Investigation of The Effects of Temperature and Humidity on Yields of a Complementary Medicine Product Under Regulatory Stability Conditions

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Abstract:

Background: The South African Health Products Regulatory Authority (SAHPRA) mandated that all complementary and alternative medicines (CAM) that were marketed and sold in the South African market be registered with the regulatory authority (RA) or have a submission for registration under review with the RA by June 2021, starting with submissions for registration from February 2020(1). The deadline was extended to February 2022. In order to apply for registration of the CAM and continue marketing the product within the South African market, stability data of the finished pharmaceutical product (FPP) was required(2). The environmental storage conditions for which stability data must be generated before registration was stipulated as 25°C ± 2°C/60% RH ± 5% RH or 30°C ± 2°C/65% RH ± 5% RH for 6 months and 40°C ± 2°C/75% RH ± 5% RH for 6 months. Product X is a CAM product that has been manufactured at a South African local pharmaceutical manufacturing company since 2020 and sold in the South African market for more than 3 years. The product uses herbal material encapsulated in a hard gelatin capsule (HGC) to deliver its effects. The batch manufacturing records (BMRs) required the recording of the environmental manufacturing temperatures (T_{ME}) and relative humidity percentage (RH %) at the time of manufacture of Product X. The percentage yield of capsules manufactured was also calculated and recorded to ensure quality control of the product during manufacture.

Problem: There is no formal stability data for the bulk of Product X to support a submission for registration with SAHPRA as a CAM. The bulk is defined as the material-filled capsules of Product X. The product was not developed using a formal stability program which would have generated the required stability data of environmental storage conditions for Product X being subjected to the conditions 25°C ± 2°C/60% RH ± 5% RH or 30°C ± 2°C/65% RH ± 5% RH for 6 months and 40°C ± 2°C/75% RH ± 5% RH for 6 months of during its product development. The final product (FP), which is a product that has undergone all stages of production excluding packaging(3), of Product X did not have any stability data for the product's storage under the environmental storage conditions as stipulated by SAHPRA, hence, there is no certainty as to how the FP would react under the stipulated environmental conditions. There is no data on the bulk product, which is large quantities of FP prior to packaging, to indicate what effect the T_{ME} and % RH conditions have on the product during manufacture. The hypothesis, based on available literature, is that high temperatures and high humidity would have a negative impact on the gelatin capsules used during Product X's manufacture, causing cross-linking and swelling. This would cause the capsules to lose stability and become unsuitable for use.

Methods: In order to establish a possible relationship for Product X with the environmental manufacturing conditions, the BMRs of the bulk product were collected and the environmental manufacturing conditions were reviewed. The T_{ME} and % RH were recorded to determine if the bulk product was being produced within or between the stipulated T_{ME} and % RH ranges. The results of the certificate of analysis (CoAs), against the specification of the FP of Product X, were reviewed and recorded to determine what effect the environmental manufacturing conditions may have had on the FP. The specification's tested against was disintegration of not more than 15 minutes, moisture content of not more than 3.0 % and

identification of the FP. The hypothesis was that if the bulk product was exposed to unfavorable T_{ME} and/or % RH conditions during manufacturing, the FP would have results that were not within the acceptable limits of the FP specification. The percentage yield of the bulk product was also recorded to be used as a proxy measurement for the effect of the conditions on the bulk product, where it was hypothesized that if the bulk product was exposed to unfavorable T_{ME} and/or % RH conditions, the gelatin capsules would become unusable, thereby decreasing the percentage yield of the bulk product.

Results: The BMRs of all batches of Product X that were produced between 1 January 2020 to 31 March 2022 were reviewed and the data was successfully analyzed. A total of 165 batches were analyzed for this study. The results of all FP analysis testing passed with no failure noted on the CoAs for all batches. The correlation coefficient between the T_{ME} and the percentage yield was found to be negative (i.e., -0.40) and the correlation between the % RH and the percentage yield was positive (i.e., 0.17). There was no statistically significant difference in the mean percentage yield between the three % RH categories. There was a statistically significant difference in the mean percentage yield between the three T_{ME} categories. The correlation coefficient between the T_{ME} and disintegration time was found to be negative (i.e., -0.10) and the correlation between T_{ME} and moisture content was negative (i.e., -0.08). The correlation coefficient between the % RH and disintegration time was found to be neutral (i.e., 0.00) and the correlation between % RH and moisture content was neutral (i.e., 0.00).

Conclusion: The data indicated that T_{ME} had a negative relationship with yield percentage as the yield percentage increased. The % RH had no detectable relationship with yield percentage as the yield percentage increased. The moisture content of the capsule had no detectable relationship with yield percentage. Disintegration time had no detectable relationship with yield percentage. Moisture content and disintegration had no discernable relationship with T_{ME} or % RH The implications of the results indicate that if the bulk capsules were to be used for stability testing in the long-term and intermediate stability testing conditions, the bulk capsules would not be stable due to the environmental temperature as there is a possibility that the capsules may cross-link and reduce the percentage yield of the batch. The cross-linked capsules would be unusable, and they would not pass the specification test of the bulk product**.** However, all batches passed the FP testing with results that were compliant within the FP specifications, indicating that despite the potential relationships with the environmental conditions, Product X remained stable at the time of release. It is recommended to test the bulk capsules under environmental conditions of a 25°C ±2°C/65% RH for at least as long as the longest expected time to be taken to encapsulate any batch which would be 7 days based on the analysed data. It also recommended to perform intermediate stability studies at 30 C ±2°^{O}C/65% RH and accelerated stability studies at 40^{O}C/ 75 RH% to provide data to support the currently marketed shelf-life.

KEYWORDS

Complementary Medicine

Capsule

Temperature

Humidity

SAHPRA

DECLARATION:

Dillon Singh…… Date……..

Signed…….

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Contents

Abbreviations:

% RH- Relative Humidity Percentage

BMR – Batch Manufacturing Record

CAM – Complementary and Alternative Medicine

CoA – Certificate of Analysis

EHGC – Empty Hard-Gelatin Capsule

FP- Final Product

FPP – Finished Pharmaceutical Product

HGC - Hard-Gelatin Capsule

SAHPRA – South African Health Product Regulatory Authority

T_{ME} – Manufacturing Environmental Temperature

CHAPTER ONE: INTRODUCTION

The SAHPRA regulates the marketing of health products within South Africa by requiring that the health products be registered before they may be sold. The process of registration requires submission of satisfactory quality, safety and efficacy information(4). CAMs were not previously registered with SAHPRA. SAHPRA published a roadmap in December 2021 in which it mandated to have all CAMs follow a new registration process and be regulated by the SAHPRA by 28 February 2022(5). The original administrative period for the provision of licensing of CAMs was initially extended to 31 January 2022(1). This was extended to 28 February 2022, at which time all marketing product owners (MPO) were expected to have a license issued for their marketed CAM or a submission would already be made to the SAHPRA for the issuing of a license.

CAMs fell under Category D Medicines (6). Health Supplements were considered to be low-risk if they declared that they were used for general health enhancement without any reference to specific diseases, were used for health maintenance or provided relief of minor symptoms not related to a disease or disorder (5). Health supplements were required to provide quality, safety and efficacy data as per the International Conference on Harmonization of Technical Requirements Common Technical Document (ICH CTD) (7). A required section within the quality information to be submitted was the stability data of the FP when stored in a bulk container prior to packaging into its final immediate containers (7). The specifications to be tested should have been attributes that are susceptible to change during storage. The environmental conditions for the Intermediate period were 30°C ±2°C/65% RH ± 5% with a minimum period of 6 months of stability data. The long-term period would be the same conditions as the intermediate period, except it would be for a duration of 12 months. The accelerated period environmental conditions were 40°C ± 2°C/75% RH ± 5% RH with a minimum period of 3 months of stability data (7). Stability studies provide information about how the product is affected by the different environmental conditions (8). Stability studies are performed on the bulk and finished products which then informs the shelf-life of the product.

