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Robotics for Powder Sample Preparation

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”Everything should be made as simple as possible, but not simpler.”

-Roger Sessions

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Resumo

Robôs sem supervisão foram aceites em muitas indústrias, mas dada a natureza delicada do produto farmacêutico, este setor é um adotante tardio. No entanto, os benefícios que esta tecnologia pode trazer às companhias farmacêuticas em todos os estágios de desenvolvimento de medicamentos estão a promover o crescimento da automação nos laboratórios, no contexto de Pharma 4.0. Devido à complexidade e importância da dosagem de pós para a fabricação de medicamentos, muitas soluções de manuseio de sólidos a granel têm emergido, mas nenhuma se provou ideal para todas as aplicações. Uma plataforma automática para criação de amostras reduziria o tempo de comercialização de medicamentos e custos de fabricação, mitigaria erros e riscos, e contribuiria para a otimização do desenvolvimento farmacêutico.

O foco principal deste trabalho foi criar uma plataforma de dosagem de pó e criação de amostras automática suficientemente flexível para ser usada com uma infinidade de recipientes e em diferentes aplicações laboratoriais. Para este fim, todas as tarefas realizadas durante a preparação de amostras manuais foram consideradas (desde manuseamento de pequenos recipientes a dosagem de pequenos volumes de pó) e dois espaços de trabalho foram desenhados para as automatizar. Vários módulos foram implementados e testados, dois para o transporte de recipientes para amostras, um para dosagem de pó usando um método pneumático, um para pesagem e um mestre para os coordenar. A sua arquitetura de software foi desenvolvida de forma a torná-los adaptáveis a mudanças. Os diversos módulos foram testados e conectados, e a funcionalidade geral do sistema foi avaliada sob diferentes condições. Foi concluido que o sistema conseguia criar amostras de pó sem supervisão com boa exatidão e repetibilidade, e que algumas adições poderiam levar à automação total da preparação de amostras, aliviando os trabalhadores do laboratório desta tarefa repetitiva.

Palavras-chave: Indústria Farmacêutica, Automação nos Laboratórios, Robótica, Amostragem Automática, Dosagem de Pó, Manuseamento de Recipientes Pequenos

Abstract

Unsupervised robots have been accepted in many industries, but given the delicate nature of the pharmaceutical product, this sector is a late adopter. However, the benefits that this technology can bring to pharmaceutical companies across all stages of drug development are promoting the growth of laboratory automation, in the context of Pharma 4.0.. Due to the complexity and importance of powder dispensing for drug manufacturing, many bulk solid handling solutions have emerged, but none has proven ideal for all applications. An automatic sampling platform would reduce time-to-market of drugs and their manufacturing costs, minimize errors and risks, and contribute to the optimization of pharmaceutical development.

The main goal was to implement an automatic powder dosing and sample creation platform flexible enough to be used with a myriad of vessels and in different laboratory applications. To this end, all tasks performed during manual sampling were considered (from handling small containers to dispensing low powder volumes) and two workspaces were designed to automate them. Several modules were implemented and tested, two for the transport of sample containers, one for powder dosing using a pneumatic method, one for weighing and a master to coordinate them. Their software architecture was developed so to make them versatile to changes. The diverse modules were tested and connected, and the overall functionality of the system was evaluated under different conditions. It was concluded that the system could create powder samples unsupervised with good accuracy and repeatability, and some additions could lead to the full sampling automation, relieving the laboratory staff from this repetitive task.

Keywords: Pharmaceutical Industry, Laboratory Automation, Robotics, Automated Sampling, Powder Dispensing, Small Container Handling

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Acronyms

API Active Pharmaceutical Ingredient.

CDMO Contract Development & Manufacturing Organization.

CMO Contract Manufacturing Organization.

CPV Continuous Process Verification.

D-H Denavit Hartenberg Convention.

DoE Design of Experiment.

DSC Differential Scanning Calorimetry.

DSCr Differential Scanning Calorimeter.

EMA European Medicines Agency.

FDA Food and Drug Administration.

GLP Good Laboratory Practice.

GMP Good Manufacturing Practice.

HP-API Highly Potent Active Pharmaceutical Ingredient.

ICH International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use.

ISPE International Society for Pharmaceutical Engineering.

PLC Programmable Logic Controller.

PSD Particle Size Distribution.

R&D Research and Development.

RF Reference Frame.

SCARA Selective Compliance Assembly Robot Arm.

T_g Glass Transition Temperature.

WHO World Health Organization.

Chapter 1

Introduction

As a result of an always growing competition, market complexity and external pressure from socio-economic factors, drug manufacturing companies are forced to transform in order to maintain their status and improve their products and services. Automation has been implemented and accepted in many areas of industry but due to the delicate nature of pharmaceutical production, this sector is a late adopter. Despite this apparent hindrance, there is a constant desire to optimize production and reduce the time and cost of the drug development. Quality, safety and process transparency are also main concerns, which is mandatory since the output product in a consumable meant to treat diseases and health issues. Automation provides means to accomplish many of these objectives and more, so although slowly, the presence of autonomous systems in this sector is increasing. One aspect where implementing automation is still a challenge is bulk solid handling, given the wide variety of products and characteristics, containers used to store them and the extreme accuracy required to achieve the dispensing of small quantities of powder.

1.1 Pharmaceutical Industry

The competitive market environment coupled with increasing costs of discovering new drugs causes noticeable changes in the pharmaceutical industry. Due to the nature of the product created, the pharmaceutical industry has very specific and distinguished characteristics. For start, the continual importance of creating a safe product with high quality standards, since its end purpose is to be used as a medicine. Secondly, drug discovery and development are lengthy and costly, which is behind the desire for a higher process throughput and for error minimization, in order to reduce the time-to-market of the products created. Some of the most important aspects of this sector, such as regulatory policies, product development process and current challenges and opportunities, are described in this section.

1.1.1 GMP and GLP regulations

Drug development is heavily regulated and during its entire process it is mandatory to obtain all the required certificates from inspection entities, such as the World Health Organization (WHO), before being able to provide any product to the customers. These organizations do not only inspect but also provide guidelines to the pharmaceutical companies, such as the ones in [1]. Referred to as Good Manufacturing Practices (GMPs) and Good Laboratory Practices (GLPs), the enforced regulations serve as a minimum guarantee of product quality and safety.

GLPs are intended to assure integrity and validity of the research studies on product safety. GMPs guarantee the quality of each batch of medical products, by making sure all operations during manufac-

turing and testing are analogous to pre-defined methods and specifications [2]. Safety studies are then performed under GLPs and testing of products should be in accordance with GMPs.

Combined, these regulations make sure the quality standards imposed are fulfilled, in all the stages of drug development: raw material acquisition, drug discovery, chemical processes, development, manufacturing, testing, quality control, marketing, packing, distribution, storage etc. This quality assurance is especially important in the case of Contract Manufacturing Organizations (CMOs) and Contract Development & Manufacturing Organizations (CDMOs), that manufacture products for different clients to be sold under their names, and therefore have large amounts of projects and materials to manage and higher quality associated risks, resulting in more pressure related to regulations and norms. Constant process monitoring of many projects mean one thing overall: big data.

