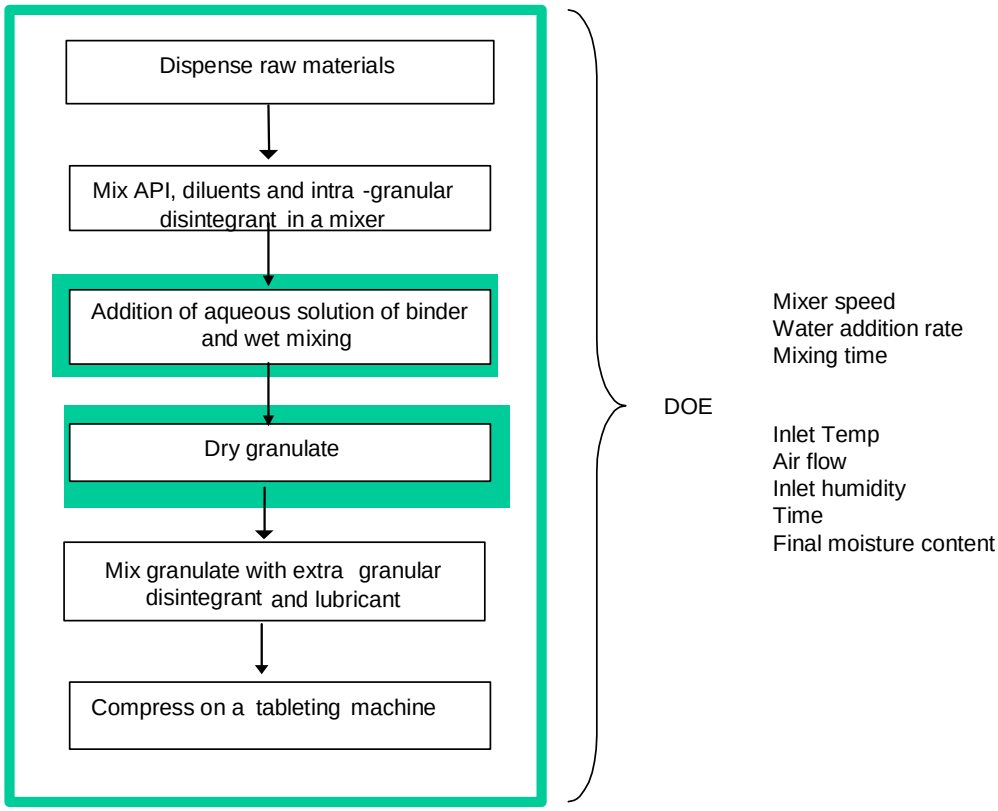
Figure 13 – Design of experiment plan for commercial manufacturing process



The process was investigated using a series of experiments that were conducted at a development scale of 1kg using a DOE approach. During the DOE the influence of varying manufacturing parameters on the quality and processability were investigated to define critical to quality parameters. Where possible prior knowledge (from previous products and process development projects) and experimental development data were utilised to provide product and process understanding and allow appropriate multivariate experimental plans to be designed.

Manufacture at 25kg scale including ICH stability lots, with in-line analytical applications in place, has demonstrated that the process is capable to work at a different scale while maintaining the required quality.

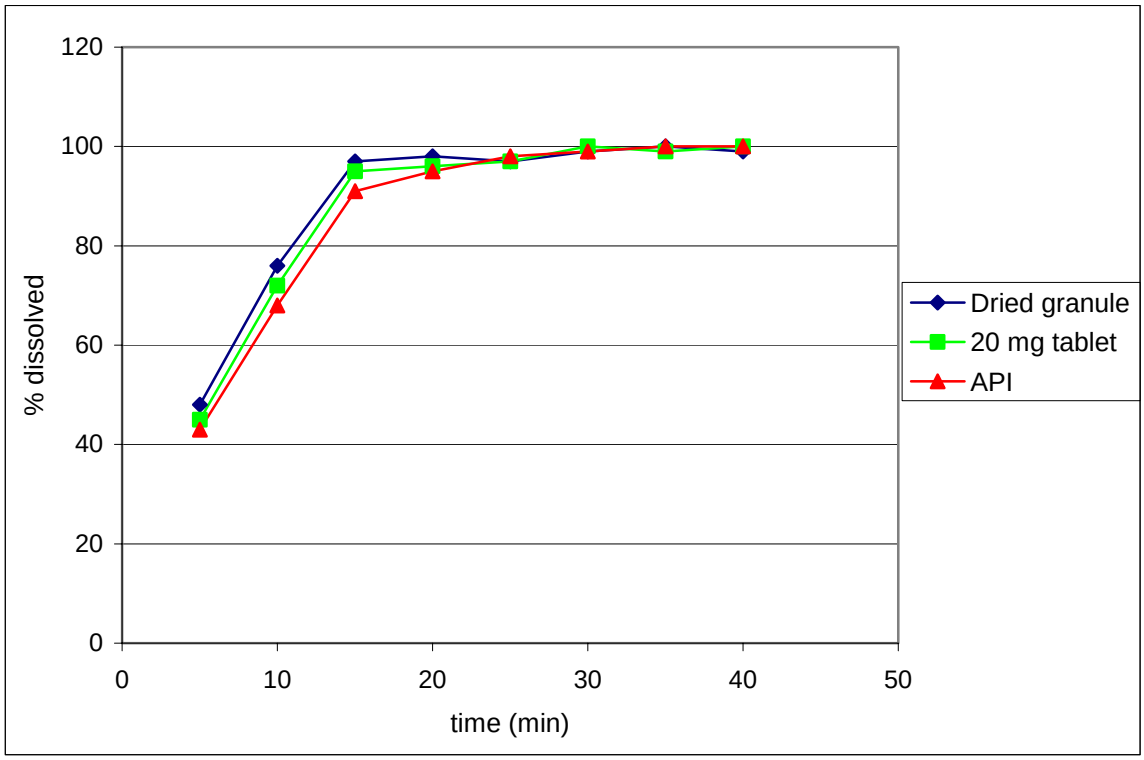
More detailed descriptions of the key elements for individual unit operations are given below.

3.2.P.2.3.1.2.1 Development of wet granulation process understanding - impact on manufacturability and dissolution and disintegration

Wet granulation is performed by addition of purified water with added binder to the dry blended powders and mixing until a suitable wet mass is formed. The binder Povidone K-30 is added to a level of 5% w/w as a 25% w/w aqueous solution. Changing the binder concentration to 4% and 6% as part of formulation development

studies showed no significant effect on tablet dissolution or disintegration. The formulation design work showed that the formulated tablet exhibits rapid dissolution properties. In 0.1 M HCl no difference could be observed between the drug substance, dried granules or the tablet whereas at pH 6.8 it was evident that the formulated product and the dried granules had slightly faster dissolution characteristics than the drug substance, (see Figure 14) below. This confirms the rapid dissolution properties of the examplain hydrochloride 20 mg tablet. The similar dissolution results in the two dissolution media are consistent with the FDA guidance for industry for determining drug product dissolution characteristics and dissolution profile similarity ("Waiver of in vivo bioavailability and bioequivalence studies for IR solid dosage forms based on a Biopharmaceutics Classification System (2000)"). This is further evidence that dissolution is unaffected by formulation and processing variables.

Figure 14 - Comparison of dissolution characteristics at pH 6.8: Examplain 20 mg tablet, dried granules and the API (examplain hydrochloride drug)



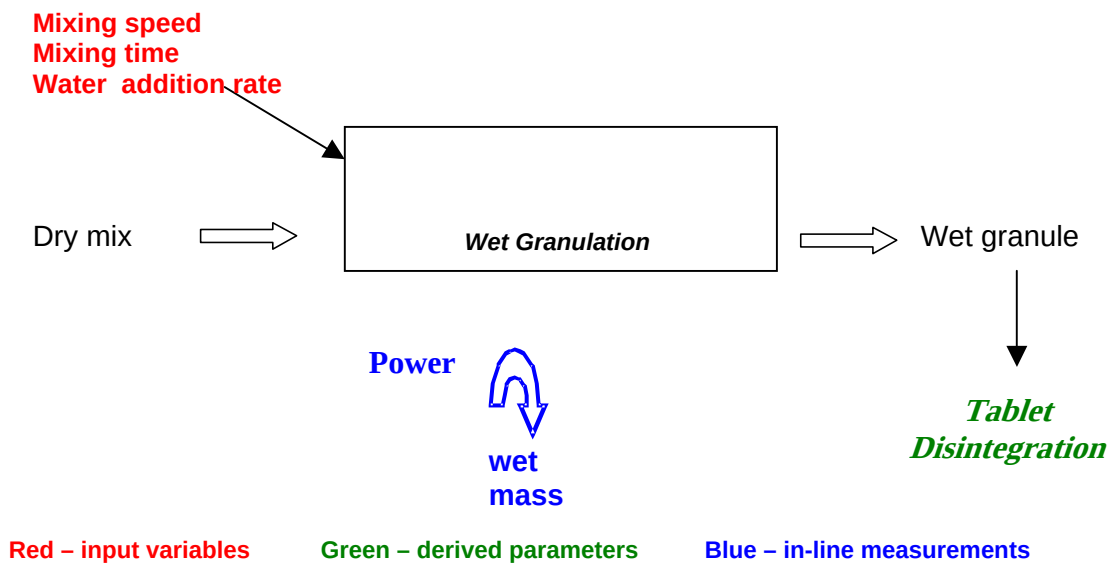
Because of the high capability of the wet granulation process in the initial process design studies to improve homogeneity and compressibility, and reduce the impact of raw material variability compared with direct compression, the Design of Experiments approach was tailored to evaluate the robustness of the process with respect to key process variables as listed in (Table 3)

Table 3 – Key process variables for the wet granulation operation

Wet granulation parameters	Input material attributes
Mixing speed	API particle size
Water addition rate	Mannitol particle size
Mixing time	

Throughout the development of the manufacturing process the dry mixing and wet granulation steps were monitored in line by power consumption, (see Figure 15)

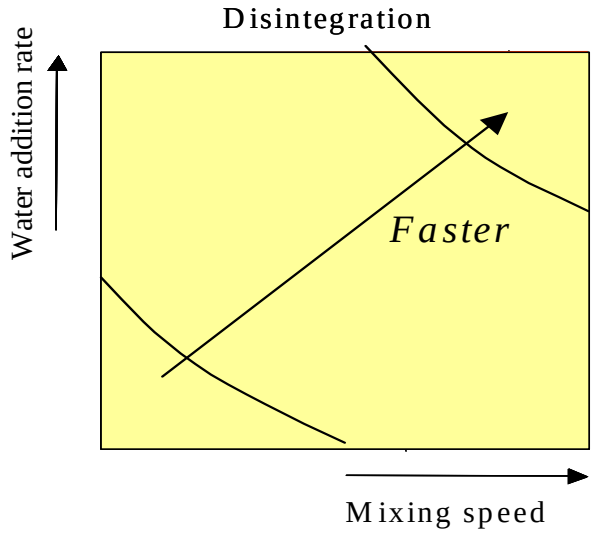
Figure 15 – Key process parameters for the wet granulation operation



A summary of the results of the wet granulation DOE studies is described below.