Product X is a health supplement manufactured by the organization based in Johannesburg, South Africa which uses Empty Hard Gelatin Capsules (EHGCs) as a capsule dosage form during its manufacture. Product X consists of a mix of herbal-powdered materials and excipients (i.e., talc and magnesium stearate) which are compressed into a pellet and filled inside the EHGC. This forms the FP. The final pharmaceutical product (FPP) consists of the bulk product being packaged inside a white high-density polyethylene (HDPE) bottle with an attached label and sealed with a tamper-evident cap. There are no other components inside the finished product. Product X is manufactured only at the Organisation. During the period reviewed for this study, the Heating, Ventilation and Air Conditioning (HVAC) system was undergoing development and qualification. As a result, the manufacturing environmental conditions were not fully controlled during the manufacture of the bulk product for Product X

This study investigated the effects of T_{ME} and % RH on percentage yields of the Product X bulk product manufactured under various environmental conditions. This study also investigated

the effects of T_{ME} and % RH on the analysis testing of the FP of Product X against its specification. These conditions and their effects on percentage yield of the bulk product were compared to the stability testing conditions stipulated by SAHPRA. The rationale for this was that understanding the effect these conditions would have on the bulk product, could provide information on how the FP may perform under the stability testing conditions. For example, if the study results indicated that a high % RH decreased the bulk percentage yield or indicated that the capsules were sticking to each other, the developer of the stability testing program, to generate the required stability data for SAHPRA, could consider testing the final packaged product with a desiccant included to potentially counteract the effects instead of placing the final packaged product in the program in its current composition and discovering the failure of the product at the first testing point.

CHAPTER TWO: LITERATURE REVIEW

2.1. Overview

This chapter provides an overview into the existing information involving regulation, manufacturing and characteristics of CAMs. A major challenge in the regulation of CAMs globally is the lack of universally defined standards to generate data in order to support product claims. SAHPRA has provided requirements for CAM registration which includes quality, safety and efficacy data for submissions. The composition of Product X is provided here as well as background on its manufacturing processes

2.2. Regulation of Complementary and Alternative Medicines

CAMs are often used to support everyday health, often stating that they can promote wellness either generally or relating to a specific disease-state. Unfortunately, CAMs do not have universally defined standards on which to generate data to support these claims. This leads to an increased risk for the use of the product by the consumer as the adverse effects of utilizing the CAM is not fully understood (9)(10). The regulation of CAMs globally is currently varied and unstandardized as each country's Regulatory Authority (RA) may review, define, and control CAMs differently (9) A difference in health claim, definition of product or origin leads to RAs performing their function differently based on the product.

The United States Food and Drug Administration (US-FDA) regulates CAMs for the United States. The US-FDA defines dietary supplements as items that are taken orally only and intended to increase a person's daily intake of a particular substance and makes no health claims while a herbal medicine contains ingredients from a plant source and makes a claim to treat specific conditions/diseases. Herbal medicines in the United States must obtain pre-market approval from the US-FDA before they may be sold (9). This is accomplished by providing data on Quality, Safety and Efficacy (QSE) to the US-FDA.

Australia treats most naturally derived products as Therapeutic Goods (TGs), regardless of whether they are classified as "Supplements" or as "Medicines". These TGs are called *Complementary Medicines* in Australia. The TGs are categorized as either low-risk or high-risk and the categorization stipulates what information must be provided for the TG to be marketed and sold (10). Only high-risk products are reviewed for QSE. Canada requires QSE data to be provided for any product that has been classified as a medicine based on their regulatory framework (9). The European Union (EU) also uses a system to classify the product as a medicine or a supplement which will guide its regulatory requirements.

The International Regulatory Cooperation for Herbal Medicines (IRCH) was established in 2006 with the objective of promoting public health and safety by improving regulation of herbal medicines (11). The IRCH was a working group of the World Health Organization (WHO) that determined there was a need for standardization around the regulation of herbal products. There are currently 31 countries who are members of the IRCH, one of them being South Africa. The WHO released a strategy document to be implemented in the years 2014-2023

which outlined the manner in which it would improve the regulation and safety of herbal medicines (12). It was noted that evaluation of the safety and quality of the product, as well as efficacy assessment continued to be a challenge when evaluating and regulating herbal medicines. To further resolve this issue, one of the suggestions of the report was to "develop and share appropriate methods and criteria for evaluating the safety, efficacy and quality of T&CM products and for assessing the value of T&CM practice ", indicating that standard methods were either not available for the numerous CAMs or they were not being used effectively.

2.3. Regulation of CAMs in South Africa

SAHPRA issued guidance in June 2020 detailing the requirements of data to be generated and submitted for the registration of CAMs by the SAHPRA (7). This data included safety information around the use of the CAM (e.g., adverse events and post-market reporting), compliance with specific-labelling requirements, toxicity data around the FP, manufacturing information around the FPP and active substances as well as specifications for the FPP, raw materials, packaging materials and processing steps in the manufacturing process. Prior to this guidance, there was no requirement to have CAMs registered by SAHPRA to be marketed within South Africa.

SAHPRA currently recognizes six major disciplines; aromatherapy, ayurveda, homeopathy, traditional Chinese medicine, unani medicine and western medicines(13). SAHPRA also recognizes combination products. Each discipline has its own related preparations that require discipline specific data to prove its safety and efficacy. Each discipline also has its own accepted Pharmacopoeia.

A CAM is defined as any substance or mixture of substances that(14):

a. Originates form plants, fungi algae, seaweeds, lichens, minerals, animals or other substance as determined by the Authority
b. Is used or purporting to be suitable for use or manufacture or sold for use
    a. In maintaining, complementing or assisting the physical or mental state; or
    b. To diagnose, treat, mitigate, modify, alleviate or prevent diseases or illness or the symptoms or signs thereof or abnormal physical or mental state of a human being or animal; and
c. Is used –
    a. As a health supplement; or
    b. In accordance with those disciplines as determined by the Authority

A health supplement is defined as any substance, extract or mixture of substances as determined by the Authority, sold in dosage forms used or purported for use in restoring, correcting or modifying any physical or mental state by –

a. Complementing health
b. Supplementing the diet; or
c. A nutritional effect

Combination product means a single product that contains (15):

a. a mixture of substances of different discipline-specific origins or philosophies;
b. a mixture of at least one substance of discipline-specific origin and one or more health supplements; or
c. a mixture of at least one substance of discipline-specific origin and one or more of its isolated constituents.

A distinction can be made based on the definitions of the products, a health supplement can be a CAM, but not all CAMs would be a health supplement. Further, if multiple discipline specific products are combined, it becomes a combination product, and this can contain a health supplement in combination with substances of other origins. SAHPRA also categorizes the CAMs as a risk-based approach. The level of risk of the CAMs is determined by the claims made by the CAMs or the intended use of the preparation. The level of risk (i.e., high-risk or low-risk) determines what information is mandatory and what information is optional in the submission of an application for registration of the CAM with SAHPRA(15).

Due to the lack of the stability data requirement, the data may not have been previously generated by the manufacturers as the development of CAMs was not subject to the same rigorous processes of development as required by registrable pharmaceutical medicines i.e., the development of CAMs did not incorporate Quality by Design (QBD) elements or processes .The guidance issued by SAHPRA attempts to bring data requirements of CAMs in line with data requirements as used for registrable pharmaceutical medicines (16) . The stability data that would have been generated would include data for the FP for a period of 25% of the approved shelf life in bulk containers (7). The stability data, along with other requirements as stipulated by SAHPRAs guidelines, would be submitted to the SAHPRA. The data would be reviewed by the authority and recommendations, if any, would be made to the product owner to remedy any deficiencies in the provided information. If the data was found to be satisfactory, the product would be registered with SAHPRA and a registration certificate would be issued to the product owner, allowing it to be further marketed in South Africa.

2.4. Manufacturing of CAMs Globally

The WHO released a guideline on the manufacturing of herbal medicines (17) . The guideline was intended to provide a baseline for technical requirements related to the manufacturing of herbal products (18,19). To ensure QSE, the WHO recommends that the production of herbal products should comply with the same principles of Good Manufacturing Practice (GMP) as required for the production of medicinal products, however, due to the nature of the herbal materials used, there should be a heavy emphasis on the Quality Control (QC) of starting materials and processing steps as the quality of the starting material greatly influences the QSE of the final herbal product. While the WHO published this as a guide, the WHO encouraged member states to develop their own guidelines outlining their requirements on GMP of herbal products based on their governed regions' needs.

The US FDA stipulates the requirements of GMP of Dietary Supplements in its Code for Federal Regulations (20). The code placed emphasis on QC personnel performing a review of

manufacturing documentation and providing a usage decision based on the review. Through the (17)decisions of appropriately trained personnel, the quality of the dietary supplement can be influenced.