The International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) promotes connections between the existing regulatory authorities in the pharmaceutical sector and discuss aspects of drug registration, with the objective of reaching worldwide understanding and harmonisation of ideas to ensure safer and higher quality drugs are developed. To this end, they have created a model for an effective quality management system for the pharmaceutical industry, called ICH Q10. In addition to these guidelines, the Food and Drug Administration (FDA) and the European Medicines Agency (EMA) provide market specific regulations, which further increase the standards for pharmaceutical companies. Therefore, the strict quality control policies are present from the initial drug discovery to the time the product is marketed.

1.1.2 Drug Development stages

According to the FDA [3], there are five main stages of drug development, illustrated in figure 1.1 acquired from [4].

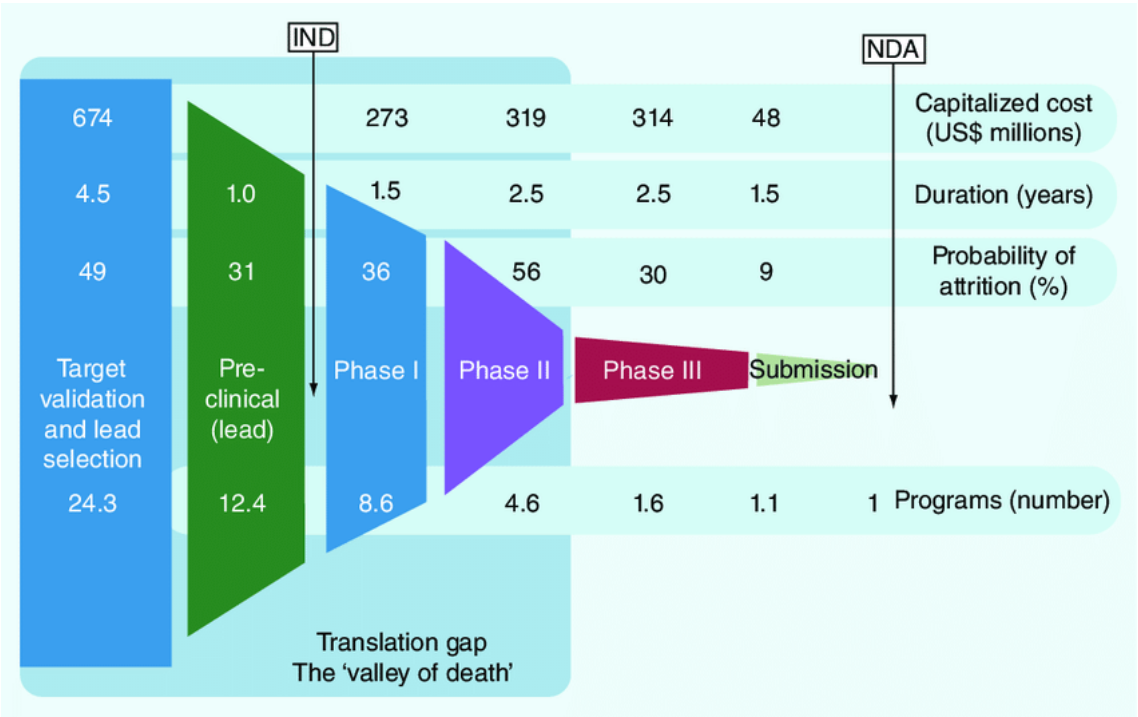

Figure 1.1: The five main steps in drug development, as defined by FDA.

- **Discovery and Development:** Many tests of new molecular compounds to find possible beneficial effects against any of a large number of diseases. From thousands of compounds, only a few show promising effects and have potential for development. These few are tested on how they behave, what are their benefits and side-effects, the best dosage, how effective they are, etc.
- **Preclinical research:** Scientists check for toxicity of the compound before administering to humans and decide if it should be developed further. Although these studies are small, they provide very detailed information about the compound, usually referred to as Active Pharmaceutical Ingredient (API). During this phase, the processes must respect the GLPs imposed by the FDA. Drug developers must submit an Investigational New Drug (IND) application to the FDA before beginning clinical research.
- **Clinical research:** The drug is tested in small doses in humans, following very strict protocols and a close contact with the FDA is maintained throughout these studies, as they provide not only supervision but technical assistance. Constant feedback is provided and once the clinical development is concluded, a New Drug Application (NDA) is submitted.
- **Drug Review:** The review team from FDA checks the NDA and decides if the product characteristics and its development meet the standards. If it does, the manufacturer gets the approval and the drug is placed on the market.
- **Post-Market Monitoring:** Even during its commercial phase, the product is kept monitored and new dosages and forms can be researched. Advertisement and product inspection are maintained by the FDA, as it also receives customer feedback if there are any problems with the pharmaceutical drug.

As seen from figure 1.1, the entire drug development process can take over ten years, with expenditures surpassing several hundreds of millions of dollars, sometimes even reaching billions. A high attrition rate between stages is also noticeable, since, on average, from over twenty programs only 1 medicine is marketed. This conclusion provides a clear view on the time and capital investment in the industry. It gives an idea of where process optimization is of great importance, by minimizing error and maximizing throughput, reducing drug development costs and time-to-market.

1.1.3 Opportunities for improvement

Drug manufacturing and development can heavily benefit from new technologies that deliver productivity increments in the industry's key focus areas. To better understand the business units that show inefficiencies, a study that involved discussions with laboratory directors, team leaders, analysts and quality personnel in the studied CDMO was conducted. together with market research. The major challenges were identified and a compilation of some of the tasks that arise as opportunities and could be enhanced with automation and digitalization is presented below, with the corresponding solutions in mind.

1. Ineffective information exchange between areas results in production delays.

- Automatic data flow with task monitoring.

2. Not enough monitoring and slow information logging procedure.
    - Automatic data logging.
3. No counteraction in response to the production mishaps.
    - Reactive model based on the data monitored.
4. Stock management in the laboratory can be time-consuming.
    - Automated material identification and information storage.
5. Safe and effective material and sample transportation is difficult to maintain.
    - Automation of material and sample transport.
6. Preparation of samples, capsules and solutions is a slow and repetitive manual task.
    - Automatic sample, capsule and solution preparation.
7. Human error when handling liquids and filling vials.
    - Automatic liquid handling.

It is easy to see in the first four issues how an improved data handling system by digitalization would bring benefits to the pharmaceutical sector, just like it does in many other industries. In the last three, the concept of automation is heavily present, giving the idea that the implementation of robotics in the laboratory provides solutions to aid and substitute human labor in the presented operations. Both of these terms are significantly correlated with the latest industrial revolution, named Industry 4.0.