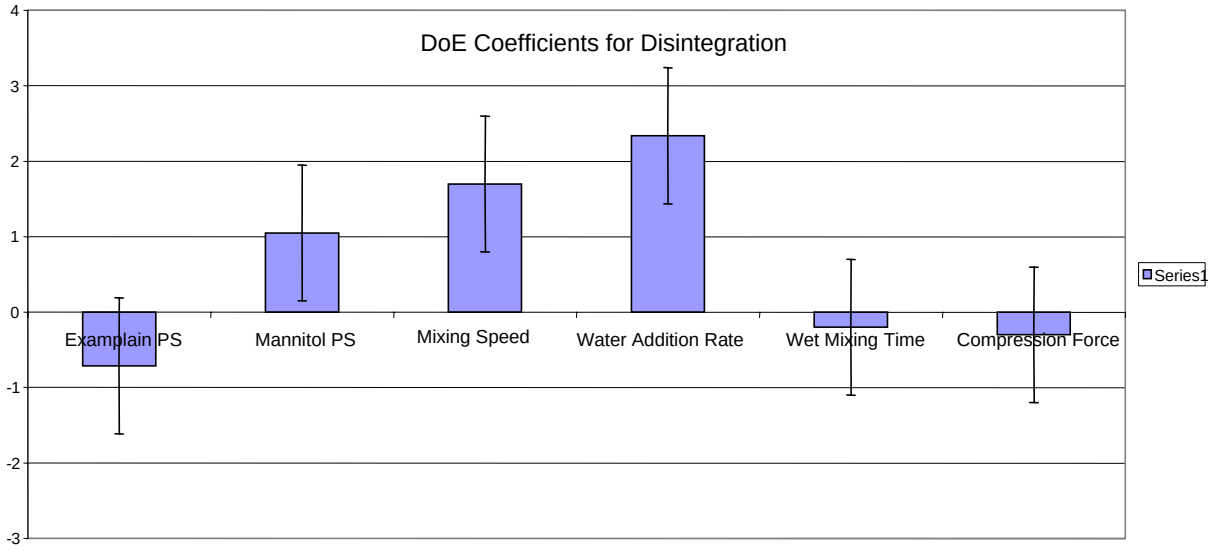
The development DOE studies conducted by spanning out the processing conditions within a wide range show that dissolution at 15 minutes is insensitive to the conditions used for the wet granulation process, whereas granulation conditions have a small effect on disintegration, which however still remains within acceptable limits. The design space for disintegration with respect to wet granulation mixing speed and water addition rate is shown in Figure 16.

Figure 16 - Effect of wet granulation mixing speed and water addition rate on disintegration, as shown by the DOE (yellow = meets Pharmacopoeial quality requirements for an immediate release dosage form)



These DOE studies also showed the relative importance of the various factors (Figure 17) on disintegration with mixing speed and water addition rate being the most important.

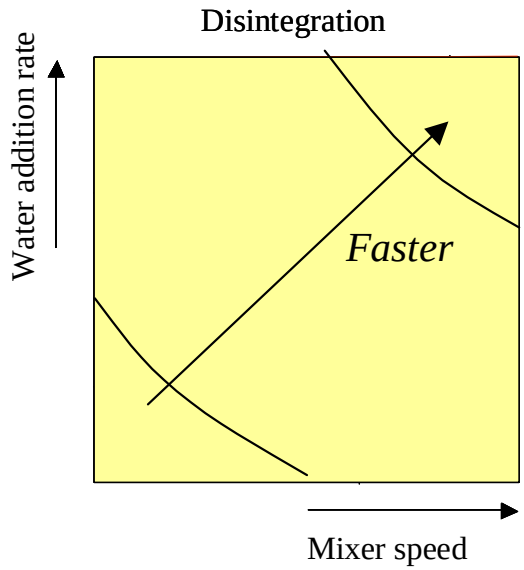
Figure 17 - Coefficient plot from the partial least squares (PLS) model for prediction of examplain tablet disintegration from key process variables



Based on the results from the DOE studies described above, a multivariate process model was derived for the purpose of confirming predictability of examplain tabletquality attributes

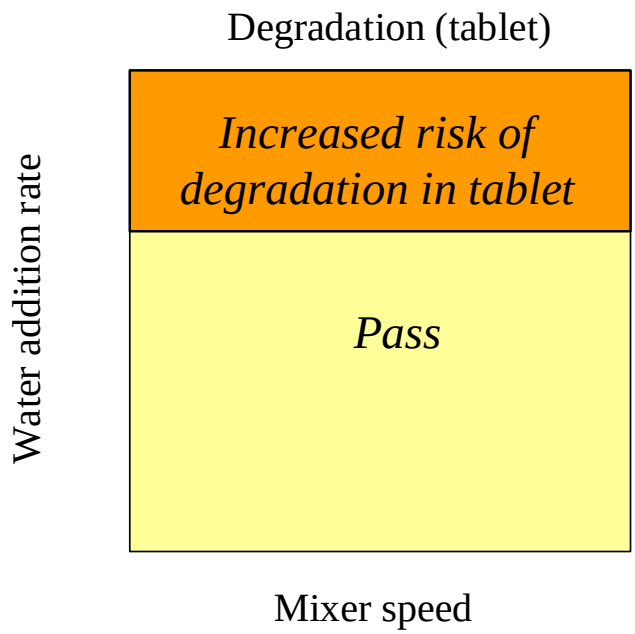
From DOE studies the effect of processing conditions on suitable quality for introduction to the subsequent unit processing operation, fluidised bed drying was investigated. The influence of mixing speed and water addition rate on granule compression properties, tablet disintegration, granule particle size and the risk for degradation in fluid bed drying were evaluated and the results are summarised in (see Figure 18 toFigure 21), the acceptable region of water addition rate and mixer speeds being given in(Figure 22). For example, in section 3.2.P.2.3.1.3, it is a requirement of the process trajectory for fluid bed drying, Figure 32 that water content of granule is in the range 17.5 to 18.5%

876 **Figure 18 – Effect of water addition rate and mixer speed on disintegration (red**
877 **does not meet quality requirements)**



878

879 **Figure 19 – Effect of water addition rate and mixer speed on degradation in**
880 **tablet (red does not meet quality requirements)**



881

Figure 20 – Effect of water addition rate and mixer speed on granule particle size (red not meet quality requirements)

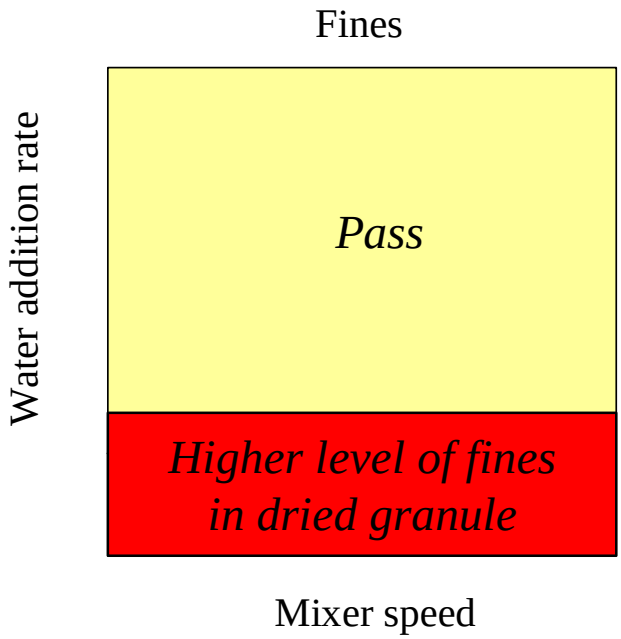
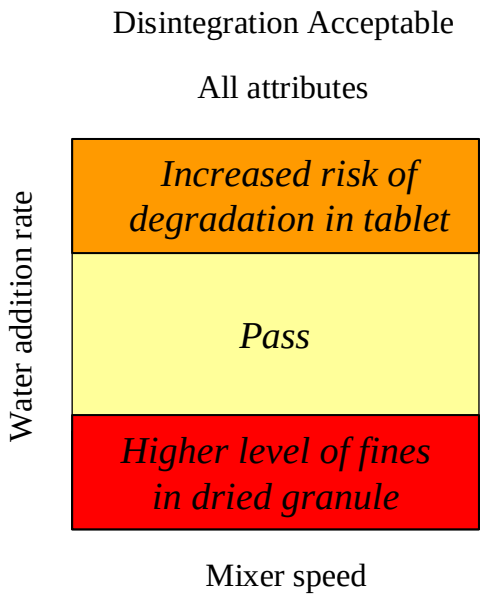
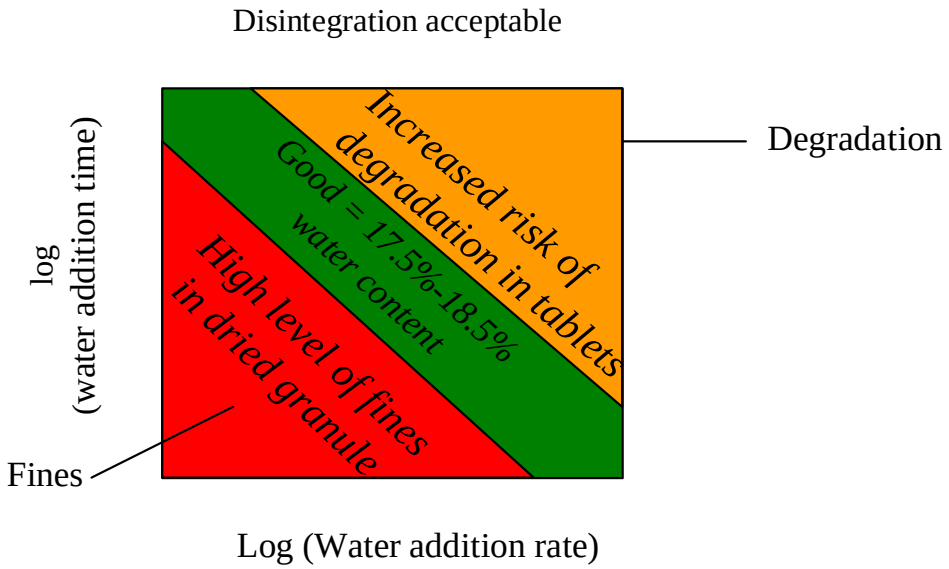


Figure 21 – Interaction of water addition rate and mixer speed with all attributes



The relationship of water addition time and water addition rate on disintegration, degradation and granule particle size is given in (Figure 22. This shows that for a limited range of mixer speeds there is a range of combinations of water addition time and water addition rate that give acceptable granule for progressing to the next unit processing operation of fluidised bed drying. This acceptable region is considered as the design space for water addition rate and time

