Development and Optimization for Generic Capsule Solid Oral Dosage Formulation Using Quality by Design (QbD) Principles

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Abstract *— Traditionally, the development and formulation of generic drugs has focused on the delivery of the product to the next phase of clinical study making the formulation design iterative and empirical. Furthermore, pharmaceutical companies have ensured quality and performance on their product by raw material testing, in-process material testing and end product testing. This traditional approach has induced a knowledge gap in understand the relationship between product quality attributes and their clinical performance. As a result of this approach, regulatory bodies are encouraging the generic companies to include QbD elements in their filling applications with the intention of improve their process understanding. This project design presents an overview of implementation of key elements of Quality by Design to develop a pharmaceutical formula for a generic product.*

Key Terms *— Critical Quality Attributes, Design of Experiment, Quality by Design, Quality Risk Management, Quality Target Product Profile.*

PROJECT STATEMENT

The formulation and development of generic drugs has shown a constant growing in the past five (5) years. Currently, regulatory bodies such as Food and Drug Administration (FDA) are encouraging the generic drug companies to include elements of Quality by Design (QbD) in their fillings. This is being encouraged as a results of drug recalls, scale up issues, regulatory burden and manufacturing failure cost among others. Based on this new initiative a design project was executed to develop a pharmaceutical formula for an oral capsule solid dosage form employing QbD principles. This pharmaceutical formula was developed for pharmaceutical company that is interested in the manufacturing generic drug for US market.

Research Description

This design project involves the development and formulation of pharmaceutical product employing QbD principles. The pharmaceutical product involved as part of this design project consists of generic oral solid dosage form (hard capsule) named as "G-2" 400mg capsules designed to treat "postherpetic neuralgia" and certain types of seizures associated with epilepsy. The formulation and development of this pharmaceutical product is considered important, because it represents a significant source of revenues and gross profit to its manufacturer company upon it is commercially launched. In addition, this formulation will be the first generic product that the company is expected to register in US market. Therefore, successfulness in the formulation of this product would provide confidence to develop and to introduce other product in the market utilizing QbD principles.

Research Objectives

The objective of this design project is to develop a generic pharmaceutical formula for "G-2" 400mg capsules utilizing QbD elements. The design process for this pharmaceutical formula involves the following aspects:

- Definition of Quality Target Product Profile to include quantitative surrogate for different quality characteristics of a drug product considering its clinical safety and efficacy.
- Usage of Quality Risk Management to prioritize knowledge gaps for further investigation.

- Identification of the critical quality attributes that must be controlled to ensure desire product quality.
- Gathering relevant prior knowledge of drug substance physicochemical to assess and mitigate potential risks during formulation studies.
- Definition of pharmaceutical formula that renders a final product in conformance to regulatory requirements.

Research Contributions

The accomplishment in developing generic pharmaceutical formula for "G-2" 400mg capsules would provide confidence to the company in developing generic drug utilizing QbD principles. In addition, the integration of Qbd principles as part of the formulation phase would allow the company the ability to design products and processes reducing the probability of potential adverse situation during scale up and validation phase.

LITERATURE REVIEW

Traditionally, the development and formulation of generic drugs has focused on the delivery of the product to the next phase of clinical study and therefore formulation design has tended to be iterative and empirical [1]. Moreover, pharmaceutical companies have ensured quality and performance on their product by raw material testing, in-process material testing and end product testing. This traditional approach has induced a knowledge gap in understand the relationship between product quality attributes and their clinical performance. Consequently, regulatory authorities have been forced to set stringent specification based on observed properties of exhibit or clinical trial to ensure quality and clinical performance. However, this approach has several disadvantages making it a not cost-effective alternative to pharmaceutical companies.

In order to overcome these road blocks, regulatory bodies are encouraging the generic companies to include QbD elements in their filling applications. Quality by Design is defined as a systematic approach to pharmaceutical development that begins with predefined objectives and emphasizes products and process understanding and process control, based on sound science and quality risk management [2]. This systematic approach means that formulation and manufacturing process must be designed and developed to ensure that the product consistently fulfill predefined quality at the end of the manufacturing process. Therefore, the use of QbD principles requires an understanding of how formulation and process variables influence the product quality [3]. It should be note that fundamental assumptions underlying QbD is that the quality of the product can be assured only if critical sources of variability is understood and is suitably mitigated or controlled within a defined design space [4].