1.2 Fourth Industrial Revolution and Pharma 4.0

Technology is nowadays in inexorable growth. Factories are quickly becoming smarter and more agile, increasing speed and efficiency while maintaining flexibility, by combining data handling, smart sensors, interconnectivity and decentralized decision-making models that are emerging with the digital revolution. The increasing pharmaceutical supply chain complexity [5], the new working procedures and products [6] and the lower return on investment in Research and Development (R&D) [7, 8] are causing a paradigm shift in drug manufacturing. It is in this context that the fourth industrial revolution, so called Industry 4.0, intertwines with the pharmaceutical sector. The buzzword used to describe this phenomenon is Pharma 4.0 and it provides the means for drug manufacturing companies to evolve in current day's demanding market. Pharma 4.0 follows the vision of the current industrial revolution, helping in or automating relevant laboratory tasks by compiling the usage of smart sensors and machines connected to intelligent systems.

The most recent automation market brings a myriad of tools for the pharmaceutical industry. The high expenditure on R&D is a big incentive for the implementation of robotics in the analytical laboratories, not only because the large amount of money invested in the sector facilitates the growth of laboratory automation and but also because there is the possibility for a large return on that investment. In 2005, the western European market of laboratory automation was estimated to be around $\$245$ million, and

of that amount, roughly 20% represent robotics for drug development applications, showing a steady growth rate throughout the years [9].

In this context, the International Society for Pharmaceutical Engineering (ISPE) Special Interest Group has created an Operating Model for the factories and supply chains of the future, illustrated in figure 1.2 and stated in their idea that Pharma 4.0 is the conjugation of the technology and digitalization from Industry 4.0 with the norms established in ICH Q10.

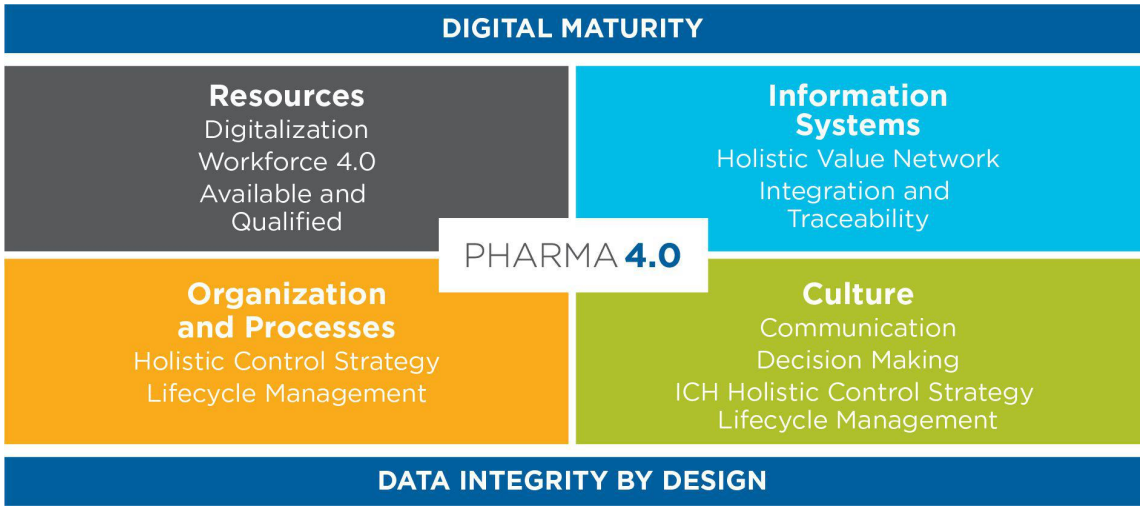

Figure 1.2: Pharma 4.0 Operating Model created by ISPE Special Interest Group

Recalling the improvement opportunities listed, it is clear that the tools and ideas that constitute the concept of Pharma 4.0 can show the next steps to be taken in the industry. Digitalization and simulation allow for better supply chain management and scheduling of activities [10, 11], for example, by predicting product demand [12], reducing overall operation costs. As for automation, from simple usages such as the electronic notebooks and bar codes to the complex implementation that is a fully automated laboratory [6], the systems that emerge have been for the most part successful.

Pharmaceuticals are one of the most regulated industries, being subject to scrutiny at every step of its product's development, not only regarding GMPs, but also other quality policies enforced by the EMA in Europe and the FDA in America. At every stage there is a need to capture data, analyze it, report it, and thus, it is a good target for digitalization [13]. Due to this ever-present requirement of having data always available, pharmaceutical companies tend to adopt a Continuous Process Verification (CPV) approach, where all information regarding the manufacturing can be checked against the mentioned guidelines. Quality control laboratories utilize information tools and databases provided by the Laboratory Management Information System (LIMS). These systems provide means for automating and integrating tasks [14] and are used to track, monitor and record performed analyses. Their objective is to increase sample throughput and reduce turnaround times. Since hundreds of variables must commonly be monitored and controlled, drug development is justified to be a great candidate for the implementation of Industry 4.0 technology. This technology offers real-time feedback of the processes involving the production, so any slight variation in parameters detected can be corrected, avoiding loss of time and product [9].

1.3 Objectives and Contributions

Analytical sample preparation poses one on the most labor-intensive tasks for which advanced automation and robotics would yield a great competitive advantage. Removing the need for analysts to perform this task could allow a faster screening and testing of powder compounds, resulting in a shorter drug development time. A survey done in 2009 indicated that a fourth of the pharmaceutical laboratories consider automation of bulk solid dosing a bottleneck and two thirds consider automation in general to be important for drug manufacturing [15]. This survey also recorded that the majority of powders used are considered difficult to handle, with the current automatic solutions not sufficing. The objective was then challenging but simple to define. Implement an automated dispensing platform that was reliable and accurate enough to work unsupervised. It should also be flexible, so it is applicable not only to sampling with different product sources and destinations but to other laboratory processes where powder dispensing is used.

The presented work was developed in the context of a partnership between Instituto Superior Técnico (IST) and Hovione Farmaciência, S.A.. In this thesis, a review of the current dispensing techniques and dosing platforms and their limitations was carried out. Several custom parts were modeled and manufactured, to be implemented in proposed solutions to the powder dosing and sampling automation problem. Two different workspaces of automated sampling were implemented and tested, combining modules designed for handling sample containers and dispensing powder, among others, with the objective of providing valid samples without human intervention.

1.4 Thesis Outline

In this chapter, the pharmaceutical industry and its characteristics were briefly discussed. Some improvement opportunities were listed, to which the tools that compose Pharma 4.0 can provide suitable solutions.

Chapter 2 will provide an overview of the main benefits of automated systems in general industry and applied specifically to the pharmaceutical sector. Then, the importance of powder dosing and the need for its automation are explored. Physics behind powder flowability briefly studied and the current methods for bulk solid dispensing were listed. Additionally, different off-the-shelf robotic systems that perform solid dosing were analyzed and their limitations presented.

In chapter 3, the sampling task is presented and two solution designs for automated sampling were proposed, inspired in the currently available platforms. The hardware used in each of the different modules is described and the manufactured parts' design explained in detail. Chapter 3 also provides an insight of the algorithm used in the sampling operation, by illustrating the tasks of each module and the communication between them. The final implementation is presented at the end of this chapter.