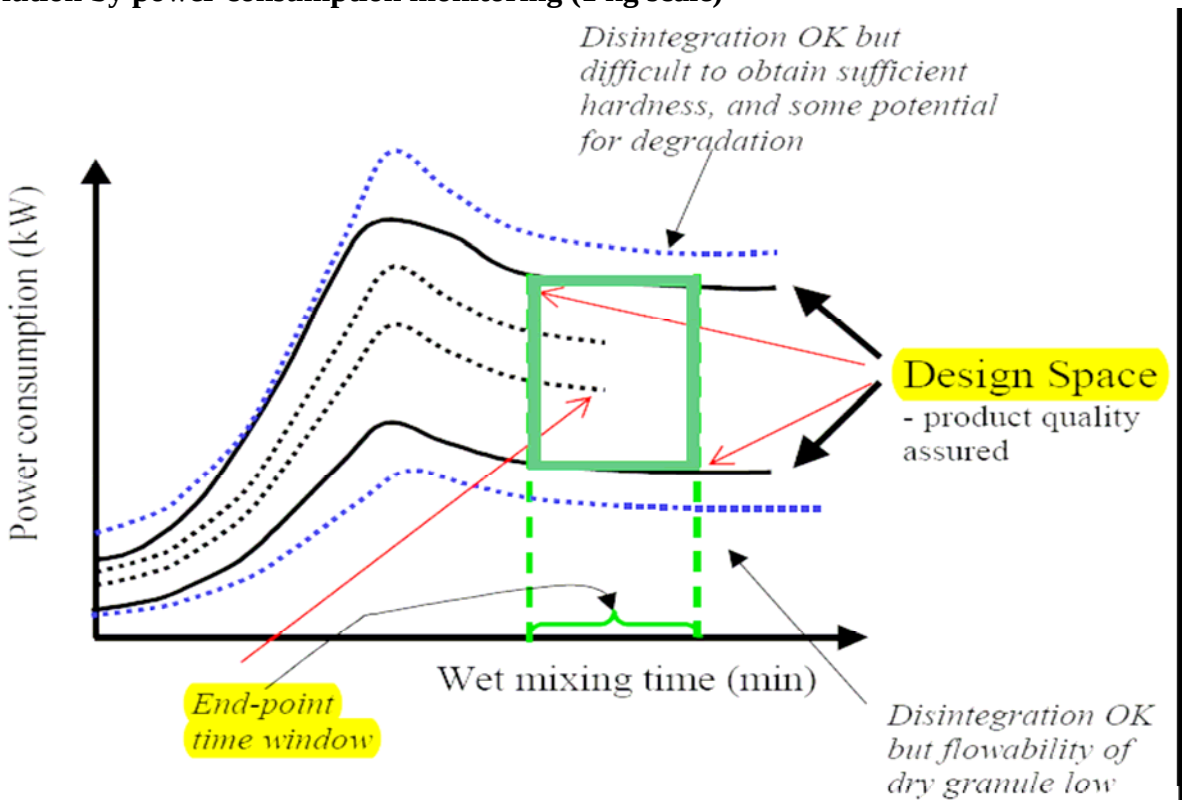
Figure 22 – Process operating region for water addition time and rate – all attributes



3.2.P.2.3.1.2.2 Development of Design Space and Control Strategy for the wet granulation operation

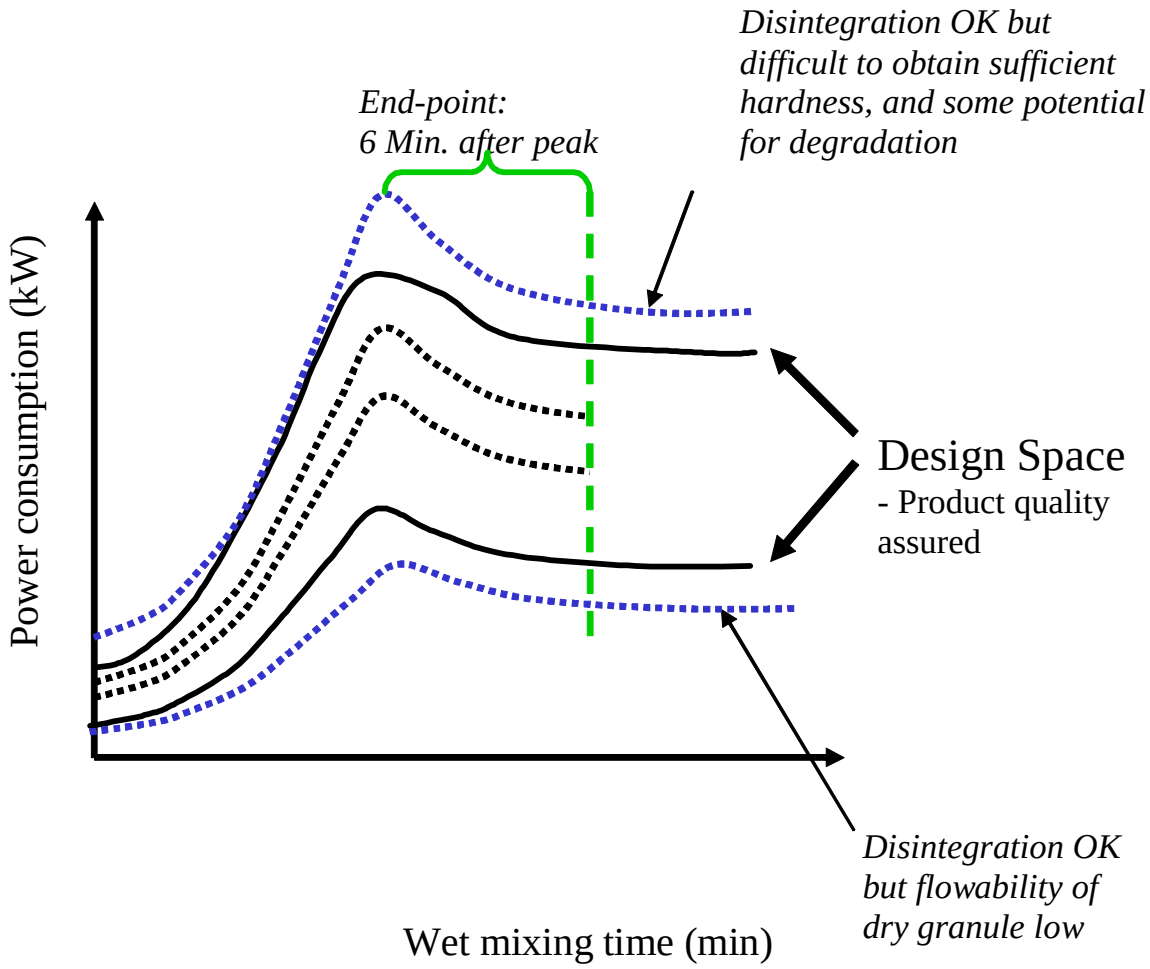
Monitoring the high shear mixing process by power consumption or other techniques such as acoustics offers PAT opportunities for better process understanding and advanced control, e.g. of end-point. As shown previously, process parameters of water addition rate and time can be continuously adjusted within the design space to obtain highly consistent granule properties mainly with respect to flowability, compressibility, degradation, and suitability as input to the next processing step. Process trajectories based on power consumption monitoring are shown in (Figure 23). Solid lines show a range that gives acceptable tablet properties within time window (green dashed lines). Blue dotted lines show process trajectories where tablet manufacturability is affected.

Figure 23 – Process trajectories for the wet granulation operation. Process evolution by power consumption monitoring (1 kg scale)



The region bounded by the solid green line is the design space for the wet granulation unit operation, and it is the region between acceptable power consumption trajectories, and within an acceptable time range. Using this information it is possible to control the wet granulation operation as proposed in (Figure 24)

Figure 24 Process trajectories for the wet granulation operation (1kg) – end point of granulation

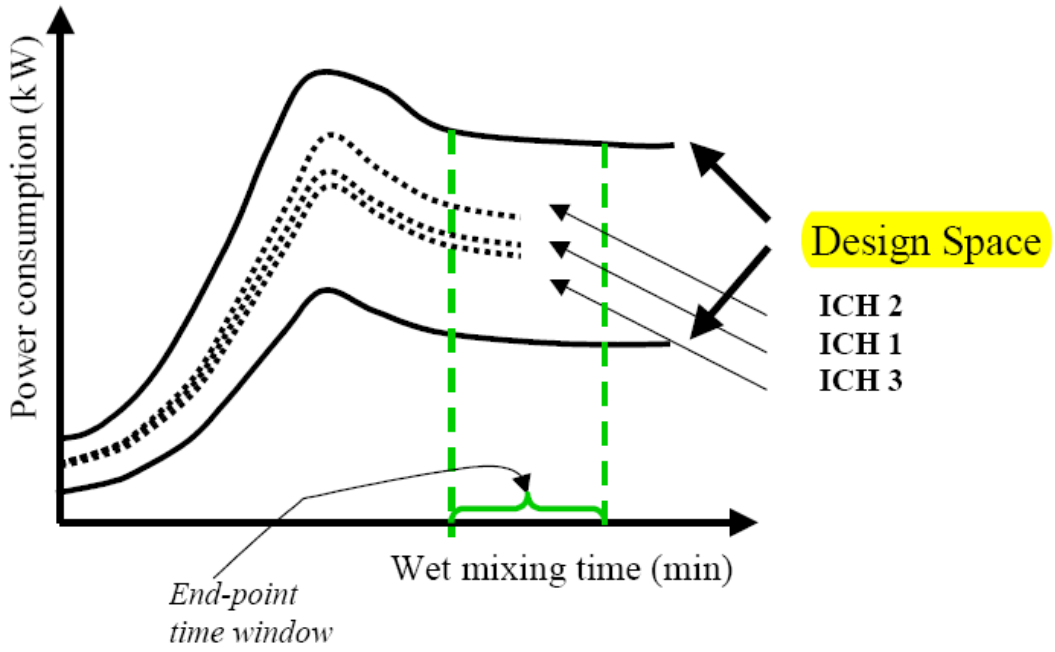


The wet granulation design space can be used as part of the control strategy to provide additional assurance of satisfactory granulation even with varying raw material input and set an optimal end point of mixing time after completion of water addition.

The effect of scale was studied.
The design space established by the DOE approach for 1 kg scale was subsequently verified at larger development scale. At 25 kg scale, a reduced DOE programme was performed to produce the water addition rate and time relationship and power consumption trajectory. (Figure 25)

Process trajectories for the wet granulation operation. Process evaluation by power consumption monitoring (25 kg)

Figure 25

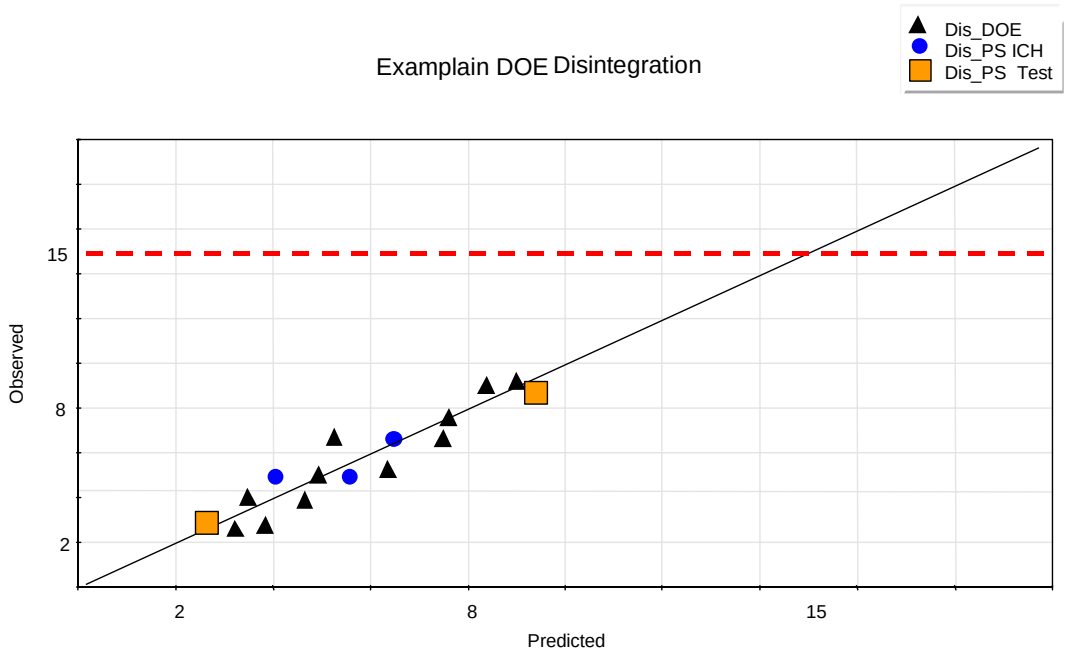


The design space at 25kg scale is the same as that established at 1kg scale. It was concluded that the wet granulation process design space is not dependent on the scale.