QbD involves several components described below: [2] [4] [5]

- **Quality Target Product Profile:** The definition of Quality Target Product Profile (QTPP) forms the basis of the design and development of products. It is defined as prospective summary of the quality characteristics of a drug product (finished good) that ideally will be achieved to ensure the desired quality, taking into account safety and efficacy of the drug product. The Quality Target Product Profile might include the following considerations: route of administration, dosage form, dosage strengths, container closure system, pharmacokinetic information, and drug product quality criteria. It shall be noted that Quality Target Product Profile only includes patient relevant product performance elements.
- **Critical Quality Attributes:** Critical Quality Attribute (CQA) is define as a physical, chemical, biological, or microbiological property or characteristic that should be within an appropriate limit, range, or distribution to ensure the desired product quality. Therefore, attributes considered as critical must be

controlled within an appropriate limit, range, or distribution to ensure product quality. Critical Quality Attributes of solid oral dosage form are typically those aspects affecting product purity, strength, drug release and stability. Examples of critical quality attributes for oral solid dosage form typically include but not limited to assay, dissolution, identity, and degradation product among others.

- **Quality Risk Management:** Quality Risk Management is defined as a systematic process for the assessment, control, communication, and review of risks to the quality of the drug (medicinal) product across the product lifecycle. Risk assessment is a valuable science-based process used in quality risk management that can aid in identifying which material attributes and process parameters potentially have an effect on product CQA. The goal of quality risk management is to identify risks within a process or event, analyzing the significance of these risks, and take appropriate measures to mitigate such risk if deemed not acceptable.
- **Design Space:** The design space is a multidimensional combination of input variables, their interactions and process parameters that have been provide assurance of quality. A design space might be constructed for a single unit operation or multiple unit operations. Based on regulatory guidelines the issuance of design space in QbD application is considered optional. This is because the product and process understanding can be established without a formal design space. However, the issuance and definition of a design space could assists to better understanding overall control of a system.
- **Control Strategy:** A control strategy is defined as a set of controls derived from current product and process understanding that assures process performance and product quality. Control strategies are designed to ensure that a product of required quality will be produced consistently and the process is within the boundaries described in the design space. Elements included as part of this strategy might relate to drug substance and drug product material and component, facility and equipment operating conditions, in process controls and finished product specification. A list of components included in control strategy are, but are not limited to, the following:
  - Control of input material attributes based on an understanding of their impact on processability or product quality.
  - Product specification(s)
  - Controls for unit operations that have an impact on downstream processing or product quality.
  - In-process or real-time release testing in lieu of end-product testing.
  - A monitoring program for verifying multivariate prediction models

The implementation of QbD elements as part of pharmaceutical development process has provided the several advantages to generic companies. A list of such advantages is described below: [4]

- The ability to design products and processes and bring fewer setbacks at critical stages such as scale up, validation, and technology transfer.
- It allows greater flexibility of adjusting variables within the design space.
- Greater regulatory flexibility based on a science-based approach to risk management.
- Ability to continue to optimize and improve the manufacturing operation without facing additional regulatory filings or scrutiny.
- Faster time to market and reduced rework, resulting in reduced costs and increased revenues.

In conclusion, the inclusion of QbD elements as part of the pharmaceutical development process of generic product is considered an essential tool. QbD will allow obtain process understanding that is essential to ensure product quality and acceptable manufacturing performance. In addition, the implementation of QbD elements will render a

robust process and potential savings in manufacturing operations.

METHODOLOGY

In order to achieve the proposed objectives, this section provides an overview of the process and methodology that was employed as part of this design project. The utilized methodology and process involved the execution of six (6) key steps. These six (6) key steps are in alignment with QbD concepts and elements established in regulatory guidelines such as ICH Q8. A brief summary of activities covered under these steps is provided below.