The experiments carried out to evaluate each module are presented in chapter 4, as well as the obtained results. The discussion of these results is also presented in this chapter (for an increased readability), which lead to fine tuning of the implementation throughout the different tests. An analysis of the final end-to-end system is presented, with the objective of quantifying the system's overall

performance.

Lastly, in chapter 5, some conclusions are drawn regarding what was accomplished in the thesis, briefly evaluating the results and the contribution to the topic. Additionally, it is mentioned what could be improved with future work, to enhance robustness of the system and provide more reliable automatic sampling.

Chapter 2

Laboratory Automation Overview

Despite the presence of automation in many of the laboratory equipment, this is usually a simple module and is applicable only to that designated task. There is no communication between devices and the input and output materials of any machine is handled manually. This means that there is very limited flexibility when trying to couple the diverse instruments and make them work as a whole, resulting in the ever-present role of the human labor as mandatory.

In this chapter, the benefits of automation that will be focused on are explored, not only in the context of any industry, but specifically for drug manufacturers. These are safety, throughput, data integrity, repeatability and staff relieving, all of which are imperative for the success of a pharmaceutical company, as discussed in chapter 1.

Some of the laboratory instruments are listed and the topic of solid bulk dosing and sampling is introduced. Given the challenging nature of the task, the physics behind powder flowability are briefly studied and the myriad of dispensing methods are explored. The current market solutions for powder dosing are listed and their main limitations pointed out, and to this end, the objectives for the robotic sample preparation are defined with more detail.

2.1 Automation and Robotics benefits

To promote productivity and reduce the man hours taken up by low value tasks, many organizations are implementing automation and digitalization [16]. Automation is also an effective tool in process monitoring and can help reduce risks and frequency of human errors. In this section, five important benefits of automation and robotics are presented, in the general industrial environment, as well as in the pharmaceutical sector. These are the main advantages that the system that is meant to be implemented would provide for drug development.

2.1.1 Safety and Risk Mitigation

One common theme across all industries is that many regulations exist to make sure the working environment is safe for everyone. In the pharmaceutical industry, many safety precautions are taken and regulations are established, but even so, the risk of accident is always present. These regulations become of greater importance when developing potent products, also referred to as Highly Potent Active Pharmaceutical Ingredients (HP-APIs), since the harm they can cause is very serious.

The last decades have been characterized by an increase in the usage of HP-APIs in the fight of many diseases. ”More than 1,000 small molecule highly potent drug products are currently in development, and market estimates project close to 10% annual growth in this space.” [17]. However, these come at a

cost, because it becomes mandatory to shield those involved in the manufacturing of these compounds. From the discovery of these molecules to the product distribution to the client, all who are involved in the handling of said drugs can be at risk [18]. Many of the New Chemical Entities (NCEs) are considered potent compounds, meaning Occupational Exposure Limits (OEL) $< 0.01 mg/m^3$, which requires special handling conditions.

The easiest way to protect the working staff if by minimizing their role in the product development, which automation contributes to. When using automated systems, there is no need for human intervention during the operation, so the risk of injury or intoxication due to product exposure is mitigated. Additionally, as long as the safety guidelines are followed, the risk inherent of utilizing a machine from is assured by its supplier, so it is a responsibility taken away from the working staff.

2.1.2 Throughput and Availability

One important advantage that process automation brings is the increase in throughput due to the higher availability of a machine compared to a human. Having no need to rest means robotic systems can work 24 hours per day, triple the amount of most analysts. In the pharmaceutical industry, this is clear, for example, in the Differential Scanning Calorimeter (DSCr). This equipment can be programmed to analyze up to 50 different samples (for over 2 hours each) without human intervention, working overnight and saving all the results for the analyst to evaluate when it is most convenient.

Related to the previous topic, the methods and procedures to guarantee safety can sometimes take a long time. The robot, however, has no risk of being intoxicated or harmed by the products, so it will take the same amount of time to handle dangerous chemicals as when handling harmless ones.

Additionally, the speed of a robot especially design to perform a specific operation will probably be higher than the adaptive but slower human hand. This is excluding the possibility of a new employee performing the task (very frequent due to the growth of the industry) whose speed will be less than of an experience one. An autonomous system is programmed and the time it takes to perform its tasks will never increase, only decrease with optimization.

2.1.3 Data Integrity and Logging

Industries are becoming aware of the power of information, since its organization and review can promote service quality and manufacturing effectiveness. Informatics are no longer exclusively related to Information Technology (IT) but can also be used in modeling and simulation of manufacturing processes [19].

Data integrity is the maintenance, assurance of accuracy and consistency of data over its entire life cycle. It is critical for the design, implementation and utilization of any data system that acquires, processes or registers data [20]. Nowadays, data integrity is of extreme importance and the pharmaceutical sector is no exception, as demonstrated by FDA's publication [21]. By allowing the instruments in the laboratory to communicate, transfer data and save it in an organized manner and respecting current GMPs, one can better assure that all the information regarding any process or project is properly secured and available for monitoring.

If decision-making models are applied, making the digital system more independent of human inter-

vention, the ability to evaluate the data and respond to events increase productivity even further.

2.1.4 Repeatability and Error Minimization

Another important positive aspect of automation is that it avoids human error and uncertainty. Humans cannot achieve the same repeatability when performing a task than a specifically designed and optimized autonomous machine. This is especially important in the pharmaceutical sector, where small errors in the preparation or screening of a compound can lead to significant negative effects on the final product. This is further noticed in a growing company, since human error increases with growth. By taking away the variability caused by human intervention, automation provides more repeatable and trustworthy results. This benefit is correlated with risk mitigation since some human error can lead not only to less accurate results or analyses, but to a product being wrongfully marked as proper for consumption. When performing operations with low volumes of drug product, better repeatability results in less waste, which can allow the possibility of performing a higher number of analytical tests and in some cases can mean significant savings.

2.1.5 Supervision Role of the staff

By performing repetitive task that were previously done by humans, machines provide more free time for them to do more cognitive tasks where human perception and interpretation is needed. The staff becomes able to supervise and control many processes simultaneously instead of being focused and occupied on one single operation. This is easily applied to the pharmaceutical industry, as many analysts doing several tasks are slowly being replaced by fewer analysts supervising machines doing those same tasks. Besides, the more autonomous the system is, the less supervision it needs, tending to a completely unsupervised process, an industry 4.0 concept called *Lights Out Manufacturing*. This concept is used for example by FANUC's Japan plant [22], where robots build other robots without human intervention for as long as 30 days. This concept could be applied to the pharmaceutical industry, implementing a laboratory or factory that can operate on its own.

Adding to the above listed benefits, robotic systems do not slow down or lose focus, meaning their production level is constant and their work quality does not deteriorate. It also reduces occurrence of defects and mitigates production loss due to labor shortage. For all these reasons, the presence of automation and robotics has been growing in many industries and more specifically, pharmaceutical laboratories.