The European Medicines Agency (EMA) regulates the traditional/herbal products within the European Union (EU). The EMA released the *Guideline on quality of herbal medicinal products/traditional herbal medicinal products* to detail the requirements for herbal and traditional medicines for human use to be marketed across the member states. This guideline places emphasis on the strict control of starting materials and processing steps. It makes a distinction between a "Standardized Herbal Substance", which has a defined quantity of chemical substance in them, and "Quantified Herbal Substances" which have a defined quantity of a marker inside it.

The Therapeutic Drugs Administration (TGA) which regulates medicines to be marketed inside Australia requires that all medicines comply with the PIC/S Guide to Good Manufacturing Practice except for annexes related to Veterinary medicines (21). The standards of this guideline are specific for the production of medicinal products and are adapted from the WHO guidelines (22). Annex 7 of the Pharmaceutical Inspection Convention Pharmaceutical Inspection Co-Operation Scheme (PIC/S) makes specific recommendations regarding the manufacture of herbal medicinal products and places emphasis on control of starting materials and process steps (23).

2.5. Specifications of CAMs

CAMs are required to have a set of specifications that are required to be met by the FP to ensure consistent quality at the time of release and throughout its shelf-life(3) A specification is a list of tests, references to procedures and appropriate acceptance criteria (24). Specifications form part of the QC process used to ensure quality of the manufactured CAMs. Acceptance criteria may be based on batches used to ensure manufacturing consistency. Aspects of a specification may include impurity contents, macroscopic characterization, microscopic characterization, dissolution testing and physical appearance. Design and developmental data may influence the setting of specifications. The relevant pharmacopoeia may stipulate specific tests to be performed for a specific herbal product or dosage form. Testing against a reference standard should be performed whenever possible. If a reference standard is not available, a herbarium sample should be used. Herbal materials may have a specification related to confirming its identify when compared to a chromatographic fingerprint from an accepted pharmacopoeia. A specific dosage form will have specifications related to it which may or may not be applicable to other forms (e.g., disintegration time for tablets but viscosity for syrups). Packaging materials may have dimensions, written-print or codes as part of their specifications.

Specifications for CAMs should be linked to the quality of the CAM, manufacturing process, and stability of the active substance in the final packaging (24). A specification should be established for each component used for the manufacture of the CAM product (25) (26). In-

process specifications should be established with documented justification as to why meeting these specifications during manufacturing of the product influences the quality of the CAM.

Stability testing of active substances is not sufficient to support the stability of final CAM product (26). The TGA requires fingerprint chromatograms to be developed alongside assay tests, physical tests, and sensory tests to support the stability claims of the final CAM product. As per the WHO, specifications should be used to define quality of the product and it is not intended to fully characterize the final CAM product (27). The WHO recommends chromatographic fingerprints to determine content change to support stability and shelf-life claims. The chromatographic fingerprint can be derived through the use of High performance liquid chromatography (HPLC) testing (28) This type of testing provides information about both the qualitative identity of the content of a material being tested, but, also the quantitative content of that material in the sample. The sample is prepared for testing using a standard method (e.g., A method as stipulated in a pharmacopoeia) or a specific method required for that particular substance. As the material is tested, a detector analyzes the material and produces a computer-generated chromatographic fingerprint (Figure 1) An optimized herbal medicine containing *Scutellaria baicalensis Georgi, Alisma orientale Juzepzuk,* and *Atractylodes japonica Koidzumi* has potent antiplatelet and antithrombotic activities. Journal of Traditional and Complementary Medicine, 13 (3), 285–296). The chromatogram is then compared to a chromatogram of a known standard (known as a reference standard). A reference standard is a material that has undergone a series of testing to ensure that it is of the highest purity and identity. If the chromatograms are comparable, it is likely to be the same material (29).

While HPLC is considered a gold-standard in terms of testing CAMs, there are challenges to this process (29). These challenges include the high-cost of reference standards to purchase for the testing of the CAM material, variation in the processing of the CAM material including the manufacturing process, phenotype of the material and cultivation time of the material itself.

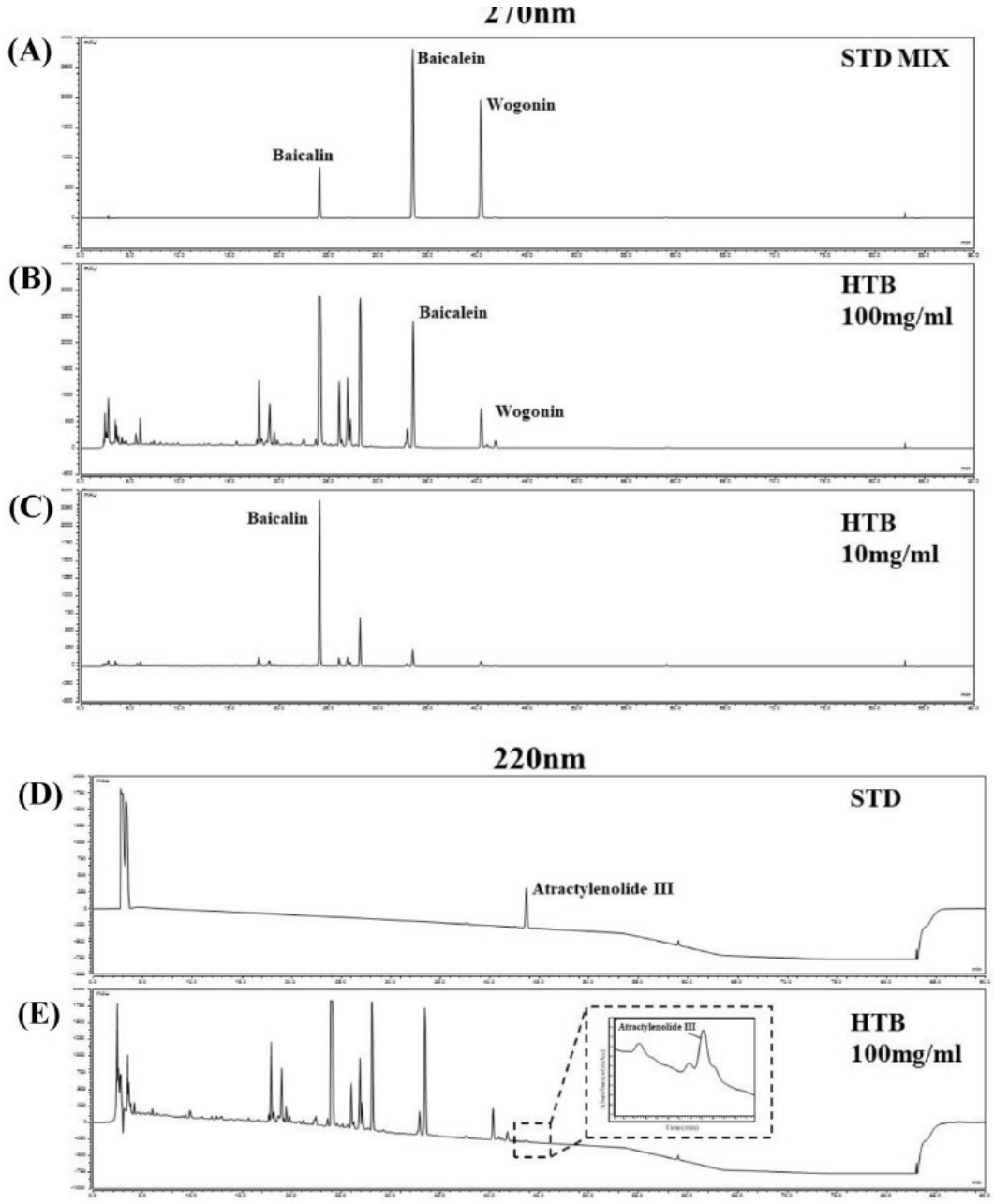

Figure. 1. HPLC chromatograms of HTB herbal medicine. High-performance liquid chromatography (HPLC) chromatogram of a standard compound mixture (30)

2.6 Composition of EHGC

CAMs are available in a variety of dosage forms such as tablets, syrups, capsules, ointments, creams, etc., which make them versatile in supporting a number of different ailments and being introduced into the body in a variety of different routes of administration.