- **Step 1: Definition of the Quality Target Product Profile for Generic Version of "G-2" 400mg Capsules** – Quality Target Product Profile for generic "G-2" 400mg was defined to include patient relevant product performance elements. These elements were dosage strength and form, pharmacokinetic characteristics, route of administration, container closure system, and quality attributes that might potentially affect the safety, efficacy and bioavailability of drug product. Information included in the Quality Target Product Profiles was used as the basis to design the pharmaceutical formula of "G-2" 400mg capsules.
- **Step 2**: **Identification of Critical Quality Attributes for Generic Version of "G-2" 400mg Capsules** - Once the Quality Target Product Profile was defined, the critical quality attributes for generic "G-2" 400mg capsules were identified. The identification of these attributes is considered an important element during formulation process, because they ensure desire product quality. The process to identify these attributes consisted in reviewing all quality attributes that might be altered by changing formulation or process variables.
- **Step 3: Evaluation of Drug Substance Attributes**: Drug substance attributes were evaluated as part of the formulation activities by executing a risk based approach assessment. The purpose of this evaluation was to identify and to understand potential linkages or relations between drug substance attributes and drug product critical quality attributes. Attributes considered as part of this evaluation were: solid state form, particle size distribution, hygroscopicity, solubility, moisture content, residual solvent, process impurities, chemical stability, and flow properties of drug substance.
- **Step 4: Selection of Excipient for Generic Version of "G-2" 400mg Capsules** - The excipients selection for generic "G-2" 400mg capsules involved a comprehensive evaluation of all common capsule excipients available in the market. The type of excipients selected for the generic version of "G-2"400mg capsules consisted of a filler, glidant and lubricant.
- **Step 5**: **Risk Assessment for Formulation Variables** - A risk based approach assessment was performed to determine the variables that will be further study as part of the formulation development studies. Formulation variables included as part of the risk assessment were: composition of Colloidal Silicon Dioxide, composition of Magnesium Stearate, and drug substance particle size distribution. These variables were considered, because they are expected to have potential effect of the identified drug product Critical Quality Attributes.
- **Step 6: Formulation Development Studies** - The goal of the formulation development study was to determine the pharmaceutical formula for generic version of "G-2" 400mg capsules. Design of Experiment (DoE) approach was selected to fulfill this requirement.

RESULTS AND DISCUSSION

This chapter presents the results and analysis of the six (6) key steps utilized to develops a generic pharmaceutical formula for "G-2" 400mg.

Quality Target Product Profile for Generic G-2 400mg Capsules

The definition of Quality Target Product Profile (QTPP) forms the basis of the design and development of products. The QTPP for generic version of "G-2" 400mg capsules was defined considering physicochemical and pharmacokinetic (PK) characteristics of the reference product (brand), properties of drug substance, and indications of Reference Listed Drug (RLD). It shall be noted that QTPP for generic "G-2" 400mg capsules only include patient relevant product performance elements. Table 1 describes the QTPP for generic version of "G-2" 400mg Capsules.

Table 1
Quality Target Product Profile for Generic "G-2" 400mg Capsules

QTPP Elements		Target	Justification
Dosage form		Capsule	Pharmaceutical equivalence requirement: same dosage form
Dosage Design		Immediate release dosage form. Product filled into hard gelatin capsule shape size 0.	Immediate release design needed to meet label claims and maintain physical equivalence with RLD.
Dosage Strength		400 mg	Pharmaceutical equivalence requirement: same strength
Route Administration		Oral	Pharmaceutical equivalence requirement: same route of administration
Pharmacokinetics		Immediate release enabling T_{max} in three (3) hours or less after ingestion. Elimination half-life between 5-9 hours.	Bioequivalence requirement: Needed to ensure rapid onset and efficacy.
Stability		At least 24-month shelf-life at room temperature	Equivalent to or better than RLD shelf-life.
Drug Product Quality Attributes	Physical Attributes	Pharmaceutical equivalence requirement: Must meet the same compendia or other applicable standards.	
	Identification		
	Assay		
	Uniformity of Dosage Units		
	Dissolution		
	Degradation Products		
	Residual Solvents		
	Microbial Limits		
Container Closure System		Container closure system qualified as suitable for this drug product	Needed to achieve the target shelf life (24 months) and to ensure capsule integrity during shipping.
Administration/Concurrence with Labeling		Similar food effect as RLD	Labeling of the Reference Listed Drug indicates that food has slight effect on the rate and extent of absorption of the API 14% increase in the AUC and C_{max}).
Alternative Methods of Administration		None	None are listed in the RLD label