2.2 Powder Dosing in Drug Manufacturing

During the preclinical stage of drug development, it is necessary to create many formulations from the discovered API. This results in a large number of different products, especially after a synthesis scale-up, to allow the testing to be representative. Bulk solid dispensing automation emerges in this context, to facilitate the creation of a much larger volume of samples with less human hours and in a shorter amount of time, and to aid in many other tasks where small volumes of powder are handled. In the drug manufacturing industry, the core product is often in powder form, and during the process that turns API into a consumable drug, it must be transported, stored and transferred between containers

many times.

A quick survey in the laboratory led to the conclusion that powder dosing is not only important for sampling, but it is also crucial in capsule filling and in the creation of pills and tablets, two widely used drug delivery methods. It is also often part of dissolution analyses, where larger quantities must be accurately mixed in liquids and in the preparation of slugs with a specific mass of product. All of these operations could benefit from the creation of a powder handling platform versatile enough to perform coupled with many different instruments and with acceptable accuracy for all ranges of powder volumes. Since sample preparation is the laboratory task that requires the most dispensing precision and with the smallest quantity of powder, while also having the most complex processing besides the powder dosing, this was considered one of the most challenging operations related to bulk solid dosing.

Many instruments in the laboratory used to analyze formulations have some sort of automation implemented. Gas chromatography mass spectrometry (GC/MS) has long been used in industry to identify and quantify unknown components in compounds and is ideal for impurity analysis and as a Quality Control (QC) method [23]. The automation of chromatographic systems is of increasing interest to industry and research laboratories in routine applications. Besides potentially saving time or making better use of available instrumentation, automation also improves the quality of results by producing more precise and more reproducible High-Performance Liquid Chromatography (HPLC) data, other widely used laboratory instrument. The need for the validation of methods and qualification of instruments is increasingly recognized in order to ensure compliance with legal requirements (e.g. in the pharmaceutical industry) and to ensure the reliability of analytical results [24]. Another laboratory equipment that was enhanced by automation is the DSCr. This instrument has an autosampler, which is not a sample preparation tool, but it is tasked with placing and removing samples sequentially in its thermal chamber, so several formulations can be analyzed individually without human intervention. However, as stated before, the built-in automation is limited to the specific task of each instrument, and is hardly adaptable to other processes, so there is always a need for the analyst to bridge the gap between laboratory equipment.

Still related to this topic of incurable human intervention, all of the referred tools need the preparation of samples done by an analyst so it would be very profitable to any pharmaceutical company to have a system that is flexible enough to create samples of small volumes of solids and liquids, from different sources and to many destination vessels. The automation of liquid dosage has matured, and some of the instruments for that task have been widely implemented in laboratories around the world. On the other side of the spectrum, bulk solid dosing, i.e. powder dispensing, still presents some unresolved challenges.

2.3 Motivation

Powder sample preparation is a lengthy and labor-intensive process. Not only is it a very repetitive task but some speed is also required, given the need to have large batches of samples for each product to be analyzed. Due to the often small sample dimensions and the value of some APIs, precision is also a requirement. These reasons make the creation of these samples a great candidate for automation.

In 2009 a market survey was made by HTStec that indicated 24% of the respondents considered

automation of powder dispensing to be a major issue in their company [15]. 62% of respondents consider the automation useful, desirable or essential, with the main motivations being to avoid time-consuming manual processing, to cut cycle time in order to increase productivity and to conserve limited amount of product available and reduce wastage. The survey also indicated that 63% of powders are considered problematic (e.g. cohesive, extremely fine and fluffy, having large granules or very high density), which is a very important issue to consider since most automated solutions presently available in the market have precision and repeatability values for free-flowing powders (the other 37%). The major concerns about automating solid dispensing are the residual product after the dispensing (powder that is wasted), the minimum dispensed mass (sometimes too large for the application), the system robustness, i.e., its ability to work unsupervised without errors, and the cross-contamination between batches of different products.

2.4 Powder Flowability Principles

Particle size is one of the most important properties which dominate the collective behavior of bulk solids [25]. In addition to size, particle shape also has a big influence on powder behavior, since more spherical particles tend to have better flowability. Another effect of irregular particle shape is the difficulty to establish a single value for particle size, so another metric is usually mentioned. Particle Size Distribution (PSD) of bulk solids can be determined by calculating the number of particles having sizes in certain ranges [26]. This metric will be used to estimate flowability when characterizing the powders used in the experiments, and it can give an estimate of how well each powder flows.

In general, feeding of large particles is rather easy because the movement of each particle is not dominated by adhesive forces but by the force of gravity. However, for smaller particles (less than several tens of microns), feeding becomes difficult because of their adhesiveness [27].

Another important factor regarding flowability related to the particle dimensions is the amount of interparticle forces. The intensity of cohesive and adhesive forces depends on particle size, the distance between particles and the interacting surfaces [28, p. 23-31]. Electrostatic effects and humidity have also been considered important in the flowability of powders due to their influence in aforementioned interparticle forces.

Density and compressibility can also provide an indication of a powder's behavior. Solid density is the actual density of a single particle, while bulk density is given by the ratio of bulk solid mass and the volume it occupies, which is always smaller due to voids inside the powder. If a container with powder is continuously tapped or the powder is subject to pressure, the bulk density increases, becoming tapped density. By comparing these densities, one can compute some of the most commonly used metrics to estimate powder flowability, such as the Carr's Index, Hausner Ratio and the Angle of Repose [25].

Despite all these known influences of mechanical properties and methods to estimate powder behavior, there is no single metric that can indicate with accuracy the flowability of all powders. "The lack of a simple test method that provides results that are widely applicable also hinders general theories of powder flow. Such limitations have not inhibited the rich variety of powder handling and dispensing devices." quoting S. Yang in [29], which also shows that the complex task of solid dosing has been actively

researched in the latest years.

2.5 Dispensing methods

In the current day, different methods are used in the dosage of solids although none has proven to be ideal for all powders properties and quantities or adequate to all applications. Below is a list of powder dispensing methods, where it is also stated how the powder weighing is done, usually by a laboratory precision balance. Note: the device used in the laboratory to measure mass is called a precision balance and not a scale, which measures weight [30]. The term is usually used interchangeably, but in this document this device will be referred to as a balance.

- **Gravimetric**- Mechanically controlled flow from a storage container into a vessel positioned under it. This vessel is on a balance that provides real time mass of the amount dispensed. In these, are included Archimedes Screw mechanisms, disposable caps and devices with controlled valves.
- **Overhead hopper**- An overhead hopper dispenses powder and the mass is calculated based on the weight loss in the hopper itself by an integrated balance. This mass will be the same as in the destination vessel.
- **Volumetric**- A sample probe is inserted in the powder and a specific volume of it is pulled into the probe's chamber. Then, as the piston is moved, a certain volume of powder is ejected to the desired container. Volume can then be used to compute the mass dispensed (based on density), but a balance is usually used for confirmation. The probe used can be cleaned or disposable.
- **Electrically charged pin**- This method works by applying a controlled and exact voltage to a pin, which creates an attractive force. This picks up small particles of powder and when the voltage is shut off, the powder is dispersed to a destination container.
- **Pneumatic**- Vacuum is created on a thin tube connected to an air inlet, where a filter prevents the powder from being sucked into that inlet. The powder stays inside the chamber created by the thin tube's tip and the filter, until the vacuum is removed and compressed air is applied. The compressed air causes an air flow that pushes the powder out of the tube tip and into the destination vessel.