As already discussed from the DOE studies described above, a multivariate process model was derived for the purpose of confirming predictability of examplain tablet quality attributes. The model was evaluated for predicting disintegration from the key process variables listed in Table 3 for the wet granulation operation. In addition to these parameters, compression force was also included in the model because over-compression has the potential to affect disintegration (see 3.2.P.2.3.1.5 Compression for details).

Calibration curves for the prediction models for disintegration are shown in Figure 26. The validity of the prediction model was shown by predicting disintegration for the three ICH pilot scale batches and the two additional test batches. Black triangles represent the DOE data for establishing the prediction model from the small scale batches (1 kg). Blue circles represent the three ICH batches at pilot scale (25 kg) whereas, the orange squares represent data from the two pilot scale test batches (25 kg) manufactured at stressed conditions. In summary, based on these data disintegration of the examplain IR tablet can be predicted using this model.

Figure 26 – Predicted values (% released) versus reference values for the disintegration model.



Using the wet granulation design space a control strategy for the granulation step is proposed whereby wet massing is finished after a preset time interval (6 min.) following maximum power consumption, and ensuring that the power trajectory is within the acceptable range.

Extensive processing studies have produced a high level of understanding of the wet granulation unit operation with the following conclusions within the ranges studied:

- measuring release at 15 minutes, dissolution is not affected (there is a small change in disintegration always within acceptance limits)
- granulation progress can be monitored and end point controlled by power consumption trajectory
- output from the granulation step in terms of water content range (17.5 to 18.5% w/w) is designed to meet input criteria for the next unit operation, fluidised bed drying
- a multivariate model has been established to understand and predict disintegration which incorporates factors from the wet granulation step
- change of scale has been introduced into process understanding
- a design space for the wet granulation unit operation is described
- mixing speed and water addition rate are the most important factors
- drug substance particle size is of low importance
- a control strategy for the wet granulation unit operation is proposed based on use of the design space

- combination of application of the control strategy for the wet granulation step and prediction of tablet disintegration is part of the control strategy for the assuring tablet quality
- all these studies have reduced the risk associated with dissolution, disintegration, content uniformity and degradation such that operating within the design space, all are now low risk

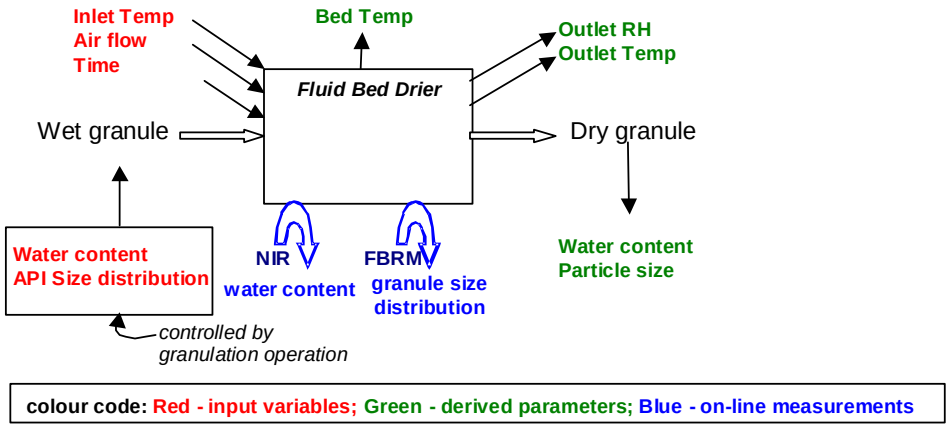
3.2.P.2.3.1.3 Fluid bed drying

3.2.P.2.3.1.3.1 Summary

Based on an FMEA risk management approach, the fluid bed drying performance was identified as a possible critical process step for the manufacture of examplain hydrochloride tablets with respect to meeting the target water content at the end of the drying and ensure less than 2% des-ethyl examplain at the end of shelf life, and to ensure that uniform tablets with appropriate disintegration and dissolution characteristics are produced. A detailed, science-based understanding of the relationship between the process parameters of the drying step, the properties of the in-going wet granulate, downstream processability and the quality attributes of the finished examplain hydrochloride tablets has been developed.

The key parameters for the drying operation are shown in Figure 27

Figure 27– Schematic representation of the fluid bed drying operation



Based on a DOE approach, it has been demonstrated that the drying operation can lead to two significant failure modes, one of which also impacts down-stream processing:

- hydrolysis of the drug substance (degradation to des-ethyl examplain)
- decreased tablet weight uniformity resulting from poor granule flow associated with the generation of fines.

The disintegration and dissolution properties of the examplain hydrochloride tablets are insensitive to the drying operation.

The two failure modes are caused by different factors, and it is necessary to select process parameters to avoid both. A conventional, univariate approach, either by control of water content or by drying time is not sufficient to guarantee avoidance of both failure modes. However, by controlling both the final water content and the time course of achieving it (the “drying trajectory”), the performance of the examplain hydrochloride tablets can be assured.

We have demonstrated that appropriate control of the drying process, coupled with appropriate storage of bulk tablets and blister packaging of the tablets, ensures a low level of the des-ethyl examplain degradant at the time of release and that it does not form at significant levels during the shelf life of the product, and ensures that the flow properties of the dried granule lead to good weight and content uniformity of the examplain hydrochloride tablets.

3.2.P.2.3.1.3.2 Quality attributes of the dried granule and impact on manufacturability and tablet quality – development of process understanding

As part of our risk management approach, relationships were established between process variables (including equipment settings and attributes of the input wet granules) and the desired quality attributes of the dried granule, incorporating a Design of Experiments approach at a 1 kg scale. In addition to monitoring the conventional equipment parameters (inlet, bed and outlet temperatures, air flow etc), appropriately validated on-line NIR spectroscopy and Lasentec FBRM methods were used to measure the water content and particle size distribution of the granule during drying. Granules from the DOE were converted to tablets to assess impact on manufacturability and tablet quality. The range of potential process variables and the granule and tablet quality attributes considered are shown in Table 4.

Table 4 – Process variables and quality attributes for the fluid bed drying operation

Process variables	
Drying parameters	**Input material attributes**
Inlet air temperature	Water content
Inlet air humidity	Granule particle size distribution
Air flow rate	
Fill level	
Filter sock cycle	
Heating rate	
Cooling rate	
Quality attributes	
Dried granule	**Tablet**
Particle size distribution (fines)	Disintegration
Water content	Dissolution
Degradation (des-ethyl examplain)	Weight uniformity
	Content uniformity

From the DOE work, the granule quality showed high sensitivity to the inlet air temperature and flow rate, and also to the water content and particle size distribution and of the in-going wet granulate, but is essentially insensitive to the other parameters. Specifically, inlet air humidity was shown to have a negligible effect in the range 20-40% RH. Since the inlet humidity is controlled within this range in all of the manufacturing facilities used for examplain hydrochloride tablets, this parameter is not critical. A strong interaction was observed between the effects of inlet air temperature and flow rate on granule properties, consistent with our previous experience of fluid bed drying of granules.

The DOE confirmed the existence of two failure modes for the drying operation – degradation / hydrolysis of the API (linked to granule water content), and generation of fines (by breaking down the granules). From the DOE experiments, contour diagrams were generated to show the projected impact of different inlet temperatures and flow rates on the amount of degradation and level of fines (Figure 28). The red areas represent combinations of inlet temperature and flow rate that lead to

unacceptable product quality. From these plots, it can be seen that different combinations of these parameters are required to avoid each failure mode.

(Figure 29)shows the intersection of the two plots, and describes the sets of parameter values that avoid both failure modes.

Figure 28 - Effect of inlet temperature and air flow on degradation and generation of fines, as shown by the DOE (red = does not meet quality requirements)

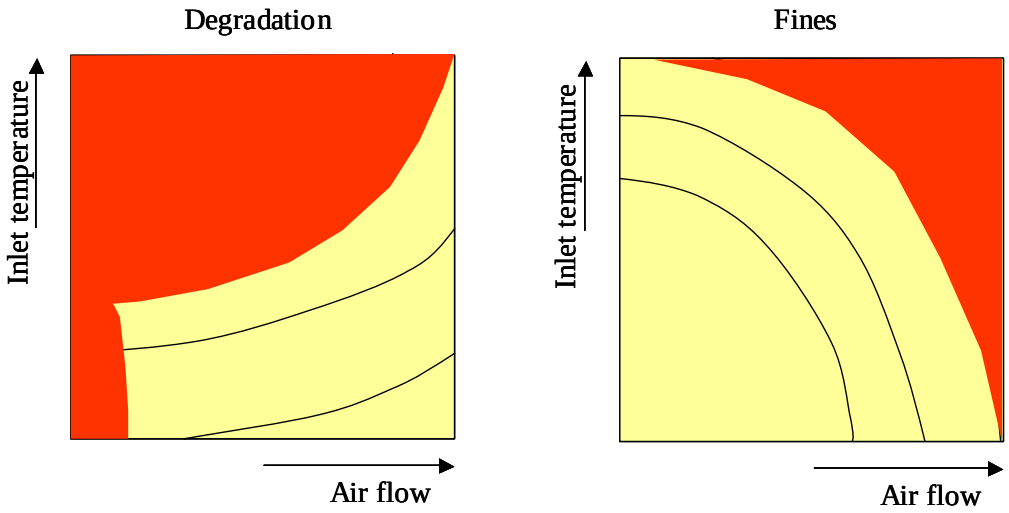
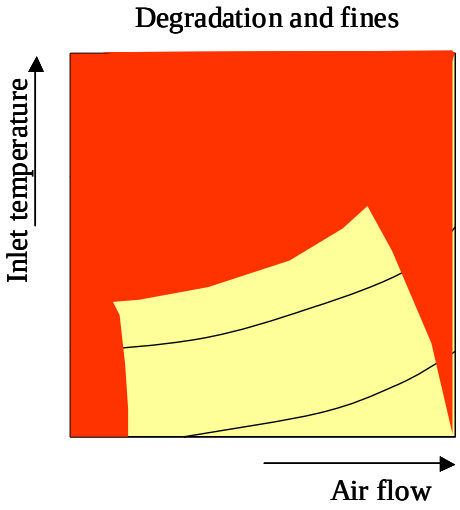


Figure 29– Interaction of inlet temperature and air flow for combination of failure modes (red = does not meet quality requirements)



3.2.P.2.3.1.3.3 Quality attributes of the wet granulate (from the previous unit operation)

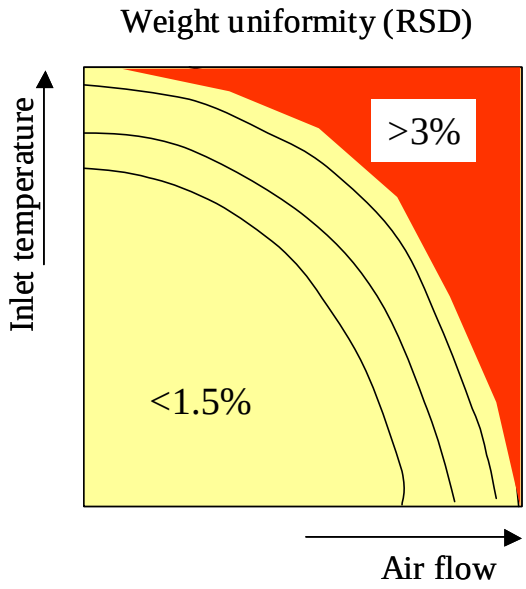
The DOE showed that water content of the wet granulate and its particle size distribution have the potential to impact finished product performance. These factors are considered important, however, they are both adequately controlled in the granulation operation itself.