Critical Quality Attributes for Generic "G-2" 400mg Capsules

Quality attributes classified as "critical" for generic "G-2" 400mg capsules are described in Table 2. These attributes were classified as "Critical" based on potential risk to patient safety (severity of harm to a patient if product fall outside the acceptable range for that attribute), literature review, process and technical understanding, and manufacturing experience. Those quality attributes are: identification, assay, uniformity of dosage units, dissolution, residual solvents, degradation products, and microbial limit. Nevertheless, only assay, uniformity of dosage, dissolution, and degradation products are considered to be potentially affected by variations in formulation variables. Therefore, the effects on the

aforementioned CQA were further investigated as part of formulation development studies.

Evaluation of Drug Substance ("G-2") Attributes

A risk based approach evaluation was performed to assess the potential impact that drug substance attributes might have in the CQA of generic "G-2" 400mg capsules. The assessment involved the evaluation of drug substance physicochemical attributes to determine its risks for each drug product CQA (assay, uniformity of dosage units, dissolution and degradation products). The risk priority that each attribute presents was categorized as "high", "medium" or "low". Attributes categorized as "high" risk would require further investigation for mitigation purpose, while "low" risk attributes are considered acceptable and would not require additional investigation. Attributes categorized as "medium" risks are considered acceptable based on technical knowledge and process understanding, and might need further evaluation to reduce the risk level as deem necessary. A total of nine (9) attributes were evaluated as part of this risk assessment and results obtained reveals the following:

- The flow properties of drug substance represent a high risk to drug product uniformity of dosage units due to its poor flow characteristics. Therefore, formulation variables and manufacturing process for generic "G-2" 400mg capsules will be designed to enhance the drug substance flow properties with the intention of mitigate any adverse effect in uniformity of dosage units.
- Drug substance chemical stability represents medium risk to drug product assay and degradation product because it showed susceptibility to dry heat during force degradation studies. Therefore, considerations will be taken during the manufacturing process design (not included in the scope of this design project) to minimize the exposure of the drug substance to any source of heat.
- Drug substance solid state form represents medium risk to degradation product. This is as a result that drug substance has different polymorphism forms which might have different chemical stability eventually affecting degradation of the drug product.

In conclusion, drug substance attributes classified as medium and low risk levels to drug product CQA are considered acceptable and no further investigation was performed as part of formulation development. It should be noted that risk classification was performed considering current scientific knowledge, manufacturing experience, technical literature and data obtained from previous experimental studies.

Excipient Selection for Generic "G-2" 400mg Capsules

Excipients are materials that are added to pharmaceutical dosage forms to aid formulation and manufacture process of subsequent dosage form for administration to patients. Actually, properties of the drug product such as stability and bioavailability mostly depend of the excipient selected, their concentration and interaction with both drug substance and each other [6]. Therefore, a comprehensive evaluation was made to determine appropriate excipients for the pharmaceutical formulation of "G-2" 400mg capsules.

The excipients for generic version of "G-2" 400mg capsules were selected considering the following aspects:

- Qualitative pharmaceutical formula of the reference listed drug
- Technical literature regarding common excipient utilized for oral capsule solid dosage form formulations
- Data from excipient compatibility studies
- Information of excipient utilized in other generic version of "G-2" 400mg capsule approved by regulatory authorities.

Based on the assessment conducted the following excipients were selected for the formulation of generic "G-2" 400mg capsules:

Table 2
Critical Quality Attributes for Generic "G-2" 400mg Capsules

Quality Attributes of Drug Product	Justification
Identification	The identification of the drug product is considered critical for the safety and efficacy and it can be effectively controlled and monitored through the site quality system. Based on the fact that formulation, process variables and drug substance attributes do not impact the identity of the drug product, this CQA will not be further studied as part of the formulation development activities.
Assay	Assay is considered a CQA and variations in this attribute would tend to affect drug product safety and efficacy. Both formulation and process variables potentially affect drug product assay. Therefore, this CQA will be further studied during formulation development activities.
Uniformity of Dosage Units	Uniformity of dosage units is considered a CQA, because variability in this attributes would tend to affect the drug product safety and efficacy. Both formulation and process variable would impact the uniformity of dosage units. Therefore, uniformity of dosage units will be further study during formulation development studies.
Dissolution	Dissolution is considered a CQA, because variability in this attribute will affect bioavailability. Formulation and process variables would impact the dissolution profile of drug product. Therefore, drug product dissolution will be further studied during formulation development studies.
Residual Solvents	Residual solvents are considered a CQA, because variations in this attribute might affect the drug product safety. However, no solvents are used as part of the drug product manufacturing process and drug product complies with criteria established in USP <467> option 1. Therefore, formulation variables are not expected to affect this CQA and no further evaluation of this CQA will be performed during formulation development studies.
Degradation Products	Degradation products would potentially impact the safety and efficacy of the drug product. In addition, they must be controlled according to compendia / ICH requirements. Degradation product A is a common degradant of "G-2" capsules and its target was set according to the acceptance criteria and guidelines established in the pharmacopeia monograph for "G-2" capsules.
Microbial Limits	Non compliance with microbial limits might impact the safety of the drug product. Nevertheless, the risk of microbial growth is considered minimal, because the proposed manufacturing process for "G-2" capsules does not employ wet granulation or film coating techniques, which are considered high to medium risk for microbial growth. Therefore, formulation variables are not expected to affect this CQA and not further evaluation of this CQA will be included as part of the scope for formulation development studies.

- Pregelatinized Starch, NF as diluent
- Colloidal Silicon Dioxide, NF as a glidant
- Magnesium Stearate, NF as a lubricant.

Risk Assessment for Formulation Variables

A risk based approach evaluation was performed to assess the potential impact of formulation variables might have in the critical quality attributes of generic "G-2" 400mg capsules. The objective of this assessment was to identify potential high risk variables that will be further investigated as part of the formulation development study. The assessment consisted in determine the risk priority that formulation variable present for each drug product CQA (assay, uniformity of dosage units, dissolution and degradation products). This risk priority was then categorized as "high", "medium" or "low". Variables categorized as "high" risk would require further investigation for mitigation purpose, while "low" risk variable are considered acceptable and would not require additional investigation. Variables categorized as "medium" risks are considered acceptable based on technical knowledge and process understanding, and might require further evaluation to reduce the risk level as deem necessary.

The formulation variables evaluated as part of this assessment were the composition of Colloidal Silicon Dioxide (SiO_2) and Magnesium Stearate (Mg. Stearate) in the formulation of "G-2" 400mg Capsules, and particle size distribution of drug substance. Pregenatalized Starch was not considered in the assessment, because it functions as a diluent to achieve the target capsule filled weight (533mg) and its composition does not impart any critical functionally in the formulation of "G-2" 400mg capsules. Based on the assessment results, the compositions of SiO_2 and Magnesium Stearate were identified as "high" risk variables, because they are expected to affect the drug product uniformity of dosage units and dissolution. Therefore, these variables were further investigated

as part of the formulation development study. Particle size distribution of drug substance did not reveal potential effect on drug product CQA. Risk assessment results for formulation variables on drug product CQA are shown in Table 3. It should be note that risk classification was performed taking in consideration current scientific knowledge, manufacturing experience, technical literature and data obtained from previous experimental studies.

Table 3
Risk Assessment Results for Formulation Variables

Drug Product CQA	Formulation Variables		
	Drug Substance Particle Size Distribution	SiO_2 Composition	Mg Stearate Composition
Assay	Low	Medium	Low
Uniformity of Dosage Units	Low	High	Low
Dissolution	Low	High	High
Degradation Product	Low	Low	Low

Formulation Development Study

Formulation development study for generic "G-2" 400mg capsules was focused on the evaluation of the high risk variables identified as part of risk assessment for the formulation variables. The objective of this study was to determine acceptable compositions of SiO_2 and Magnesium Stearate in the formulation of "G-2" 400mg capsules.