Capsules, in particular, are oven produced from Gelatin to create hard or soft gelatin capsules depending on the type of material being encapsulated. Gelatin is a biopolymer, which can be

animal derived in origin or synthetically produced in clinical settings, which is used to manufacture EHGCs (31). The capsules can be used to encapsulate various materials, allowing their administration into the human body. Gelatin consists primarily of proteins, minerals, and water. Gelatin capsules form cross-links in high % RH and temperature conditions which results in poor dissolution (32). The cross-linking causes the molecules of adjacent gelatin capsules to form bonds between them. This promotes cohesion between the gelatin, resulting in sticking of the capsules and thereby hindering the dissolution process which is vital in delivering the material to the patient and influencing the performance of the CAM. Pharmaceutical chemicals may also be transformed into products that further promote cross-linking in capsules in conditions of high temperature and high RH% (31). Formaldehyde and ammonia in environments of high RH% can cause cross-linking of the gelatin capsules. The capsules show reduced dissolution when stored at high temperatures and high % RH conditions (33). The properties of Gelatin can also be affected by the origin of the raw material used to manufacture it (34). Gelatin of fish origin can demonstrate low water vapor permeability when compared to Gelatin derived from beef or pork. Gelatin capsules are affected by the stored moisture content (35). Gelatin capsules become brittle when in environments of low % RH at room temperature (36). Gelatin capsules can swell in environments of high RH%. They will stick and adhere to each. According to Kontny et al, raising humidity (at a constant temperature) or decreasing temperature (at a constant RH%) will cause swelling and sticking while inverting the conditions will cause the capsules to become brittle. Brittleness occurred in environments which had less than 40% RH%. In other studies, gelatin capsules stored at 37^{O}C become unstable when RH% is greater than 80% RH% (37).

Figure 2. Image of a brittle/broken capsule due to transfer of the moisture of the capsule to the encapsulated contents (https://www.sensum.eu/posts/reasons-for-most-common-capsule-defects/)

2.7 Stability studies on CAM products

A section of data that must be generated is stability data for the CAM product under various environmental conditions (38). These conditions are stipulated under ICH Q1A (R2) which has been adopted by the EMA from which SAHPRA derives its requirements on stability data (see Table 2.6.1).

Table 2.6.1. Storage Conditions for Stability Testing (International Conference on Harmonisation of Technical Requirements For Registration of Pharmaceuticals For Human Use, 2003(4)**)**

Condition Name	Storage condition	Minimum time period covered by data at submission
Long-term	25 °C[1] ± 2°C/60% RH[2] ±5% RH or 30°C ±2°C/65% RH ± 5% RH	12 months
Intermediate	30°C ± 2°C/65% RH ± 5% RH	6 months
Accelerated	40°C ± 2°C/75% RH ± 5% RH	6 months

The purpose of stability testing is to provide data to confirm or dispute whether a product can maintain its quality attributes throughout its intended shelf-life when exposed to sustained extremes of conditions of Temperature and RH %. The stability data generated both during the manufacture of the product, storage of the bulk product and the finished product influences the product development process. If the product does not maintain its quality attributes through the testing, the product may need to be reformulated to achieve the desired results or specific guidance will be provided with the medication stipulating the conditions under which it must be stored to maintain its quality (38)

2.8 Manufacturing of Product X

During the period reviewed for this study, the Heating, Ventilation and Air Conditioning (HVAC) system was undergoing development and qualification. As a result, the manufacturing environmental conditions were not fully controlled during the manufacture of the bulk product for Product X. This variation provided a useful scenario in which to study the performance of Product X under the varied and uncontrolled conditions during manufacture. Product X was manufactured according to instructions stipulated in the BMR and all actions should have been recorded in the BMR as it was performed by the authorized person.

The manufacturing of Product X occurs in a step-wise approach. The process begins with each ingredient being dispensed and weighed out and the weight confirmed before processing can begin. Excipients are weighed out first and then the active ingredient in order to minimize the effect of the environment on the active ingredient. The materials are passed through a

vibrating sieve in order to ensure the materials are of a uniform particle size. The materials are then blended together for approximately 20 minutes. The blended material is then weighed and transferred to an encapsulator. The encapsulation process can vary, taking hours to days depending on the speed and if any breakdowns of the machine should occur.

In order to reconcile the amount of capsules manufactured with the amount of raw materials that were used for the manufacture, a tally of the actual quantity of filled capsules produced is compared against the expected quantity of filled capsules is reported as a percentage. This percentage is known as the percentage yield of the bulk product, referred to going forward as the percentage yield. The BMR had a set quantity of capsules to be produced per batch (i.e., 250 000 capsules), however, percentage yield was used as a measure for the batch control and success as batches with less than 250 000 capsules were intentionally produced to meet demand of the product and orders. A manner to demonstrate control of a manufacturing or packaging process is the calculation of yield of material as a percentage of the expected yield of material to be produced (39) The calculation can be found below:

*(Actual Yield of Material/Expected Yield of Material) * 100 = percentage yield of the bulk product*

The CAM has stability indicating criteria performed on its bulk capsule material which includes moisture content (of not more than 3%) and a disintegration time (of not more than 15 minutes). Assay content testing is not performed on the CAM due to the challenges in obtaining a reference standard for the material. The Percentage Yield of the bulk product is not a direct specification of the CAM itself, but it serves as an indirect measure of environmental effects on the CAM bulk of Product X. Only successfully encapsulated samples (excluding brittle or sticking capsules) will be tested for moisture content and disintegration. However, any CAM lost due to environmental conditions will reduce the total bulk produced, which will be reflected in the Percentage Yield and may indicate the environmental impact on Product X.

2.9 Conclusion/Summary

In conclusion, the regulation of CAMs is greatly varied globally due to the lack of defined standards that are universal across regions. While international efforts like the WHO's IRCH aim for standardization, challenges in evaluating CAMs still exist. SAHPRA has formalized CAM regulation, requiring registration of the CAM and specific data submissions to accompany it. Manufacturing of CAMs requires adherence to GMP, with an emphasis on the quality control of starting materials. Specifications are critical for ensuring the consistent quality of CAMs throughout their shelf life. Dosage forms like gelatin capsules are susceptible to environmental conditions affecting their stability, making stability studies essential for determining shelf life. The case of Product X illustrates how uncontrolled

manufacturing conditions can impact the final product, with percentage yield serving as an indirect indicator of environmental effects.

CHAPTER THREE: AIMS, OBJECTIVES AND RATIONALE

3.1. Introduction

This chapter will develop the aim of this study by elaborating on its intended objectives, the working hypothesis based on the literature review and the rationale for conducting this study.

3.2. Aim

The aim of this study was to determine the effects of the T_{ME} and % RH during manufacture on the Percentage yields of Product X.

3.3 Objectives

The objectives of the study were to:

I. To collect BMRs for Product X between the period of 1 January 2020 to 31 March 2022
II. To collect information on the T_{ME} and % RH and the percentage yield of the manufactured bulk batches
III. To analyze the T_{ME}, % RH and percentage yield of the bulk batches and determine the correlations between them.

3.4. Hypothesis

It was hypothesized that as T_{ME} and % RH increases, the percentage yield of Product X will decrease.

3.5. Rationale

Since Product X has no analyzed data on what effect variable T_{ME} and % RH has on the percentage yield of Product X, achieving the aim of this study will allow the Product owner to understand what the correlation is between the environmental factors and the percentage yield of bulk product. The study can rather assist the product owner with further optimization of the product, understand the storage conditions, understand the selection of packaging material such as a desiccant can be added. These changes can help to improve the product performance during stability and generate successful stability data for registration purposes.

3.6. Conclusion

This chapter elaborated on the aim, objectives, hypothesis and rationale for the study being conducted

CHAPTER FOUR: METHODS

4.1. Introduction

This chapter outlined the methodology used in the study. It describes the data collection process, which involved retrieving and reviewing BMRs and how this data was handled and at what point of the process it was collected. It also stipulates what data resulted in a BMR sand their data being excluded from the study analysis. The background behind the confidentiality to be maintained when collecting this data is also elaborated upon in this chapter

4.2 Data collection

BMRs of Product X produced during the period of 1 January 2020 to 31 March 2022 were collected. This period was selected as records before this time were stored at a repository that was not accessible during the study and permission was granted by the Organisation, only to use the data until 31 March 2022, as the CAM had undergone a reformulation which may have skewed results. A list was compiled from the release registers which denoted the BMRs that were retrieved for review. The list is Appendix A: BMR List. Each BMR was retrieved from the document retention area of the Organization. The T_{ME} and %RH at the time of encapsulation were reviewed and recorded. A total of 165 batches were produced at the single manufacturing site. The data was recorded onto the Data Collection Form (see Appendix B) and then grouped in their respective environmental categories and the percentage yields were assessed for each category. The data was then captured into an Excel Spreadsheet for further data analysis. Any batches which had comments of “Spillage” of capsules (empty or full) were excluded from the analysis sample set as this did not fall under environmental factors affecting the percentage yield.