3.2.P.2.3.1.3.4 Granule water content after drying

See Section 3.2.P.2.2.1. Formulation Development

Generation of a high level of fines leads to poor flow during tableting, and manifests itself as increased variability in unit dose mass, as shown in (Figure 30). A smaller impact is seen on content uniformity, however there is no significant effect on disintegration or dissolution. The edge of failure was defined as RSD > 3%, as this gives a significant probability of failing the pharmacopoeial test.

Figure 30 – Effect of inlet temperature and air flow on tablet weight uniformity, as derived from the DOE (yellow = does meet quality requirements)



Formulation development studies show that a water content of up to 2% w/w in tablets produces acceptable drug product stability, and studies have shown that water content does not change after granulation upon tableting and packing.

It was also observed that over-drying (to a final water content of <1.5%) generated increased levels of fine particles, which led to flow problems during tableting and to variable tablet weight. The production of fines is attributed to forced removal of water from inter-particle bridges, leading to breakdown of the granules. Hence it is necessary to control the end-point of the drying process to give a final water content in the range 1.5-2.0% to avoid both degradation in the finished tablet on stability and manufacturing problems due to over-drying.

The DOE, however, showed that control of water content of granule alone is not sufficient to assure the quality of examplain hydrochloride tablets.

3.2.P.2.3.1.3.5 Impact of the time course of the drying process

A series of drying experiments was performed at 1 kg scale using wet granulate with water content of 18±0.5% (as is routinely produced by the granulation process), and the inlet temperature and air flow were varied. Each drying operation was stopped when the water content was in the range 1.5-2.0%. The water content of the granules, and their particle size distribution were monitored on-line. (Figure 31) shows the time course of water removal for each of these experiments, and the results of the experiments are summarised in Table 5.

Figure 31 - Process trajectories for drying of examplain hydrochloride wet granulate (see text for description)

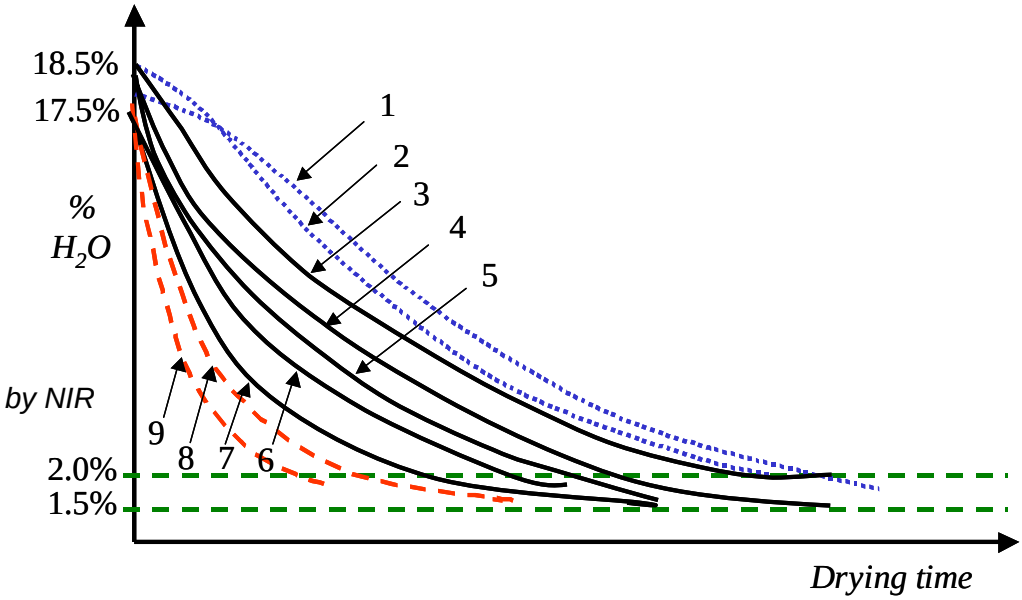


Table 5– Summary of results of varying drying process trajectory

Experiment / Process Trajectory	% des-ethyl examplain (<1.0%)	% fines (< x µm) (<15%)	Weight uniformity (RSD)	Acceptable quality?
1	1.7	4	1.3%	No – high des-ethyl level
2	1.3	7	1.7%	No – high des-ethyl level
3	0.3	5	1.5%	Yes
4	0.3	5	1.4%	Yes
5	0.2	6	1.7%	Yes
6	0.3	4	1.3%	Yes
7	0.2	7	1.6%	Yes
8	0.2	17	3.4%	No – poor flow impacts weight uniformity
9	0.2	20	5.3%	No – poor flow impacts weight uniformity

The granules made using the slowest drying conditions shown by the blue (dotted) lines gave elevated levels of des-ethyl examplain, but satisfactory amounts of fines. In contrast, the most rapid drying trajectories shown in red (dashed lines) resulted in granules with very low levels of degradation, but increased quantities of fine particles. As before, this was demonstrated to lead to flow problems during tableting and to increased variability of tablet weight. All of the process trajectories shown by black lines gave granules with acceptable values for the particle size distribution for downstream processing and the amount of des-ethyl examplain.

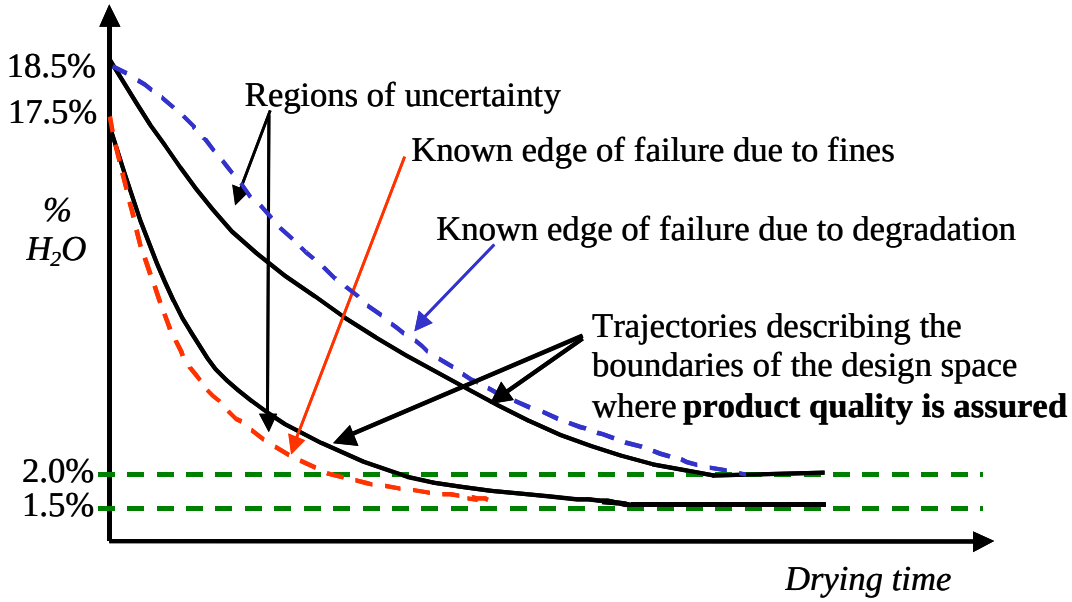
In conclusion, these experiments demonstrate that extended exposure to high water content at elevated temperature leads to degradation of the examplain hydrochloride in the granule and can result in tablets containing unacceptably high levels of des-ethyl examplain at the time of release, despite the water content of the dried granule being at an acceptable level. On the other hand, over-rapid removal of the water

results in breakdown of the granules and production of large quantities of small particles. This, in turn, leads to flow problems in the tablet press.

3.2.P.2.3.1.3.6 Development of Design Space and Control Strategy for the drying operation

Based on our detailed understanding of the process, incorporating results from the DOE investigations, it is clear that the time course of the water removal (the drying trajectory) in conjunction with control of the final water content is critical to assure both quality attributes simultaneously. All of the drying trajectories shown by black lines in (Figure 31) produced granules of appropriate quality, hence these trajectories can be used to define a region where product quality is assured. As described in ICH Q8, this is a representation of the design space for the drying operation. This is shown in (Figure 32) A wide range of combinations of air flow and inlet temperature have been shown to give trajectories inside this design space in experiments at 1 kg scale.

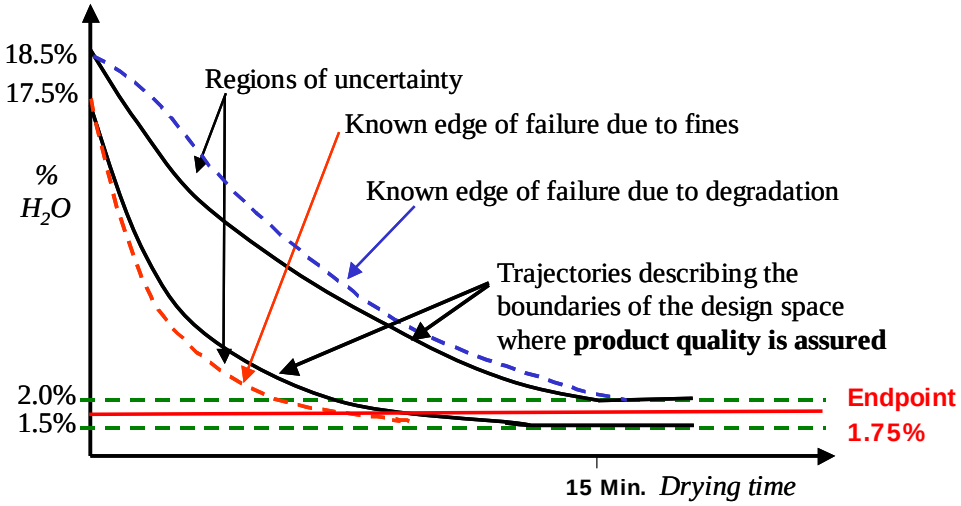
Figure 32 – Graphical description of the design space for the drying operation for examplain hydrochloride tablet manufacture



For a fluid-bed drying operation, there is no good scientific model to predict performance for theoretical process trajectories between those known to produce acceptable quality product (in black in Figure 32), and those known to fail (in red and blue). Hence no extrapolation beyond the experimental results is possible and the boundaries of the design space are defined by the outermost black trajectories. Outside this design space there is a region of uncertainty (where no experiments have been performed) and then trajectories are reached where an unacceptable region is observed, as shown by the dashed lines in Figure 32. It is possible that future experiments would explore the regions of uncertainty and would allow us to move the edge of the design space closer to the known failure points. Any changes of this sort would be submitted for approval in the usual way.

In accord with ICH Q8, we believe that any process trajectory within the design space will produce material of appropriate quality, and that we should therefore have freedom to operate the process anywhere within this range without notification. A control strategy for the fluid bed drying unit operation is described graphically in Figure 33, where the process can be controlled by adjusting either the inlet air temperature or the flow rate or a combination of the two to keep the trajectory in the design space. Drying is stopped when the water content falls to 1.5-2.0%, as measured by on-line NIR spectroscopy (set point 1.75%).