A two (2) factors and two (2) level full factorial design (2^2) with two (2) replicate was utilized to study potential effect and interactions of Magnesium Stearate and SiO_2 compositions in response variables such as assay and uniformity of dosage units among others. In addition, one (1) center point was included in the factorial design to confirm linearity of the effect for the formulation variables. Formulation variables that were kept constant during the execution of this experimental design were the amount of drug substance per capsule and capsule filled weight. The amount of drug substance per capsule was fixed to 400mg (75% wt.) based on the RLD label, strength, and capsule filled weight. A target filled weight of 533 mg was utilized for all runs by adjusting the amount of Pregelatinized Starch in the formula.

The studied composition of Magnesium Stearate and SiO_2 ranged from 0.75% (wt.) to 1.25% (wt.) and from 0% (wt.) to 0.125% (wt.), respectively. These ranges were selected according to results obtained from previous experimental studies and experience gathered from other oral capsule dosage form formulations, which employs Magnesium Stearate and SiO_2. Furthermore, selected range for Magnesium Stearate and SiO_2 compositions is in alignment with Handbook of Pharmaceutical Excipients.

The manufacturing process of "G-2" 400mg capsules utilized as part of this formulation development study employed blending/lubrication and capsule filling stage. The blending/lubrication involved a mixing of drug substance with Pregelatinized Starch and SiO_2. Then, the mixture containing the drug substance was lubricated with Magnesium Stearate and finally filled into empty hard gelatin capsule shell size 0 using capsule filling machine. The formulation development study of "G-2" 400mg capsules was conducted at laboratory scale (7 kg or 13,133 units). Table 4 details the equipment and the associated process parameters used for this study.

Table 4
Equipment Process Parameters

Process Steps	Process Parameter	Parameter Configuration
Drug Substance Delumping	Equipment	Quadro Comil Model 196
	Impeller Type	1607-25 square arm
	Screen	Round Hole Screen Size: 1575 microns.
	Impeller Speed	approximately 924 RPM
Blending and Lubrication	Equipment	Patterson Kelly 16 quarts (~18L) V-Blender without intensification bar.
	Blender Speed	25 RPM
	# Revolution	200 Revolution (Blending) and 75 Revolution (Lubrication)
Capsule Filling	Equipment	Dosator Type Capsule Filling Machine
	Powder Fill level in the Rotary Disk	25mm - 45mm
	Speed	2,000 Capsule per hour

Experimental Design Results

A total of nine (9) runs were performed as part of the experimental design for the formulation variables of "G-2" 400mg capsules. The responses evaluated during the execution of this experimental design are related to either drug product CQA and intermediate material attributes or properties. Those responses are: assay, uniformity of dosage units, dissolution at 20 minutes, degradation products (related compound "A"), tapped density, flow function, and angle of repose.

Data analysis (ANOVA) was performed at 95% confidence level to gather information regarding the effect and interaction of Magnesium Stearate and SiO_2 compositions in the identified responses. The data analysis was performed using Minitab Statistical Software and results are presented in Table 5. It shall be note that Tablet 5 only reported results for responses associated to intermediate material attributes and CQA which formulation variables shown strong influence. Results obtained for other responses not listed in Table 5 were satisfactory conforming to respective acceptance limits.

The data analysis reveals that composition of SiO_2 and Magnesium Stearate significantly affects the flow function of the powder blend. Flow function of the powder blend would tend to increase when the composition of Magnesium Stearate is decreased and the composition of SiO_2 is increased. Thus, optimum compositions of SiO_2 and Magnesium Stearate, which maximize the flow function of the powder blend, are 0.15% wt. and 0.75% wt., respectively. Contour plot in Figure 1 illustrates flow function as a function of Magnesium Stearate and SiO_2 compositions. In addition all powder blends produced exhibited flow function values equal or higher than nine (9). According to literature, powders with flow function higher than 8 are expected to have excellent flow performance [7].

In terms of angle of repose, data analysis revealed that it is strongly influenced only by the composition of SiO_2 in the formulation. This observation follows the expected behavior, because SiO_2 functions as flow aid ingredient (glidant) assisting material flow characteristics.