4.3 Data Analysis

The T_{ME} and related percentage yields and % RH and related percentage yields were divided into three categories per environmental variable (i.e., two sets of three groups). An ANOVA was performed between the groups of each set to determine if there is a statistical difference between the groups. The p value used was 0.05 to determine if there is a statistical difference between the groups or not. If there is a statistical difference, student t-tests are performed between pairs of groups to determine where the statistical difference is occurring. The data points for T_{ME} and percentage yields were plotted on a scatter plot and the correlation was determined. The data points for % RH and percentage yields were plotted on a scatter plot and the correlation was determined. Microsoft Excel was the statical software used to perform the statistical analysis

4.4 Confidentiality and Consent

The Applicant of CAM was not identified during the study. The name of Product X was changed to maintain the confidentiality of the Applicant. The manufacturer of Product X has granted permission to access and analyze the raw data of Product X so long as confidentiality of the Applicant was maintained as well as the formula and active ingredient.

4.5. Conclusion

This chapter elaborated on the data collection methods, data analysis methods and the confidentiality conditions to collect and utilize this data

CHAPTER FIVE: RESULTS

5.1. Introduction

A total of 165 batches were identified as relevant to the study based upon the manufactured batches within the study period of 1 January 2020 to 31 March 2022. Following the collection of the raw data, five batches were excluded from the data analysis based on the following: (i) two batches were excluded due to the documentation missing information/pages which contained the information being collected for the study; (ii) one batch was excluded as the machine had broken down, resulting in a significant portion of the batch being rejected and discarded, affecting the bulk batch percentage yield; (iii) two batches were excluded as they noted carry over from previous batches in the campaign which increased the percentage yield of the batch

5.1.1. Environmental Manufacturing Temperature and Percentage Yield Correlation

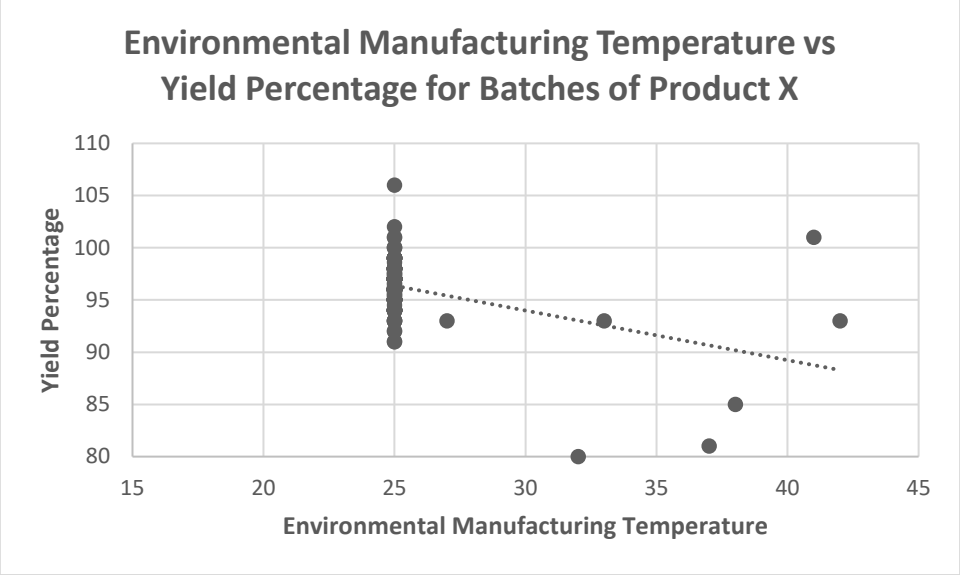

Figure 1.: Environmental Manufacturing Temperature vs Yield Percentage for Batches of Product X (n =165)

Figure 1. shows a correlation co-efficient of -0.40 between environmental manufacturing temperature and yield percentage where n=165. This indicates that a potential negative relationship exists between T_{ME} and the Yield Percentage (%), although the correlation co-efficient is low. The yield percentage appears to drop as T_{ME} increases with two batches between the 35-40^{O}C intervals having yields of below 85% which is outside the targeted range of 95-105%. The yield percentage appears to return to normal above the 40^{O}C interval. The majority of batches manufactured under the T_{ME} of 25^{O}C cluster around the 90-105% Yield

percentage which implies that is the optimal condition to be manufacturing at when compared to the intervals about 25^{O}C.

5.1.2. % RH and Percentage Yield Correlation

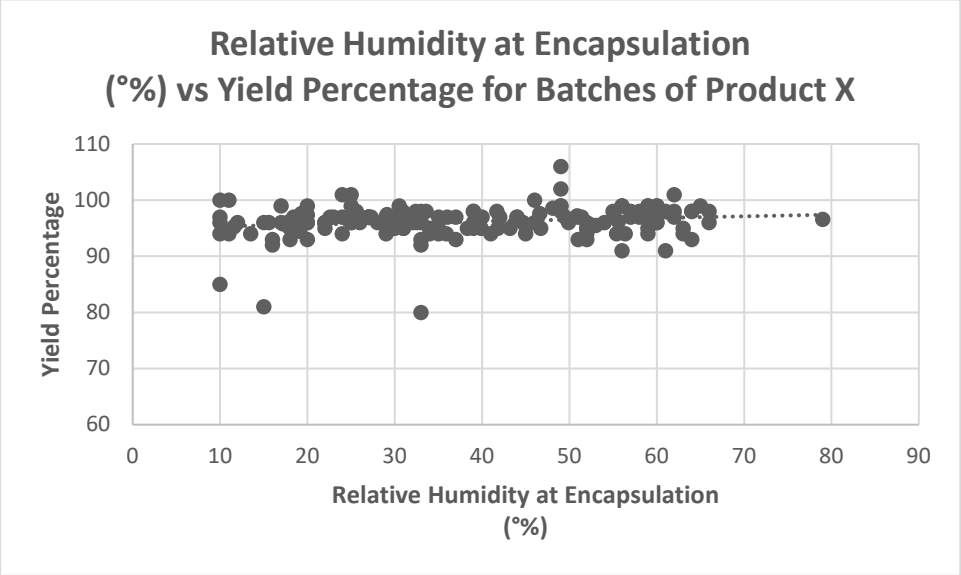

Figure 2.: Relative Humidity at Encapsulation (%) vs Percentage Yield for Bulk Batches of Product X (n =165)

Figure 2. shows a correlation co-efficient of 0.17 between T_{ME} and yield percentage where n=165. This indicates that a potential positive relationship may exist between % RH and the Yield Percentage (%) according to the correlation co-efficient, however the correlation co-efficient is very low, and the percentage yield appears to remain relatively constant when plotted against % RH, showing a neutral relationship exists. The Yield Percentages appear to be achievable across a % RH of 10% to 80% with a few outliers showing lower Percentage Yields as 80 %, 81 % and 85 % as % RH drop below the 35. This would indicate that keeping the environmental conditions above 35% RH would be ideal for manufacturing.