Figure 33



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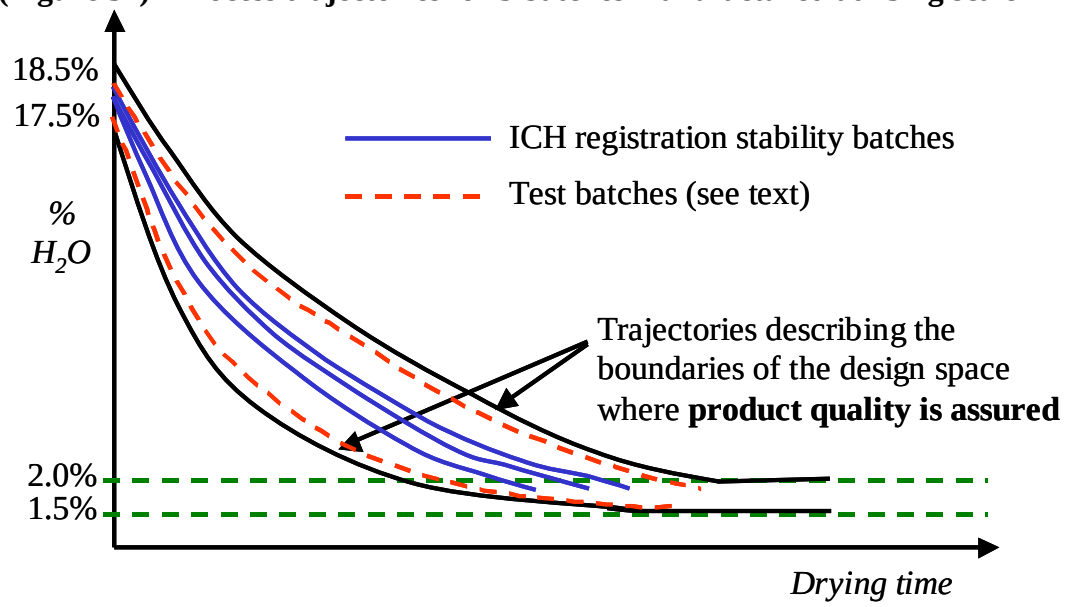
The effect of scale was studied

The appropriateness of this description of the design space for the drying operation has been verified at larger scales (10 kg and 25 kg), including the manufacture of ICH registration stability batches. Drying trajectories for the three 25 kg ICH batches are shown in blue in.(Figure 34) Two additional 25 kg batches were manufactured to confirm that product of appropriate quality was produced if the drying trajectory approached the boundaries determined at smaller scale. Trajectories for these batches are shown in orange in This confirms that the design space for drying, as characterised by the process trajectories shown in (Figure 32), is independent of scale, and that operation within these trajectories will ensure material of appropriate quality.

(Figure 34)– Process trajectories for 5 batches manufactured at 25 kg scale



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A model can be established for predicting degradation as a function of drying rate. This model (Figure 35) summarises data presented in Table 5, and (Figure 31) and (Figure 34), the red line representing the limit for degradation at time of manufacture of not more that 1% des-ethyl examplain.

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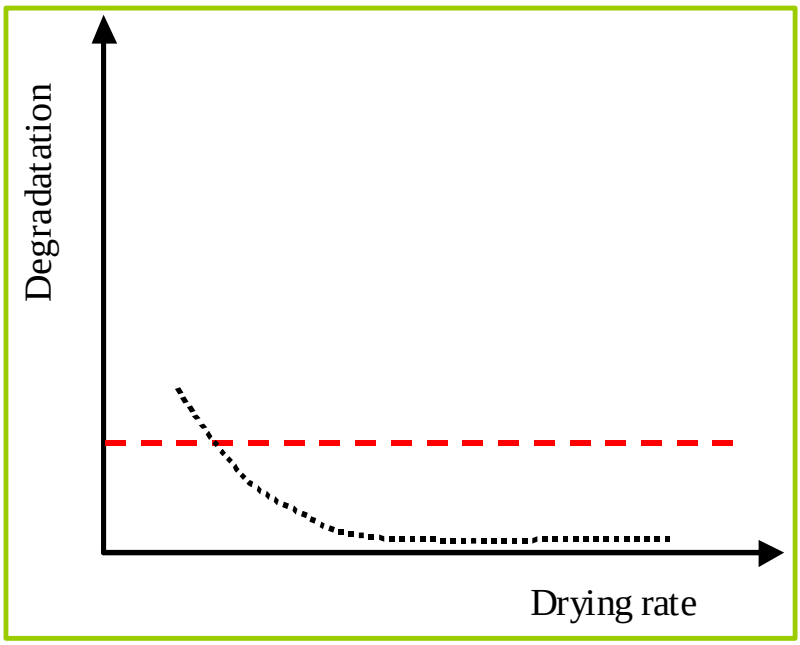
Figure 35 : Degradation as a function of the drying rate



3.2.P.2.3.1.3.7 Impact of process understanding for the fluid bed drying operation on the quality control of examplain hydrochloride tablets.

Des-ethyl examplain is the only degradation product observed in examplain hydrochloride tablets and, as described in Section 3.2.P.5.4, an appropriately validated test exists for measuring its level at release and on stability and acceptance criteria have been proposed consistent with ICH Q6a and Q3b.

In addition to the early formulation studies relating level of tablet water content on formation of des-ethyl examplain stored in Aclar blisters at 40°C/75% RH (Figure 10), further confirmatory accelerated studies of samples resulting from the 1kg scale work (Trajectories 2, 3, 5 and 7) and 25kg scale (test batches coloured red in (Figure 31) were conducted. A batch with a water content close to the upper limit of 2.0% (2.1%) was also placed on long term stability at 25°C/60% RH packed into Aclar blisters (Trajectory 3). In all cases accelerated testing for 6 months at 40°C/75% in Aclar blisters showed rates of degradation lower than the batch containing 2.4% water content in (Figure 10). Furthermore, the batch with an initial water content of 2.1% and des-ethyl examplain level of 0.3% has satisfactory stability after 12 months at

25°C/60% in Aclar blisters, with the level projected to be less than the acceptance limits of des-ethyl examplain at the end of shelf life of 2%.

The process understanding described above for the fluid bed drying operation shows that control of the trajectory of the drying process within defined limits (as determined by on-line NIR spectroscopy), coupled with a final water level in the granule of 1.5-2.0%, ensures that the level of the degradation product in the tablets at time of release will be significantly below the acceptance criterion (1.0%) and that no significant amount of degradation will occur during the shelf life of the product when it is packed in Aclar blisters.

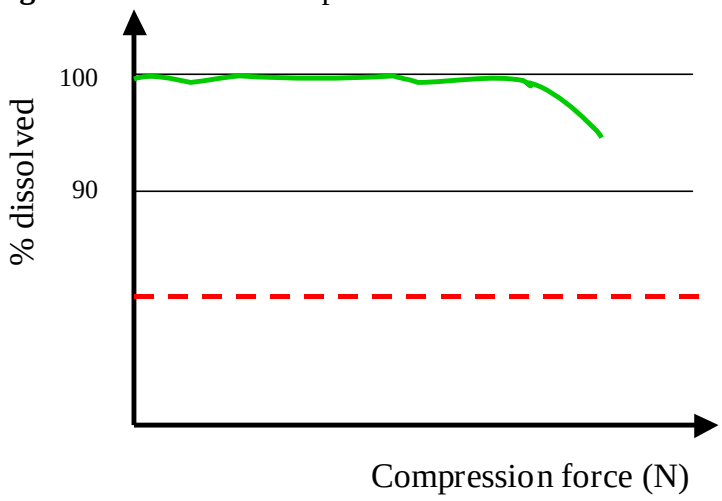
3.2.P.2.3.1.4 Granulation / lubrication

No detail is included for this operation in the mock submission.

3.2.P.2.3.1.5 Compression

In-process limits for tablet parameters of weight, thickness and hardness are used to ensure consistency during the compression process and to ensure that tablets of good quality are produced. For examplain 20 mg tablet, control of tablet weight assures drug content, while control of hardness assures that tablets are hard enough to withstand the packing operation but not too hard to affect disintegration and dissolution of the drug substance. Development studies showed that there is a small reduction in dissolution rate and an increase in disintegration when high compression force conditions are used, data are shown in Figure 36 and Figure 37, however for both cases values are always within acceptance criteria for the ranges of compression force studied.

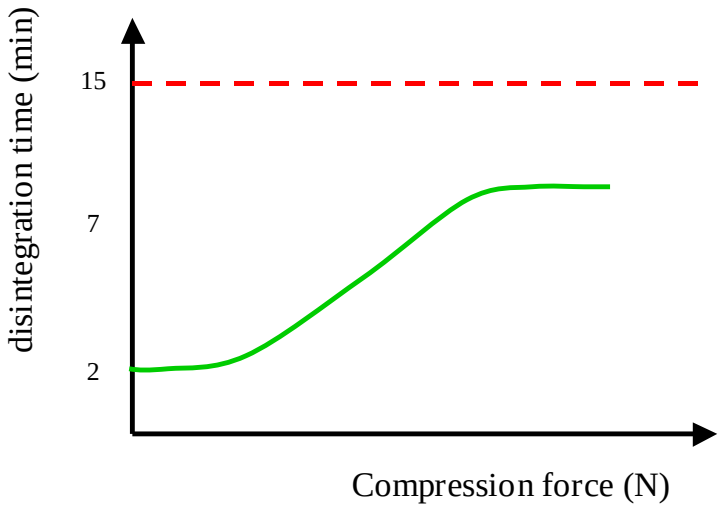
Figure 36– Effect of compression force on dissolution



The range for tablet hardness can be reliably achieved provided that granules have been generated according to the design space described for the wet granulation and fluid bed drying process steps, see 3.2.P.2.3.1.2 and 3.2.P.2.3.1.3.

An upper limit for mean tablet hardness has therefore been set and monitored using at-line NIR measurements in order to assure that dissolution of examplain 20 mg tablet is not reduced by over-compression.

Figure 37 - Effect of compression on disintegration



3.2.P.2.3.2 Conclusion

A robust formulation and manufacturing process have been developed for examplain tablets, 20 mg. Using quality risk management tools and appropriate design of experiment studies, in combination with characterisation of drug substance and raw materials, individual unit operations, and combination of unit operations have been examined to derive process understanding and identify important to quality process parameters. Only one processing step, fluid bed drying, has been shown to be critical, through its impact on degradation product level at time of manufacture and end of shelf life.

Studies summarised in this submission show that there is a clear link between the critical unit operation fluidised bed drying and the critical attribute from that unit operation, water content, which is the major factor leading to formation of the degradation product, des-ethyl examplain. Limits for des-ethyl examplain of 2% at end of shelf life have been qualified in toxicology studies and assure safety of the patient.

Extensive studies performed at laboratory scale, confirmed at larger scales, have shown that control of the trajectory of the drying process (as measured by on-line NIR spectroscopy) within defined limits to give a final granule water content of 1.5 to 2.0% ensures an appropriately low level of degradation, independent of scale.

3.2.P.2.4 Container Closure System

A range of container closure systems were investigated during development of examplain hydrochloride tablets. Clear, colourless Aclar UltRx 2000 unit dose blisters have been selected for commercialisation and were used for the formal stability program (see 3.2.P.2.8 *Stability*). The selected container closure system has been demonstrated to be suitable for use with examplain hydrochloride tablets in terms of protection, compatibility, safety and performance. A detailed description of the container closure system is presented in section 3.2.P.7 *Container Closure System*.

Protection

Examplain hydrochloride is known to be sensitive to hydrolysis under extremes of temperature and humidity. Aclar UltRx 2000 unit dose blisters with aluminium foil backing have been demonstrated to provide effective protection of the tablets, leading to <0.1% degradation after 6 months at 40ºC/75% RH (see 3.2.P.8 *Stability*). Examplain hydrochloride tablets are not photosensitive, so there is no need for opaque or tinted blister materials.

Compatibility

The blister materials meet Pharmacopoeial requirements. Studies reported in 3.2.P.8.1 *Stability Summary and Conclusion* I indicate that the proposed commercial pack is compatible with examplain hydrochloride.