Table 5
Data Analysis (ANOVA) Results

Source	Responses (p value)		
	Flow Function	Angle of Repose	Related Compound A
SiO_2 (A)	0.000*	0.011*	0.000*
Mg. Stearate (B)	0.002*	0.152	0.184
(A)(B) Interaction	0.615	0.311	1.00
Curvature	0.249	0.515	0.662

Note: (*) = significant term

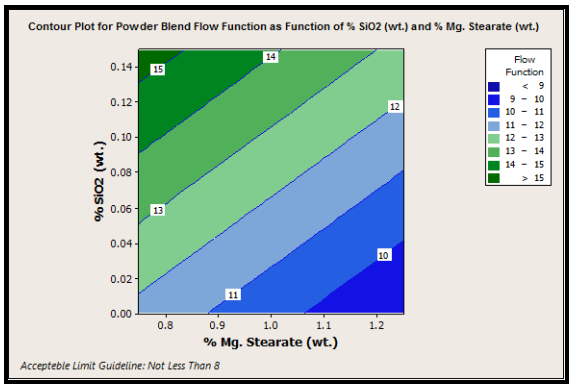

Figure 1
Contour for Powder Blend Flow Function

The produced "G-2" 400mg capsules were tested for degradation product to study the effect in the formation of related compound "A". The analysis was conducted after sixty (60) days of manufactured. Data analysis shown that composition of SiO_2 has strong influence in the formation of related compound A. According to result obtained, increasing the composition of SiO_2 in the formulation would tend to increase the amount of related compound A in the finished product. Therefore, this behavior suggests potential incompatibility between SiO_2 and drug substance.

In terms of Magnesium Stearate composition, data analysis did not reveal any significance influence of this variable in related compound "A". Contour plot in Figure 2 illustrates the concentration of related compound "A" as a function of Magnesium Stearate and SiO_2 compositions.

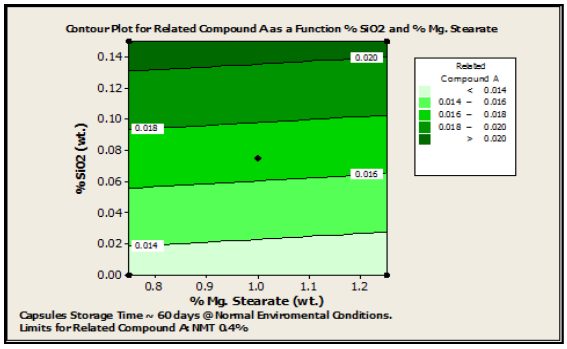

Figure 2
Contour for Related Compound A

CONCLUSIONS

Based on the results obtained during the execution of this formulation study the selected composition of SiO_2 and Magnesium Stearate for "G-2" 400mg capsules formulation is 0% (wt.) and 0.75 (wt.), respectively. These compositions were selected based on the following:

- The selected composition for SiO_2 and Magnesium Stearate shown acceptable flow characteristic of the powder blend. Therefore, the risk of performance situations related as a result of poor material flow characteristics is considered minimal.
- The selected composition of Colloidal Silicon Dioxide and Magnesium Stearate shown satisfactory results for assay, dissolution, uniformity of dosage units (weight variation), and degradation products. Therefore, results obtained provide confidence that product resulted from selected compositions of SiO_2 and Magnesium Stearate will conform to specification limits established in the pharmacopeia monograph.
- The selected composition for SiO_2 and Magnesium Stearate did not show to promote the formation of related compound "A". Therefore, data obtained provide confidence that selected composition for SiO_2 and Magnesium Stearate does not represent an adverse risk to the stability of finished product. However, it is highly recommended execute informal stability studies to this formula prior further development. This will ensure that selected formula for "G-2" 400mg capsules is stable during target shell life established in the Quality Target Product Profile.

The proposed formula for generic version of "G-2" 400mg capsules is described in Table 6.

Table 6
Pharmaceutical Formula for "G-2" 400mg Capsules

Material Description	Functionality	mg/cap	% wt.
G-2	Drug Substance	400	75.05
Pregenatalized Starch	Diluent	129	24.20
Magnesium Stearate	Lubricant	4	0.75
Empty Hard Gelatin Capsule Shell Size 0	Product Container	(-)	(-)
Total		533	100

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