5.1.3. Yield Percentage and Moisture content of the filled capsule

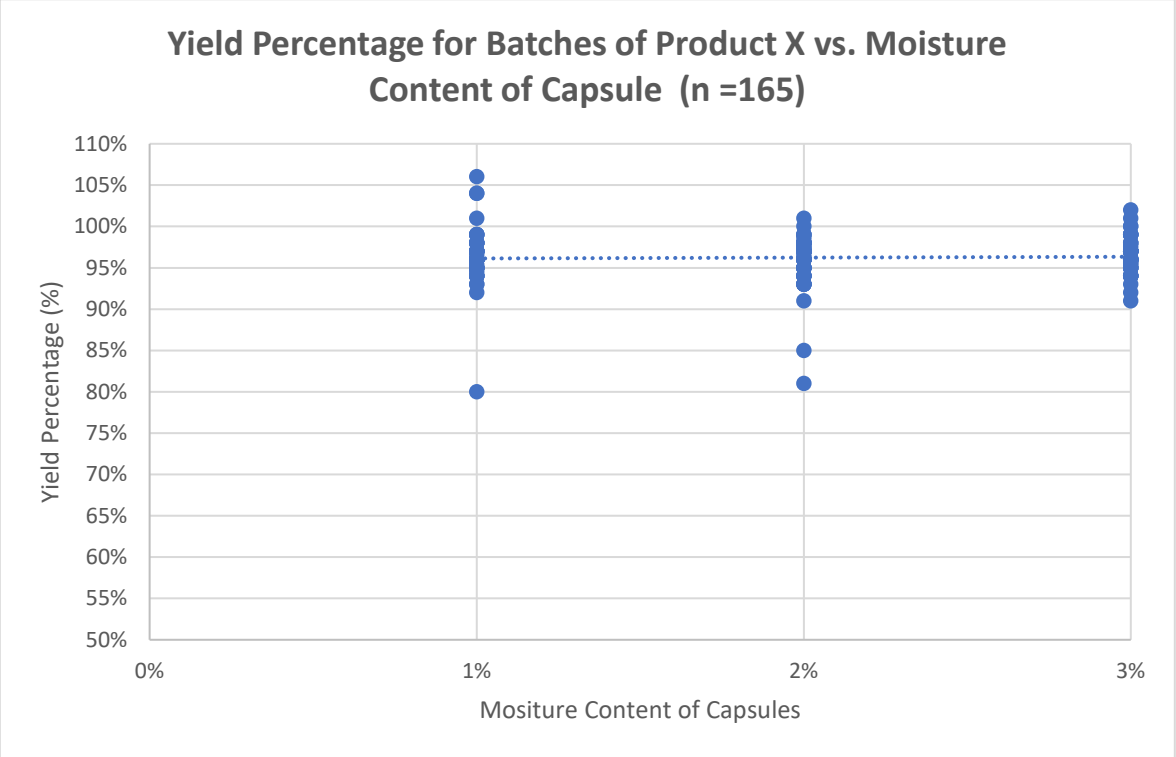

Figure 3.: Yield Percentage for Batches of Product X vs. Moisture Content of Capsule (n =165)

Figure 3. shows a scatterplot of between Yield Percentage and Moisture Content of Capsule. The correlation co-efficient was calculated to be 0.01 between Yield Percentage and Moisture Content of Capsule. The Moisture Content of Capsule ranged from 1-3% while the Yield Percentage (%) ranged from 80 % to 106 %. As the correlation co-efficient is very low and the Yield Percentage (%) appears to be constant when plotted against the different values of Moisture Content of Capsule, and since all batches (including batches that had Yield Percentages outside the target range) passed the moisture content testing, there appears to be no definitive relationship present between the variables.

5.1.4. Yield Percentage and Disintegration Time of the Capsule

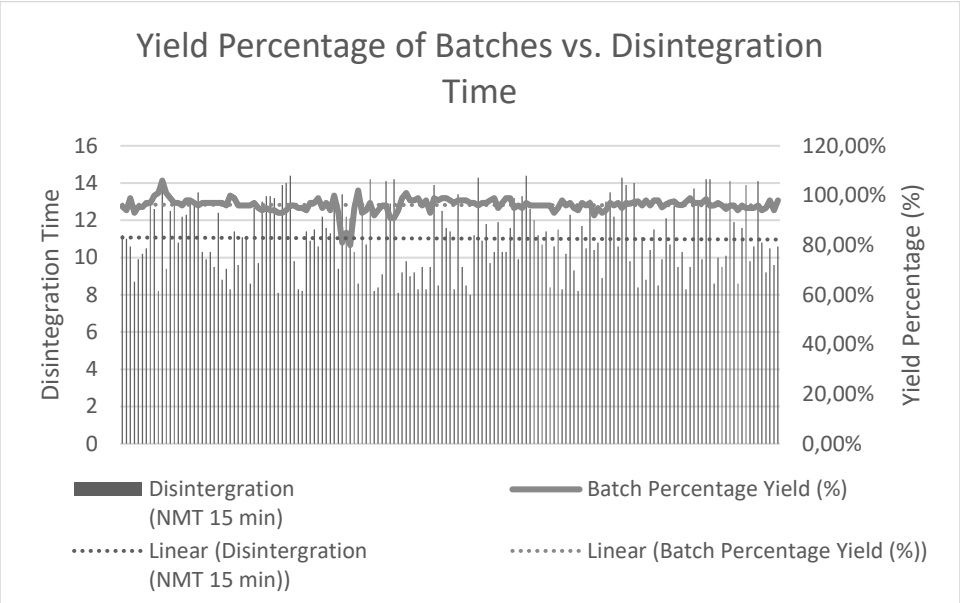

Figure 4.: Yield Percentage of Batches vs. Disintegration Time (n =165)

Figure 4. shows a correlation co-efficient of -0.10 between Yield Percentage and Disintegration Time. The Disintegration Time ranged from 8 minutes to 14.4 minutes while the Yield Percentage (%) ranged from 80 % to 106 %. As the correlation co-efficient is very low and since all batches (including batches that had Yield Percentages outside the target range) passed the disintegration testing, and the added trendlines appear to relatively constant as well, there appears to be no definitive relationship present between the variables.

5.1.5 Environmental Temperature and Disintegration of Capsules

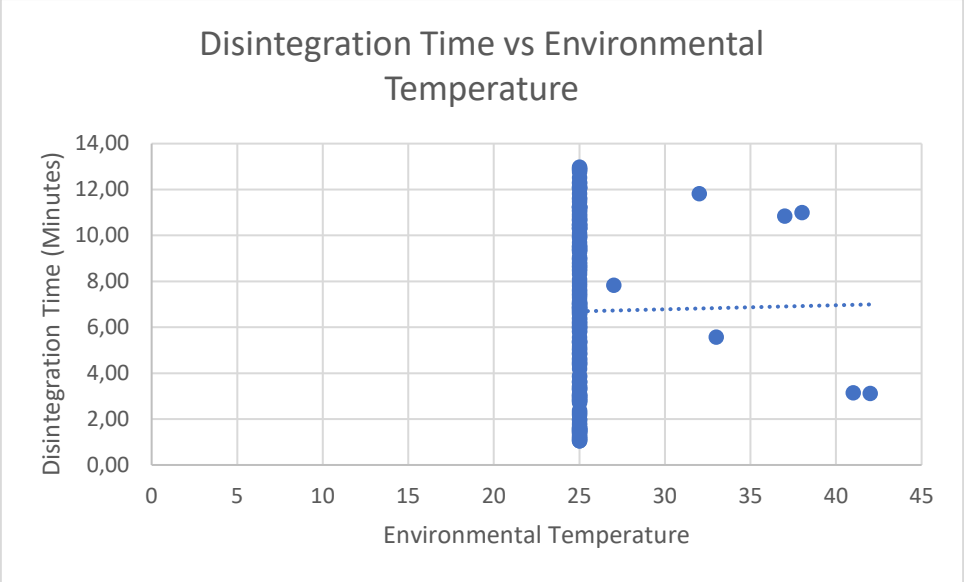

Figure 5.: Environmental Temperature vs. Disintegration Time (n =165)

Figure 5. shows a correlation co-efficient of 0.01 between Environmental Temperature and Disintegration Time. The Disintegration Time ranged from 8 minutes to 14.4 minutes while the Environmental temperature ranged from 25^{O}C to 42^{O}C. As the correlation co-efficient is very low, all batches passed the disintegration testing, and the added trendlines appear to relatively constant as well, there appears to be no discernable relationship present between the variables in the analyzed data sets

5.1.6 Environmental Temperature and Moisture Content of Capsules

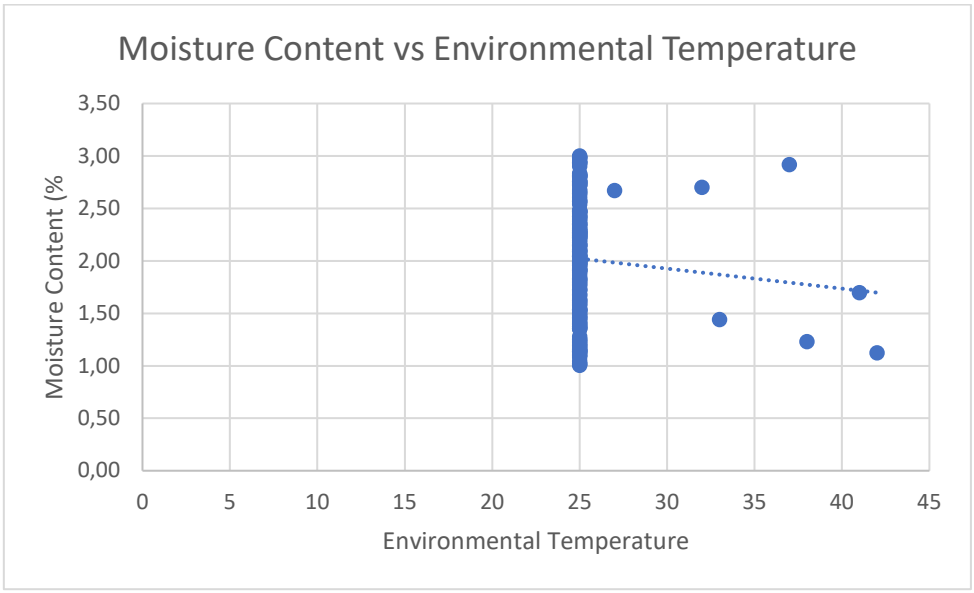

Figure 6.: Environmental Temperature vs. Moisture Content (n =165)