Safety

There are no safety issues with the proposed commercial packaging materials. All of the packaging components used are listed as "Generally Recognised as Safe" (GRAS) or "suitable for direct and indirect contact with food", as per 21 CFR 174-186. More detail of the composition of each component is given in Section 3.2.P.7 *Container Closure System.*

Performance

The container closure system for examplain hydrochloride tablets is designed to provide adequate protection for the drug product until use. The stability studies described in 3.2.P.8 *Stability* support the use of the container closure system.

Design space for packaging materials

Based on the extended understanding of the degradation of the product and the dominating influence of residual water to long term stability as well as the conclusions of the ICH Q1A stability program, it can be concluded that the design space for packaging material for Examplain hydrochloride tablets is given by the permeability of the packaging material. All packaging material that has an equal or better permeability than Aclar UltRx 2000 will lead to a stable product throughout the shelf life in moderate climates (zone II). This is also supported by the outcome of additional stability studies in less protective packaging material and in very tight containers for climatic zones III and IV, hot and humid climates. In these studies the influence on degradation in tight containers (full aluminium blister and high density polyethylene bottles) were studied. These studies have shown, as expected from the understanding of the degradation, that also under hot and humid storage conditions the product is stable if protected from uptake of additional humidity.

3.2.P.2.5 Microbiological Attributes

The microbiological requirements for the starting materials are monitored based on the specifications in their approval procedure. The water used for the granulation step has the defined quality of "purified water"..

3.2.P.2.6 Compatibility

This section is not applicable for solid dosage forms.

3.3 Control Strategy as result of the quality risk management

The control strategy is based on a Quality Risk Management Process and will ensure that the product meets its specifications without recourse to further testing. The finished product specification is given in P4.

Critical to Quality Attributes (CQA)

Our present formulation and process understanding has shown that the only critical to quality attribute is the level of degradation product, des-ethyl examplain. Des-ethyl examplain is also the main metabolite in animals as well as in humans and is qualified at the level of 10%. It is considered that des-ethyl examplain is not of any safety risk to patients up to the level qualified.

Quality Risk Management

Using the initial quality risk management (see Table 2) development activities as described above have generated an enhanced level of formulation and process understanding of possible critical unit operations. This high level understanding was used to define critical and non-critical process parameters and unit operations. The Quality Risk Management analysis using FMEA analysed all possible failures, their impact, probabilities and the detectability. The full FMEA is available for inspection. A summary is described in Table 6.

Table 6: Classification of unit operation to have an impact on quality

Unit operations / Quality attributes	Dispensing (Raw Material Properties)	Granulation	Drying	Blending (Magnesium Stearate)	Tableting	Packaging
Dissolution	Particle size API	Power consumption	Prior knowledge	Not critical to quality	Not critical to quality	Prior knowledge
Disintegration	Particle size API	water amount and feed rate	Prior knowledge	Not critical to quality	Not critical to quality	Prior knowledge
Hardness	Prior knowledge	Prior knowledge	Prior knowledge	Not critical to quality	Not critical to quality	Prior knowledge
Assay	Prior knowledge	Prior knowledge	Prior knowledge	Prior knowledge	NIR measurement	Prior knowledge
Content uniformity	Prior knowledge	Power consumption	Not critical to quality	Not critical to quality	NIR measurement	Prior knowledge
Degradation	Prior knowledge	Water amount and feed rate	Not critical to quality	Prior knowledge	Prior knowledge	Prior knowledge
Stability	Prior knowledge	Prior knowledge	Control water content	Prior knowledge	Prior knowledge	Prior knowledge
Appearance	Prior knowledge	Prior knowledge	Not critical to quality	Prior knowledge	Not critical to quality	Prior knowledge
Identification	NIR of raw material	Prior knowledge	Prior knowledge	Prior knowledge	Prior knowledge	Prior knowledge
Water	Prior knowledge	Prior knowledge	Control water content	Prior knowledge	Prior knowledge	Prior knowledge
Microbiology	Specification of starting material	Purified water used	Prior knowledge	Prior knowledge	Prior knowledge	Prior knowledge

Influence:

low	Prior knowledge
Original high	Controlled by a) process understanding or b) included in the control strategy
Process understanding	Original high influence: Development studies have shown to be not critical to quality
Control Strategy	Original high influence: Development studies have shown to have potential influence to quality. Therefore control measurements have been introduced.

Based on the Quality Risk Management the optimal control strategy was defined so that all possible failures were reduced to an acceptable level. Therefore process controls including end point controls were established based on direct and timely measurements of relevant material attributes and relevant process parameters (Table 6)

Proposed Controls

The control strategy proposed ensures that the process can manage the natural variability of raw materials to give a consistent product. The process is therefore adjusted to give target quality endpoints of material attributes that are relevant for the next processing steps.

Dispensing

The NIR spectra of all raw materials (drug substance and excipients) are recorded and checked for identity. The NIR spectra are also used to detect differences in physicochemical properties by correlating the NIR spectra in a multivariant way with

end product quality characteristics. Normal GMP double-checking of weighing and transfers assures correct weights of materials are added.

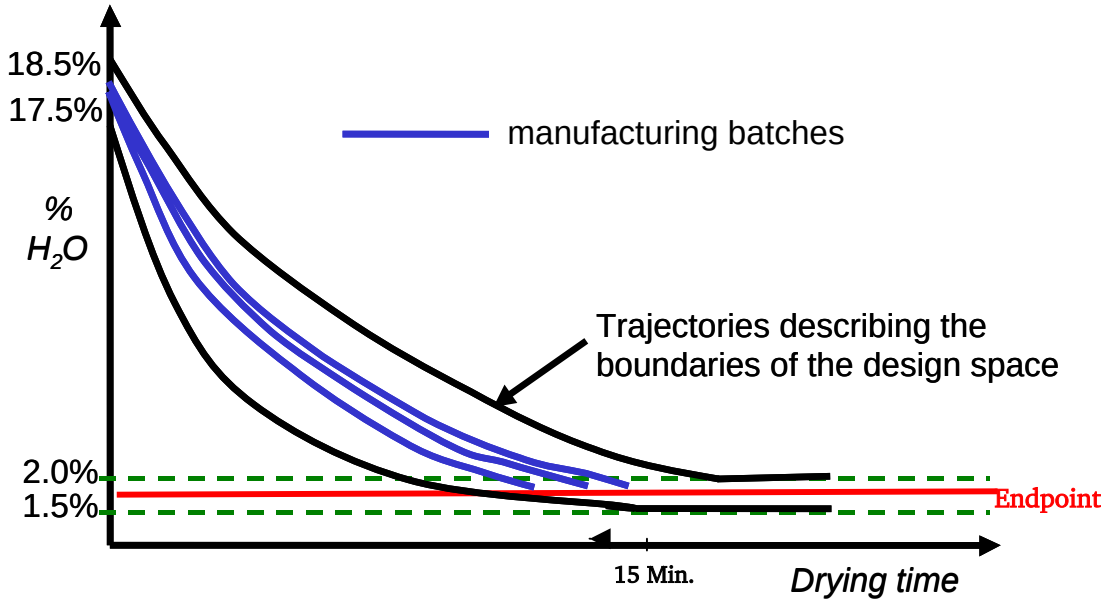
Granulation

The granulation process is controlled by measuring the power consumption during granulation. The water amount per mass of granulate and the addition rate are fixed based on our process understanding and DOE as described above. Wet massing is finished after a preset time interval (approx. 6 min.) following the peak of power consumption. This compensates for differences in the raw materials properties e.g. batch-to-batch differences of water content and particle size distributions and allows a process to operate independent from raw material properties, leading to a consistent quality of granules.

Drying

The progress and end point of drying are monitored by on-line NIR and on-line laser particle size measurements. The critical material attribute, water content of the granulate is controlled by adjusting air flow and inlet air temperature to stay within the defined design space. The particle size distribution is monitored by laser diffraction on-line measurements to ensure that the fraction of fine particles is not too high and may impact processability of the granulate for tabletting. The end point of the drying is defined when the water content measured by on-line NIR reaches the range 1.5% to 2.0% (target of 1.75%) (see Figure 38). By this end point control proposed for drying, the granulate has the defined critical material attribute that is necessary for the following unit operations and ensures a final quality of the product that is stable over the full proposed shelf life.

Figure 38 : End point control of Drying



Blending

The end point of the blending is determined by on-line NIR. This ensures that magnesium stearate is evenly distributed, and that content of active remains uniform.

Tableting

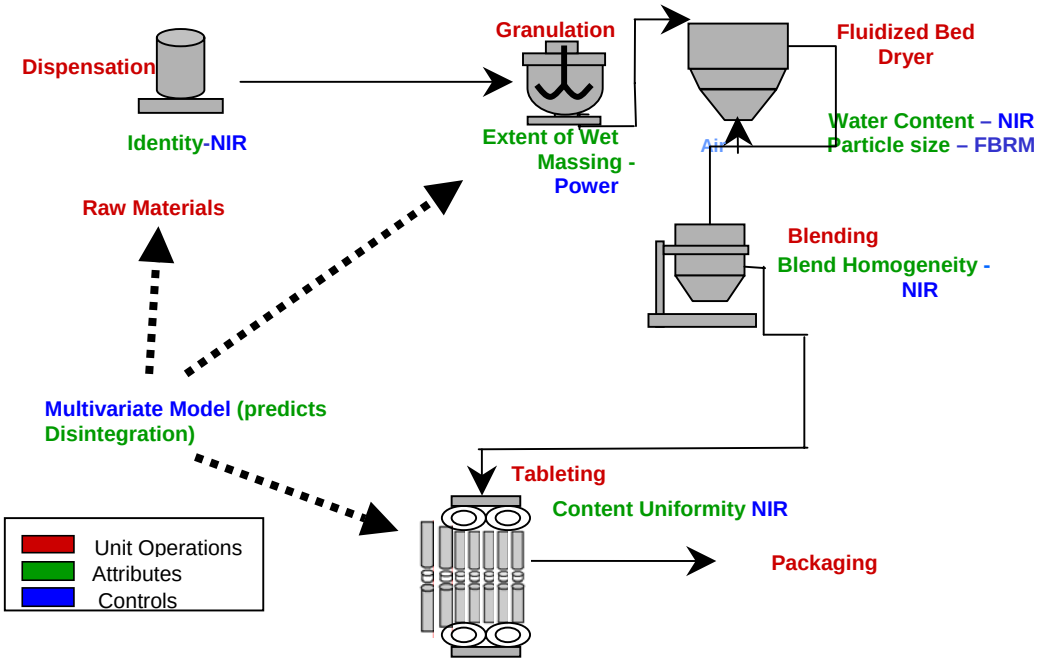
The compression machine is equipped with a modern compression force feedback control that adjusts the granulate feed to ensure target tablet weight and consequently content uniformity. An automated weight control and at-line NIR measurement system allows feedback to the feed control and compression force system of the compression machine. The compression control system with 100% control of all tablets eliminates any risk of not acceptable compression forces during tabletting.

At-line NIR confirms content uniformity and can detect any unexpected segregation of the blend during compression. The NIR also allows the monitoring of water content of the final tablets. A multivariant model for hardness, disintegration and dissolution allows prediction of hardness, disintegration and dissolution.