The dispensing system intended to implement should handle the most problematic powders: low density/fluffy, sticky/cohesive, large crystals/granules, high density, beads/spheres, micronized materials (very small diameter particles).

As a dispensing tool that uses a pneumatic method, Zinsser has introduced the DryPette [31]. An electronically controlled powder pipette for the manual handling of difficult powders which could potentially be activated by an end effector. This product seems to have been discontinued in May 2019. Similarly, Innovate Engineering & Design have developed the Electronic Spatula [32], which transports powder in a collector pin, by action of an electrical voltage. Still, these solutions only help achieving the powder dispensing done by analyst and they do not automate it, so they do not fall under the scope of automation solutions.

Many studies have been carried out to find a universal and precise method of bulk solid dispensing. Some use vibratory nozzles [33] or tubes [34] to control the flow of powder. Others use coring tools and powder beds to create powder plugs of constant volume [35]. The existing methods and their reliability and accuracy have been compared by S. Yang in [29], where even a radial dispenser was evaluated.

2.6 Automatic sampling solutions

Many solutions have been invented both for dispensing the powder into small vials and for handling these and other containers. Designs are based on a turntable setup for quicker, more accurate dispensing and robotic arms for handling tasks such as opening and closing vials.

In the turntable category are included the Gironex Cube [36] and the QS30 Autosampler from Metter Toledo [37]. Both use gravimetric dispensers with stirring and have built in balances in their turntable setup. However, both only handle vials and capsules as containers. Most importantly, the turntable setup provides much less adaptability to the addition of new tasks.

Mettler Toledo has also made an automated dispensing platform based on a cartesian robot with a 2-finger gripper. The dispensing is controlled by a self-adaptive algorithm with live balance feedback, which controls the turning speed of an Archimedes Screw and a tapping mechanism[38]. This system's gripper is designed to handle only vials as containers. Besides, just like the QS30 Autosampler the flexibility is very limited, due to it being inside a closed frame.

The SWING FlexyWeigher Plus from Chemspeed, is capable of dispensing some of the most problematic non-flowable powders with good precision into vials, microplates and other smaller containers [39]. "What makes Chemspeed unique is the overhead gravimetric dispensing unit (GDU) it has developed with a precision balance inside." [15]. It can close vials with screw caps, but the implemented gripper is not precise enough to handle more fragile containers.

The GraviTracPlus is another powder dispensing robot with good potential [40]. Made by Sirius Automation, it dispenses powder at a customizable rate and can have up to 4 powder sources. It weighs the samples in the connected Mettler Toledo balance with a learning algorithm that increases dosing accuracy. However, it can only use vials of bigger dimensions. Its large footprint is also a disadvantage in relation to the other solutions.

DisPo1500, 3400 and 6000 are models by BioDot that allow the choice of different powder sources and destination vessels, vials and microplates (one of the smallest sampling containers) [41]. The dispensing is done volumetrically from a sample probe, the weighing is automatic via an integrated 5 decimal place balance, and its footprint is small for the tasks it performs. It has three very useful built-in features: vibration of powder samples, to uniformize the powder, electrostatic control and a wash station to avoid cross-contamination in the dosing probe. As disadvantages it works inside a glass compartment, making in not flexible and the closing of the destination containers in not a feature it has.

Powdernium by Symys is very versatile and used by many top pharmaceutical companies [42]. It can work with vials as well as the very small DSCr crucibles. As notable features, it uses a specialized algorithm that coupled with real-time automatic weighing provides a very accurate gravimetric dispensing, even using low density or cohesive powders. The powder flow is induced by whisks and metered by

a robotically controlled valve while its SV variant, optimized for vials, uses vibration to cause the powder flow (which gives it a better precision). The valve cap is disposable, which avoids cleaning after a batch of samples is obtained, making it GMP compatible. Its software also records the batch ambient conditions, to provide extra data for the sample analysis. This product heavily focuses on the dispensing into many different containers, while providing very limited versatility regarding the addition of new tasks and adaptation to upstream or downstream equipment.

Unchained Labs have made a solution based on the Powdernium's dosing algorithm called Junior [43], with slightly different powder dispensing by usage of a classical hopper with stirring but presents the same limitations as the original. The interesting change is that the system has a software that saves in its database the best dispensing conditions for each powder, a feature that is desirable if it is intended to create a system versatile enough to work with different types of bulk solids.

Zinsser Analytic's Redi automated sampler uses volumetric dispensing and it's the only one without dead volume (no powder is wasted in the dispensing process) [44]. It has built in powder source uniformization using stirrers and an anti-static module. The cross-contamination is avoided since the powders stay in their original containers and the dispensing tip is changed for each powder, while the probe is also washed and dried. Despite the great capabilities regarding the dispensing, this product presents the same limitations as most solutions. Although the lack of a physical barrier could allow the implementation of more tools to work along it, the system is not prepared to handle all types of desired containers.

The Nova CCS by INNOVATE Engineering and Design has the desired structure for a flexible automated sampling in mind, but with a problem of oversize [45]. Able to grab, uncap and recap vials, this robotic arm can perform most of the tasks. It dispenses the powder using the electrically charged rod method just like the spatula from this same supplier. Given its large dimensions and the 2-finger end effector featured, adaptation to handle a much smaller object such as the DSCr crucibles or microplates with precision, could be unfeasible. The robotic design makes the implementation much easier than with the turntable or Cartesian solutions.

A very flexible and accurate solution is the CHRONECT Quantos by Axel Semrau, which uses the dispensing and weighing tools from Mettler Toledo and an anthropomorphic arm from Universal Robots [46]. This collaboration created an automated powder dispensing and sampling platform that can dispense many different powders with a large throughput of samples (288 per batch). Precision is down to the $0.1mg$ and it uses a quite small workspace. Due to its rather big dimensions however, grasping the smallest containers would be challenging, so a new end effector would be required. Once again, its robotic arm setup is more flexible to adding new tasks than other existing solutions.