Figure 6. shows a correlation co-efficient of -0,08 between Environmental Temperature and Moisture Content. The Moisture Content ranged from 8 minutes to 14.4 minutes while the Moisture Content ranged from 1% to 3%. As the correlation co-efficient is very low, all batches passed the moisture content testing, and the added trendlines appear to relatively constant as well, there appears to be no discernable relationship present between the variables in the analyzed data sets

5.1.7 Relative Humidity Percentage and Disintegration of Capsules

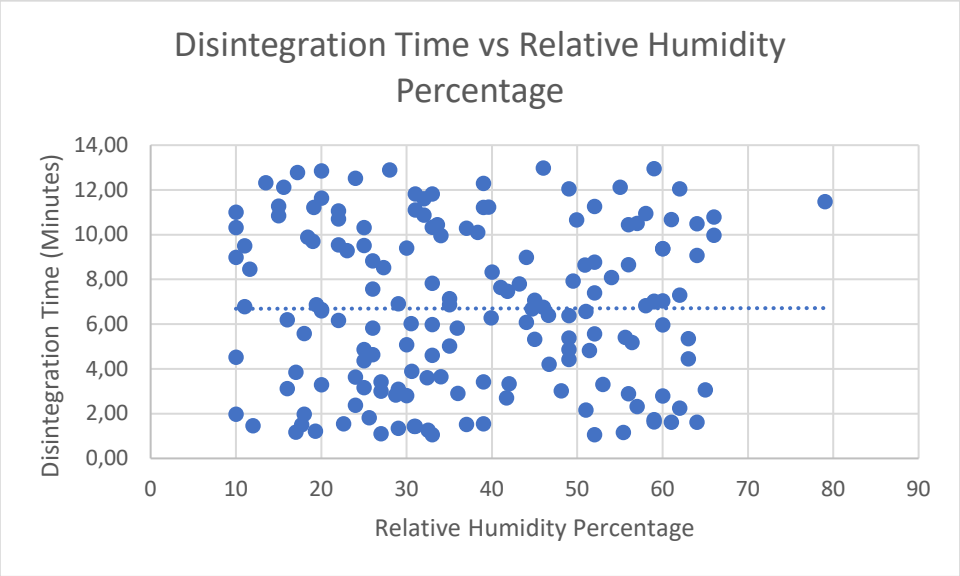

Figure 7.: Relative Humidity Percentage vs. Disintegration Time (n =165)

Figure 7. shows a correlation co-efficient of 0.00 between Relative Humidity Percentage and Disintegration Time. The Disintegration Time ranged from 8 minutes to 14.4 minutes while the Relative Humidity Percentage ranged from 10 % to 79 %. As the correlation co-efficient is very low, all batches passed the disintegration testing, and the added trendlines appear to relatively constant as well, there appears to be no discernable relationship present between the variables in the analyzed data sets

5.1.8. Relative Humidity Percentage and Moisture Content of Capsules

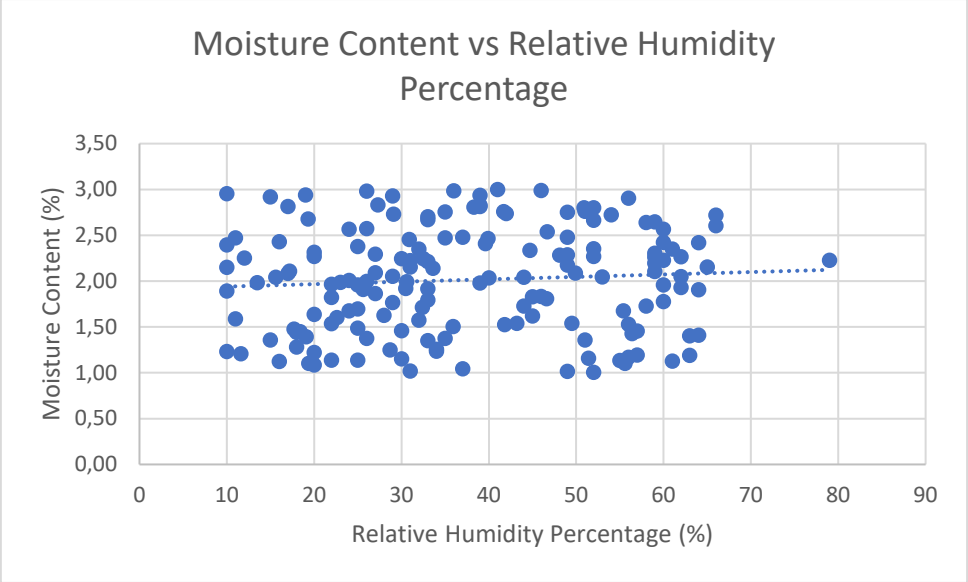

Figure 8.: Relative Humidity Percentage vs. Moisture Content (n =165)

Figure 8. shows a correlation co-efficient of 0,08 between Relative Humidity Percentage and Moisture Content. The Moisture Content ranged from ranged from 1% to 3%. while the Relative Humidity Percentage ranged from 10 % to 79 %. As the correlation co-efficient is very low, all batches passed the moisture content testing, and the added trendlines appear to relatively constant as well, there appears to be no discernable relationship present between the variables in the analyzed data sets

5.2. Statistical comparisons between the different % RH categories

Table 1. ANOVA between the three categories of % RH to determine if there is a statistically significant difference between the groups.

% RH Category	*N =*	*Average Yield Percentage*	*Standard Deviation*	*Anova P-Value*
Less Than 60 % RH	140,00	96,38	3,98	0,67
60 % RH - 70 % RH	18,00	96,83	5,91	
Above 70 % RH	7,00	96,60	4,38	

Table 1. shows the calculated p-value using the one-way ANOVA to determine if there was a statistically significant difference between the 3% RH groups was 0,67 where the $\alpha = 0.05$. The largest % RH group contained 140 batches, with the other two groups having smaller .sample numbers of 18 and 7 batches. The average Yield Percentage (%) was relatively constant across

the different % RH groups. The standard deviation within groups was also relatively constant, with the largest difference in range being 1,93 %.

5.3. Statistical comparisons difference between the different T_{ME} categories

Table 2. ANOVA between the three categories of T_{ME} to determine if there is a statistically significant difference between the groups

Environmental Manufacturing Temperature	*N=*	*Average*	*Standard Deviation*	*Anova P-Value*
Less than 28 Degrees Celsius	159	96,42	4,15	0,00
28 Degrees Celsius to 38 Degrees Celsius	4	84,75	34,92	
Greater than 38 Degrees Celsius	2	93	4,12	

Table 2 shows the calculated p-value using the one-way ANOVA to determine if there was a statistically significant difference between the T_{ME} groups was 0,00 where the $\alpha = 0.05$. The largest T_{ME} group contained 159 batches, with the other two groups having smaller sample numbers of 4 and 2. The average Yield Percentage (%) was varied in range with across the different T_{ME} groups with the largest difference between 11,67 % when comparing the Less than $28^{O}C$ group and the 28 ^{0}C to 38 ^{0}C group. The standard deviation within groups was also relatively large, with the largest difference in range being 30,8 % when comparing the 28 ^{0}C to 38 ^{0}C group and Greater than 38 ^{0}C group.

5.4. Conclusion

This chapter presented data amongst the various parameters collected. It shows the analyzed relationships between the different parameters of T_{ME}, % RH, percentage yield, disintegration and moisture content. It presented the calculated statistical data for correlation coefficients, p-values, averages and standard deviations

CHAPTER SIX: DISCUSSION

A total of 165 batches which were produced between 1 January 2020 to 31 March 2022 were analyzed in this study. The T_{ME} and yield percentage for all batches were plotted on a scatter plot to determine the correlation between the two variables (see Figure 1.) the correlation coefficient was calculated to be -0.40. Correlations of above 1 implies perfect correlation, values between ±0.50 and ±1 suggest a strong correlation, values between ±0.30 and ±0.49 indicate a moderate correlation and values below +0.29 are considered a weak correlation while values of 0 implies no correlation. The correlation relationship of T_{ME} and Yield Percentage is therefore implied to be moderate in nature based on the data.