In summary the following process controls will ensure robust and consistent processes leading to consistent end product quality (see Figure 39)

- NIR for raw materials on receipt or when dispensing
- power consumption for granulation end point
- on-line NIR and laser diffraction of the drying process
- on-line NIR for blend uniformity
- compression force control and at-line NIR during compression for content uniformity, prediction of hardness, disintegration and dissolution

Figure 39 : Control Strategy Summary



3.3.1 Impact of the control strategy to end product quality specification

Dissolution – Disintegration

The mechanistic understanding of the disintegration and dissolution of Examplain tablets together with the established multivariant prediction of disintegration and dissolution allows an excellent understanding of factors influencing disintegration and dissolution. The conclusion of this understanding is that no process or product formulation parameter within the established design space can be considered as critical for these quality attributes. The properties of the drug substance, and design of formulation and process meet the requirements given in ICH Q6A (Decision Tree # 7(1)) for replacement of dissolution with disintegration. In conclusion, the product can be considered to be insensitive to the variability of the raw materials and of the processing parameters investigated during development and scale-up with respect to disintegration and dissolution and we propose to not perform dissolution and disintegration on finalised product. Dissolution will not be included in the drug product specification.

Hardness

For this product hardness is mainly influenced by wet granulation and by the compression force during compression. Control of all unit operations ensures that the processing properties of the granulate are reproducible. This ensures that together with the compression force feedback control during compression, the variability of hardness is low and predictable. DOE has demonstrated that disintegration and dissolution are not significantly influenced by hardness. The NIR measurements at line to compression also allow an excellent prediction of hardness based on the correlation of NIR predictions of hardness with conventional hardness measurements. Hardness is not a critical quality attribute for Examplain hydrochloride tablets and will not be included in the drug product specification.

Assay and Unit Dose Uniformity

Mechanistic understanding of the relevant unit operations and the impact on variations on content uniformity and assay together with the extensive process controls and monitoring that allow the adjustment of all unit operations to defined material attribute end points lead to reproducible results of assay and content uniformity. Control of the fluid bed drying step, to operate within defined drying trajectories and to avoid over-drying, ensures that excessive amounts of fines are not produced. As a consequence, the dried, lubricated granule flows well, ensuring that there are no weight uniformity issues during compression. The at-line monitoring of content uniformity by NIR and the weight measurements ensures that all deviations from expected performance will be detected and corrective adjustments of feed and the compression force can be made, obviating the need for end point testing. The results from the at-line NIR measurements will be used for the release decision on content uniformity and the mean of the NIR value will be the assay for release.

Degradation

Process and formulation understanding showed that the formation of des-ethyl Examplain at time of manufacture is influenced by water addition rate during

granulation, by the trajectory of the fluid bed drying process, and the water content in resultant tablets. During processing, temperature and water content of the granulate are controlled and ensure that hydrolysis is minimized. Experience and process understanding show that the drying process influences the level of degradation during manufacturing. The controlled drying process leads to product that has consistently reproducible low levels of degradation and water content. All other processing steps when operated within relevant design spaces have been shown not to influence the level of water content and degradation in the end product, therefore neither moisture content nor degradation product levels will be tested in finished product.

Stability

Extensive supportive stability studies and the ICH Q1A stability studies have shown that the stability of the product is predominantly influenced by the water content that leads to hydrolysis. Except at stress temperatures, no degradation products other than the formation of des-ethyl Examplain are found at relevant levels. The uptake of humidity during storage is minimized by adequate protective (moisture tight) proposed packaging material. As a consequence of this understanding the control of the water content at the time of manufacture of bulk product was considered as critical. The proposed controls of the only critical process step, the drying of the granulate, has shown to effectively guarantee that water content is less than 2% w/w at the end of manufacturing. The monitoring of water content by NIR during compression provides assurance that any deviation from the established product characteristics will be detected.

Based on development data which demonstrates the high level of understanding of the stability of the product and the high level of reproducibility of manufacturing of the product due to extensive real time control of the manufacturing process a reduced annual stability monitoring is proposed. It has been shown that the rate of production of des-ethyl examplain is related to moisture content of tablets at time of manufacture and the uptake during storage. Based on this underpinning science of water uptake and degradation rates, the selection of the packaging material, the control of storage of bulk product before packing, design of package, long term data on pilot batches, supported by long term testing of the first 3 production batches, it is proposed to conduct confirmatory stability testing after changes of equipment, scale or site, or other changes as assessed by a quality risk management exercise by comparing accelerated testing of changes of samples stored in Aclar blisters at 40°C/75%R.H. for up to 3 months. The degradation level and disintegration will be tested only and degradation levels compared with rates produced from development studies, described in Sections 3.2 P.2.2.1 (Figure 10) and Section 3.2 P.2.3.1.3.7, and initial accelerated studies as part of ICH pilot and full scale stability programmes.

3.3.2 Conclusions: Proposal for real time release

Based on the high level of formulation and process understanding, the extensive Quality Risk Management and the sophisticated control strategy including advanced on-line and real time measurements of relevant material attributes the consistent acceptable quality of the end product is guaranteed. No additional batch wise end product testing is needed.

3.3.3 Monitoring program

A monitoring program is proposed for adjusting the multivariant model to manufacturing experience. In regular intervals (at least quarterly) conventional end product tests will be performed and the prediction models will be verified and if needed recalibrated.

3.4 SCIENCE- AND RISK-BASED REGULATORY APPROACH

Development of a formulation and process which is understood and characterised has produced using quality risk management approaches a series of design spaces for unit operations (exemplified by granulation and fluid-bed drying unit operations). Based on the knowledge and understanding we propose the following regulatory flexibility:

Continuous Improvement

Changes to the manufacturing process within the established design space will not be submitted, if required, for regulatory prior approval.

Scale

Knowledge from development studies leading to mechanistic process understanding, and using quality risk management, has resulted in design spaces for fluid bed drying and wet granulation. These design spaces have been demonstrated to be transferable to and reproduced for different process equipment, representing different processing scales. Provided that the process continues to operate within these design spaces, it is proposed that changes of scale will be made immediately without notifying authorities.

Site

Mechanistic process understanding, control of the process to critical quality attribute end points , and the use of quality risk management have resulted in a design space that transferable between different process equipment and therefore allows transfer of the process from one site to the other. It is therefore proposed that, providing the process continues to operate within this design space, a transfer from one site to other sites is made immediately with authorities being notified of change of address. The site change will use the presented procedure and means for reproducing design space at other sites with equivalent equipment, equivalent sources of raw materials, inspected GMP status of the site and with equivalent quality systems. For the first 3 batches full end product testing will be performed to confirm the validity of the process model and the first batch will be put into the confirmatory stability program and monitored according to the proposed confirmatory stability study protocol.

Process Validation

Assurance is given that each process step (granulation and fluid-bed drying are examples) is routinely and reproducibly producing material for the next processing step ensuring compliance with the finished product specification. This assurance is given by good process understanding and control, which includes process verification, compliance with the design space and application of the control strategy, which includes key attributes for a processing step. Therefore the 3 batch validation is replaced by a continuous process verification.

Real Time Release

Based on application of the control strategy it is not proposed that any additional end product tests will be applied for release.

Reduction in Confirmatory Stability Studies

Based on development data which demonstrates the high level of understanding of the stability of the product and the high level of reproducibility of manufacturing of the product due to extensive real time control of the manufacturing process a reduced annual stability monitoring is proposed. It has been shown that the rate of production of des-ethyl examplain is related to moisture content of tablets at time of manufacture and the uptake during storage. Based on this underpinning science of water uptake and degradation rates, the selection of the packaging material, the control of storage of bulk product before packing, design of package, long term data on pilot batches, supported by long term testing of the first 3 production batches, it is proposed to conduct confirmatory stability testing after changes of equipment, scale or site, as assessed by a quality risk management exercise by comparing accelerated testing of changes of samples stored in Aclar blisters at 40°C/75%R.H. for up to 3 months. The degradation level and disintegration will be tested only and degradation levels compared with rates produced from development studies, described in Sections 3.2 P.2.2.1 (Figure 10) and Section 3.2 P.2.3.1.3.7, and initial accelerated studies as part of ICH pilot and full scale stability programmes

Drug Substance Manufacturing Changes (only limited data given in this mock document)

Studies on drug substance leading to development of appropriate drug substance specification with limits for degradation product and particle size indicate that changes in drug substance manufacture will not impact on drug product stability, hence it is proposed not to perform stability studies on drug product following changes in drug substance manufacturing providing that drug substance complies with specification.

Information will be available at the appropriate site for inspection if required.

3.5 CLINICAL TRIAL FORMULAE

All clinical investigations conducted in connection with acute anxiety following regulatory submission used either an intravenous solution or immediate release tablets. The 1 mg, 10 mg and 20 mg tablets were initially developed for clinical trials. The qualitative tablet formulation has remained the same throughout the clinical program. A single 20mg strength is proposed for commercialisation.

Qualitative and quantitative formulae are described in this section for the proposed commercial tablet formulation, registration stability studies, and tablet and intravenous solution formulations used in clinical studies.

APPENDIX

Table 6. Index

	Described in Table
The Proposed Commercial Formulation of examplain hydrochloride IR tablets 20 mg	Table 7
Research Formulations of examplain hydrochloride IR tablets 1mg, 10mg and 20 mg	Table 8
IV Formulation of examplain hydrochloride (1 mg/mL)	Table 9

Table 7. The Proposed Commercial Formulation of examplain hydrochloride IR tablets 20 mg

Component	20 mg [b]
Examplain hydrochloride	21.46 [c]
Mannitol, Ph. Eur.	80.00
Microcrystalline cellulose, [a] Ph. Eur.	78.54
Povidone, Ph. Eur.	10.00
Croscarmellose sodium, Ph. Eur.	6.00
Magnesium stearate, Ph. Eur.	4.00
Purified water, Ph. Eur.	(As required) [d]
TOTAL (mg/tablet)	200.00
Use: **Proposed commercial formulation and registration stability studies**	

[a] Microcrystalline cellulose is referred to in Ph. Eur. as "Cellulose, microcrystalline"
[b] 8 mm round, biconvex, white tablet, with "Tabs'R'Us" script on one side of the tablet and "EXA 20" on reverse
[c] Equivalent to 20 mg of examplain based on a theoretical drug substance potency of 93.2% w/w
[d] Evaporated during processing and Does not appear in the finished product

Table 8. Research Formulations of examplain hydrochloride IR tablets 1mg, 10mg and 20 mg

Component	1 mg [(b)]	10 mg [(b)]	20 mg [(b)]
Examplain hydrochloride	1.07 [(c)]	10.73 [(c)]	21.46 [(c)]
Mannitol, Ph. Eur.	80.00	80.00	80.00
Microcrystalline cellulose, [(a)] Ph. Eur.	98.93	89.27	78.54
Povidone, Ph. Eur.	10.00	10.00	10.00
Croscarmellose sodium, Ph. Eur.	6.00	6.00	6.00
Magnesium stearate, Ph. Eur.	4.00	4.00	4.00
Purified water, Ph. Eur.	(As required) [(d)]	(As required) [(d)]	(As required) [(d)]
TOTAL (mg/tablet)	200.00	200.00	200.00
Use: **Phase 1, Phase 2 and Phase 3 clinical studies**			

[(a)] Microcrystalline cellulose is referred to in Ph. Eur. as "Cellulose, microcrystalline"
[(b)] 8 mm round, biconvex, white tablet, with "Tabs'R'Us" script on one side of the tablet and "EXA 123" on reverse.
[(c)] Based on a theoretical drug substance potency of 93.2% w/w
[(d)] Evaporated during processing and Does not appear in the finished product

Table 9. Intravenous Formulation of examplain hydrochloride (1 mg/mL)

Component	1 mg/mL (S01187EA)
Examplain hydrochloride	1.073 [(a)]
Glucose anhydrous Ph. Eur.	50.500 [(b)]
Water for Injection Ph. Eur.	to 1.000 mL

Notes on Injection:
[(a)] Equivalent to 1 mg of examplain based on a theoretical potency of 93.2% w/w
[(b)] As D-glucose anhydrous