Table 2.1 summarizes the market options for automatic sample preparation and shows their features and limitations:

As seen in the table 2.1, the dispensing precision is rather satisfactory with all of the products available, but the values given are for free-flowing powders (the easiest to dispense) and most solutions do not guarantee that there is no cross contamination without disposing of the dispensing tool. The next big challenge is the handling of the small containers, since in most cases, the dispensing tool moves to

Supplier	Product	Setup	Dispensing Method	Typical Container	Container Closing	Dispensing Precision
GiroNEX	GiroNEX Cube	Turntable	Gravimetric	vials / capsules	no	$\pm 0.01mg$
Mettler Toledo	QS30 Autosampler	Turntable	Gravimetric	vials / capsules	no	$\pm 5\%$
Mettler Toledo	FlexiWeigh	Cartesian arm	Gravimetric	vials	yes	$\pm 0.3mg$
Chemspeed	SWING FlexyWeigher Plus	Cartesian arm	Hopper	vials / plates	yes	$\pm 0.1mg$
Sirius Automation	GraviTracPlus	Cartesian arm	Gravimetric	vials	yes	$\pm 0.1mg$
BioDot	DisPo1500	Cartesian arm	Volumetric	vials / plates	no	$\pm 10\%$
Symyx	Powdernium (SV)	Cartesian arm	Gravimetric	vials / capsules / crucibles	no (yes)	$\pm 0.1mg$
Zinsser Analytic	Redi	Cartesian arm	Volumetric	vials	no	$\pm 2\%$
Innovate Engineering & Design	Nova CCS	Anthropom. arm	Electric	vials	yes	$\pm 0.2mg$
Axel Semrau & Mettler Toledo	CHRONECT Quantos	Anthropom. arm	Gravimetric	vials	yes	$\pm 1mg$

Table 2.1: Compilation of the off-the-shelf solutions available in the market. As seen from the typical containers used, performed tasks and precision limitations, there is no end-to-end implementation for automated powder sampling

them, as opposed to carrying them. Even products that can handle microplates, their designs are optimized for vials. Regarding flexibility, only the systems that use robotics arms and are not in an enclosed environment can reliably adapt to external tools for addition of new tasks or usage in other operations were powder dispensing is required. This means that the flexibility of the off-the-shelf solutions is very limited, and when present, very expensive.

Another important nuance to note is that most of the automated solutions have trouble dispensing low volumes of powder, as shown in a research done in 2018 [47]. It was concluded that most existing platforms for automated powder dispensing presented much higher relative errors of dispensed mass when dosing smaller quantities of product (less than $10mg$). Abysmal variations were evidenced for even smaller volumes, such as $2mg$, much closer to the amounts stored in microplates and DSCr crucibles. Additionally, this study showed that many of the solutions had high chance of stalling, especially the SWING from Chemspeed. There was also a large occurrence of outlier data and zero mass dispensing runs across all platforms.

Finally, off-the-shelf solutions have a big disadvantage in common. Software integration with external equipment is always a challenge, since suppliers do not allow for changes in their instrument's program-

ming. They work independently when performing their tasks, and changes to these routines are not always possible. This can cause issues in data transfer and overall automation of different instruments working in the same operation.

For these reasons, it can be said that there is no robust and simultaneously flexible solution for powder dispensing, which explains why end-users remain skeptical about applicability of market products to their problematic solids. This results in most companies still relying on manual transport, dispensing and weighing of their drug products, despite recognizing the need for automation.

The desired solution for powder dispensing must be modular, so the sampling is only one of the many applications for its powder dosing capacities, meaning it is desired to be adjustable to other processes that involve solid dispensing. The dispensing tool must be compatible with different powder properties and amounts and cross-contamination should be minimized. Regarding the other tasks in the sampling process, the system's module responsible for the transport of the containers must be adaptable to the myriad of vessels used in the laboratory. The data acquired must be easy to transfer and store, and flexibility to attach to or work along with other instruments is crucial.

Chapter 3

Implemented Solutions

In this chapter, the studied sampling operation is described and the manual process explained, with the most relevant tasks emphasized, with the proposed solutions for said tasks following.

The two envisioned automated workspaces for sample preparation are explored, in a very high-level manner and their components listed. One of them inspired in a robotic arm setup and the other in a turntable or carousel. The objectives and challenges for each of them are mentioned, as well as the options for tasks to perform during the sample preparation and what external tools would be added. For both workspaces, the modules and components that constitute them, meaning the hardware setup used for the implementation, are elucidated. Within the five modules, dispensing, transport (A and B), weighing and master, the acquired devices and the manufactured components are presented, as well as the methods used for assembly of the created sampling platform.

The software architecture is extensively explained and illustrated in several flowcharts, so the automatic sampling operation and the tasks performed by each module are better understood. The coordinate transformations necessary for the experimental implementation are presented and the final implementation of the system in the laboratory is shown.

3.1 Task description

In the studied CDMO, the sampling process that was considered the most relevant and challenging to automate was the creation of Differential Scanning Calorimetry (DSC) samples. These are used in the screening process of many formulations and provide very useful information for the decision makers during drug development. Since it uses very small containers with low powder amounts, if an automation solution works for this technique, adapting it to another where less precision is required should be easy.

DSC is a thermoanalytical technique developed in 1962 that measures the amount of heat transfer necessary to increase the temperatures of a sample and the reference, as function of their temperature. During the DSC process, these temperatures vary with time but there should be minimal difference between sample temperature and reference temperature. Since the energy transferred will be different, the analysis can provide specific properties of the samples, which can be used to determine its components and purity. It can also help identifying phase transition temperatures, such as the Glass Transition Temperature (T_g), the melting temperature and the crystallization temperature, by registering heat transfer at constant temperature. This aids in determining compound purity and proportion of components. In the pharmaceutical industry it is necessary to have well-characterized drug compounds in order to define processing parameters. For instance, if it is necessary to deliver a drug in the amorphous form, it is desirable to process the drug at temperatures below those at which crystallization can occur [48].

The DSCr uses small powder containers, called crucibles, with only about $4mg$ of powder each, composed of a pan, where the powder is dosed into, and a lid, that covers the pan afterwards. The crucible should be permanently closed in a sealing press and the lid may be desired to have a small hole as an air outlet. The sample's weight must be known and registered in order to understand the results, since the heat measured during the DSC analysis depends on the mass of powder present in each sample.

Powder sample preparation is then divided in the following tasks:

- Pick up the crucible (both pan and lid) and move them to a balance, where their weight is obtained, and set as reference;
- Get the powder from a source and dispense it to the pan, checking for the new weight shown in the balance, i.e., the powder's mass);
- Close the powder filled pan with the lid;
- Transport the sample to a sealing press, where it is permanently closed;
- Pierce a small hole in the lid, using a needle (optional). Only the lid should be pierced and contact with the powder should be avoided, so this task is usually done first.

It would be possible to program a single robotic arm to do the above tasks, but its end effector would hardly be flexible enough to perform well in all of them like a human hand. This means up to four end effectors could be needed. The most important should handle the powder or a powder dispensing tool. Another one is used to grab and carry the crucible, and perhaps two others might be needed to press and to pierce it.

3.1.1 Manual DSC sample preparation

Currently, most of the sample preparation for DSC is made by hand. Figure 3.1 represents the workflow for the manual process, in which every task is done by the analyst.