The % RH at encapsulation and yield percentage for all batches were plotted on a scatter plot to determine the correlation between the two variables (see Figure 2.) the correlation coefficient was calculated to be 0.17. This implies a weak correlation in nature based on the data. The data was then divided into percentage yield and the T_{ME} categories to reflect the intervals for long term, intermediate and accelerated stability storage conditions for environmental temperature i.e., less than $28^{O}C$, between $28^{O}C$ and $38^{O}C$ and greater than $38^{O}C$. The three groups were then tested using a single factor ANOVA to determine if there was a statistically significant difference between the means of the groups (see Table 1). The p-value obtained was 0,00 with $\alpha = 0.05$, indicating there was a statistically significant difference between the means of the groups. The categories of Less than $28^{O}C$ and between $28^{O}C$ and $38^{O}C$ were analyzed using a single sided t-test to determine if there was a statistically significant difference between the groups. The p-value was calculated to be 0.01 indicating there was a statistically significant difference between the groups. The categories of between $28^{O}C$ and $38^{O}C$ and greater than $38^{O}C$ were analyzed using a single sided t-test to determine if there was a statistically significant difference between the groups. The p-value was calculated to be 0.02 indicating there was a statistically significant difference between the groups. The statistical difference between the groups was hypothesized as available literature indicated that high temperatures negatively affected gelatin capsules due to melting of the capsules.

The categories of less than $28^{O}C$ and greater than $38^{O}C$ were analyzed using a single sided t-test to determine if there was a statistically significant difference between the groups. The p-value was calculated to be 0.30 indicating there was no statistically significant difference between the groups. This difference could be due to the lack of data points for batches above the $38^{O}C$ T_{ME} interval.

The data was then divided into yield percentage and the % RH categories to reflect the intervals for long term, intermediate and accelerated stability storage conditions for environmental temperature i.e., less than 60 % RH, between 60 % RH - 70 % RH and greater than 70 % RH. The three groups were then tested using a single factor ANOVA to determine if there is a statistically significant difference between the means of the groups (see Table 2). The p-value obtained was 0.67 with $\alpha = 0.05$, indicating there was no statistically significant difference between the means of the groups. This result was not expected as the available

literature indicated that RH% played a role in whether the gelatin capsules would start to swell due to a environment with a high RH%, forcing the capsule to absorb the moisture or they would be come brittle in low % RH conditions, causing them to break. However, batch Yield Percentages, remained above 80% even at low RH% conditions of 10%.

Additional data was collected on the moisture content of the capsule and disintegration time of the capsule for each batch that was produced. Moisture content was analyzed for correlation with the yield percentage of the batches and the coefficient was calculated to be 0.01, which implies a weak correlation. None of the batches (including batches that were outside the targeted yield percentage) showed a moisture content of more than 3% w/w (which was the upper limit of acceptance of the test). There appeared to be no correlation between the moisture content of the capsule and the yield percentage of the batch. The passing of these tests for each batch can be attributed to the testing process where only successfully encapsulated capsules would be sent for testing, thereby, skewing the results.

Similarly, all of the batches did not have a disintegration time of the capsule of longer than 15 minutes (which was the upper limit of acceptance of the test). The passing of these tests for each batch can be attributed to the testing process where only successfully encapsulated capsules would be sent for testing, thereby, skewing the results.

CHAPTER SEVEN: CONCLUSION

This study sought to determine the effect of the T_{ME} and % RH on the yield percentage on batches of Product X produced at the Organization. The objectives of reviewing the BMRs of all batches of Product X that were produced between 1 January 2020 to 31 March 2022 and analyzing the collected data was successful. The data indicated that temperature had a negative relationship on yield percentage as it increased, which is consistent with the literature review where high temperatures negatively impacted gelatin capsules due to cross-linking of the capsules and reducing stability. There were statistical differences between the temperature groups of less than 28^{O}C and between 28-38^{O}C, and between 28-38^{O}C and greater than 38^{O}C but not less than 28^{O}C and greater than 38^{O}C. This is consistent with the between 28-38^{O}C category having the lowest average and largest standard deviation of the 3 groups. The implications of these results indicate that when if the bulk capsules were to be used for stability testing in the long term and intermediate conditions, there is a possibility that the capsules may cross-link and not pass the specification test. The results also indicated that there was no statistically significant difference in mean between the three % RH groups. There was also a positive correlation between the % RH at encapsulation and yield percentage. The data indicated that there was no discernable relationship between the moisture content of the capsules when compared against various T_{ME} values or % RH values. The data indicated that there was no discernable relationship between the disintegration time of the capsules when compared against various T_{ME} values or % RH values The literature review indicated that swelling of gelatin capsules would occur at high % RH conditions. The implication of this is that the possibility exists that the bulk capsules should fare well in all stability categories if used to generate stability data for submission to SAHPRA.

The Product owner can now use this information to optimize Product X for stability testing and registration. The information allows the product owner to make adjustments to the formulation of Product X to address the impact that the environmental temperature may have on it during stability testing or submit the information as it is to SAHPRA and wait on recommendations from the Regulatory Authority.

The study encountered the several limitations during the execution of the protocol which may affect the results obtained. The T_{ME} was only captured manually onto the BMRs by operators at the time of encapsulation and only in exceptional situations. When it was not recorded, the investigator was informed that the temperature was 25^{O}C. This created the risk for errors of omission since it is recorded manually by operators and the risk for errors during recording for T_{ME}. The T_{ME} data which was collected did not occur concurrently with some % RH categories which meant that no data was available for those composite conditions to be analyzed. There was significantly less data which fell into the higher limits of the categories (individual and composite) which may skew the sample statistics. T_{ME} and % RH was only recorded once at the initiation of encapsulation for Product X; hence, it did not represent a consistent set of conditions that Product X would have experienced. The structure of the BMRs requires recording of T_{ME} and % RH at the beginning of encapsulation, not throughout its encapsulation process which can vary between 1 – 7 days, hence, the T_{ME} and % RH is not fully representative

of the entire encapsulation process. Staff were encouraged to record any abnormal occurrences during manufacturing of a batch; however, human error is still present in the documents in that staff may have forgotten or omitted such data. Due to the nature of environmental control, the HVAC systems were still in the process of being qualified and validated, T_{ME} and % RH conditions could not be adequately isolated from each other or controlled.

For future studies, a few recommendations can be made to improve the data collection and analysis process. It would be beneficial for the testing of the capsules to also include moisture content of the capsules that appear to be brittle during manufacture and not only test capsules that were successfully encapsulated. This would provide insight as to how the % RH is affecting the structure of the gelatin capsule. The addition of assay content testing would also be beneficial as a direct measure can be made of the environmental conditions and its effect on the content of Product X's active ingredient during manufacture. The recording of the environmental conditions during the course of manufacture and not at initiation will also provide additional data of the effects of the environment on Product X's bulk.

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Appendices

Appendix A

APPENDIX A: BMR LIST: PAGE _____ OF _____	
Release Date	**Bulk Batch ID**
2020	B1901624
2020	B1901625
2020	B1901626
2020	B1901905
2020	B1901906
2020	B1901907
2020	B1901908
2020	B2000099
2020	B2000100
2020	B2000102
2020	B2000103
2020	B2000101
2020	B2000104
2020	B2000415
2020	B2000106
2020	B2000413
2020	B2000414
2020	B2000105
2020	B2000417
2020	B2000409
2020	B2000410
2020	B2000411
2020	B2000412
2020	B2000501
2020	B2000500
2020	B2000503
2020	B2000700
2020	B2000701

2020	B2000989
2020	B2000990
2020	B2000991
2020	B2000992
2020	B2000993
2020	B2001318
2020	B2001319
2020	B2001321
2020	B2001347
2020	B2001349
2020	B2001350
2020	B2001351
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Appendix B

APPENDIX B: DATA COLLECTION FORM: PAGE _____ OF _____

Bulk Batch ID Number	Temperature at Encapsulation (°C)	Relative Humidity at Encapsulation (°%)	Batch Percentage Yield (%)	Additional Comments