The analyst starts by opening the containers for the pans, lids and powder, and cleaning every tool to be used. He grabs a lid from its box and places it in a rubber base, in order to pierce it with a needle without deforming it. He then moves the pierced lid to the balance's weighing platform, picks a pan from the box and places it next to the lid. The weight of the crucible is now set as the tare weight in the balance and the pan is moved to the table. A funnel shaped tool is placed over the empty pan to help channel the powder into it. The analyst grabs a spatula, takes some powder from the bottle or flask and drops it in the pan. It is also sometimes necessary to flatten the powder to make the surface uniform, depending on its behavior. Now the analyst takes the filled pan to the balance and checks its weigh. If the powder weigh in not between $3mg$ and $5mg$, the analyst must take the pan from the balance, place it on the table and add or remove powder. This is where the most time is spent especially when the analyst is not an expert in DSC sampling. After this possibly lengthy iterative process, once the mass is valid, it is registered on a notebook or printed. Now the analyst must cold weld the pan and lid set using a tabletop sealing press with compatible dies. He starts by inserting the upper die into the top slot of the

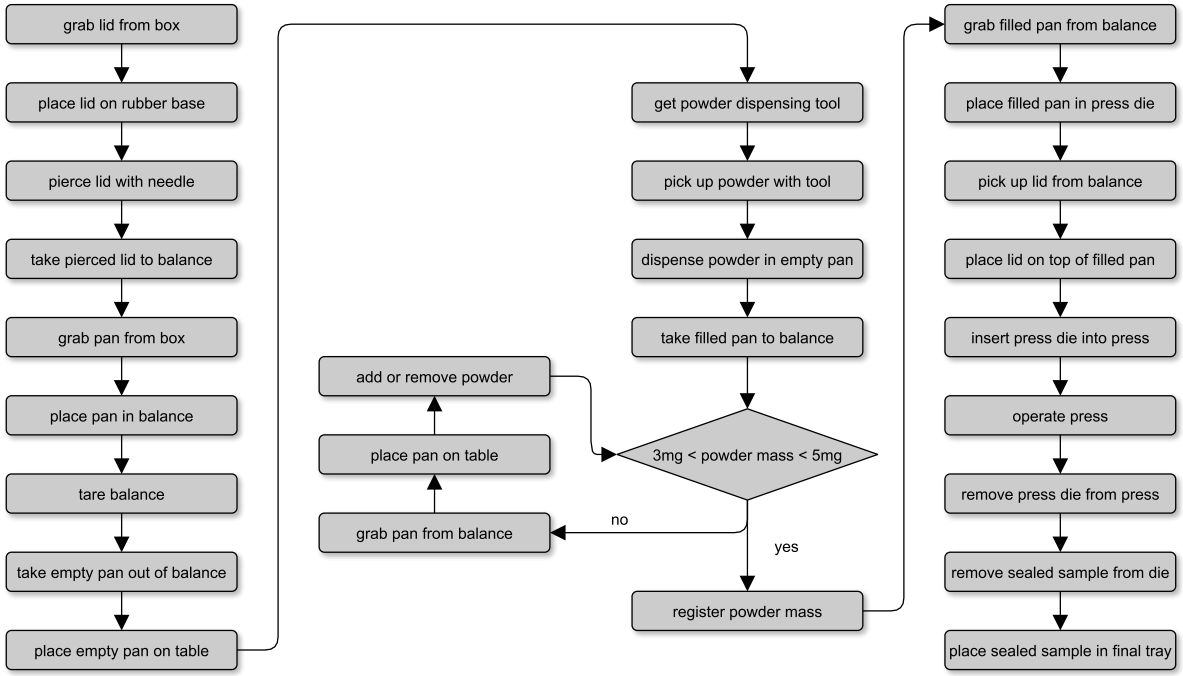

Figure 3.1: DSC sample preparation manual workflow. Note the possible dispensing loop to achieve the right amount of powder mass.

press and it is fixed by magnets. Then he takes the filled pan from the balance and places it on the lower die, followed by the lid on top of the pan. Finally, he moves the lower die to the bottom slot of the press and actuates the lever on the press, moving the upper die into the lower die and effectively sealing the crucible together by press-fit cold welding. The lower die is removed from the press and the closed pan is taken to a final tray, where the finished samples are placed. These are ready for the DSC analysis. The entire process takes around 5 minutes, an approximate average of 10 timed sample preparations between 2 experienced analysts.

For the manual process, the following components are necessary:

- Dispensing tool (e.g. laboratory spatula)
- Balance ($0.01mg$ precision recommended)
- Laboratory notebook or printer (for mass registration)
- Sealing Press (to cold weld the crucibles)
- Pans
- Lids
- Needle
- Tweezers (to grab the pans and lids)
- Source of powder (e.g. bottle)
- Tray for finished samples

3.2 Workspace A – Robot with gripper as Transport Module

Based on the robotic arm setups available in the market, the first possible solution was designed. This option for a sampling workspace is composed of the following components:

- Robot + gripper (to carry the pans and lids)
- Robot + dispensing tool
- Balance
- Source of powder
- Trays for pans, lids and finished samples
- Sealing Press (optional)
- Piercing Tool (optional)

The main task for the transport module is to manipulate the pans and lids, pick them up, carry them around the workspace and place them in different sections. Given the round shape of the containers used, a 3-finger or 4-finger gripper (also called self-centering grippers) would have better results in the manipulation. With such a small object, most of the grippers used in pick-and-place applications were not adequate. The choice was what kind of jaws to use, pneumatic or electric, and what kind of fingers. Parallel fingers provide more flexibility but grabbing the lid from a flat surface would be very challenging given its $0.2mm$ height. Angled fingers could make the picking up easier but having the surface of contact not perpendicular could cause the parts to sit diagonally on the fingers, which would be a problem when placing them. The DSCr's autosampler fingers are also interesting. They are curved and create a perpendicular contact but with a different motion from standard parallel fingers. The available grippers in the market where not adequate for the described task, so the possibility of building a custom one emerged.

Regarding the dispensing, this would have to be done by the other robot, since the end effector must be compatible with a tool for powder dispensing. From the methods listed in chapter 2, some can be immediately excluded due to the incompatibility with the workplace where the sampling system is to be implemented. Usage of an electrically charged rod, due to the unavailability of the apparatus and the safety measures in the laboratory. Gravimetric methods (mechanical and overhead hopper) are also not compatible, because despite their precision, they rely on a filled source container that is above the destination vessel. This container is previously filled and is changed or cleaned between each batch, which a requirement that cannot always be met. This leaves volumetric and pneumatic dispensing methods, which both have similar limitations regarding cross-contamination and precision. However, they have some important differences. A pneumatic approach has higher risk of powder splashing, but the vacuum allows the usage of a less controlled powder source, since it is not necessary to create a slug when taking powder from the source. Volumetric is then less susceptible to powder properties but it needs a compacted, uniform and flat powder surface to be able to grab powder.

Due to its availability in the laboratory and easy implementation, the chosen dispensing method to test was the pneumatic one. This method does not need the changing of the entire tool, only its tip, because it is designed to avoid cross-contamination, and the adaptation to the end effector would be minimal, since it is externally actuated. As a downside, since this tool had not been used yet for such small containers and wide range of powders, the achievable precision was unknown, so many tests had to be made.

By using a pick-and-place approach to the sample transport, the system would be very flexible to the addition of a press and piercing tool, since they would be separate modules in specific positions, that the transport module would take the samples to. An alternative to the pressing and piercing is discussed in section 3.4.10, where two types of lids are compared.

For the above options for the two most important task and adding tools for pressing and piercing, the default automated workflow is the one shown in figure 3.2, where yellow corresponds to the transport module, blue to the dispensing module and gray to other modules.

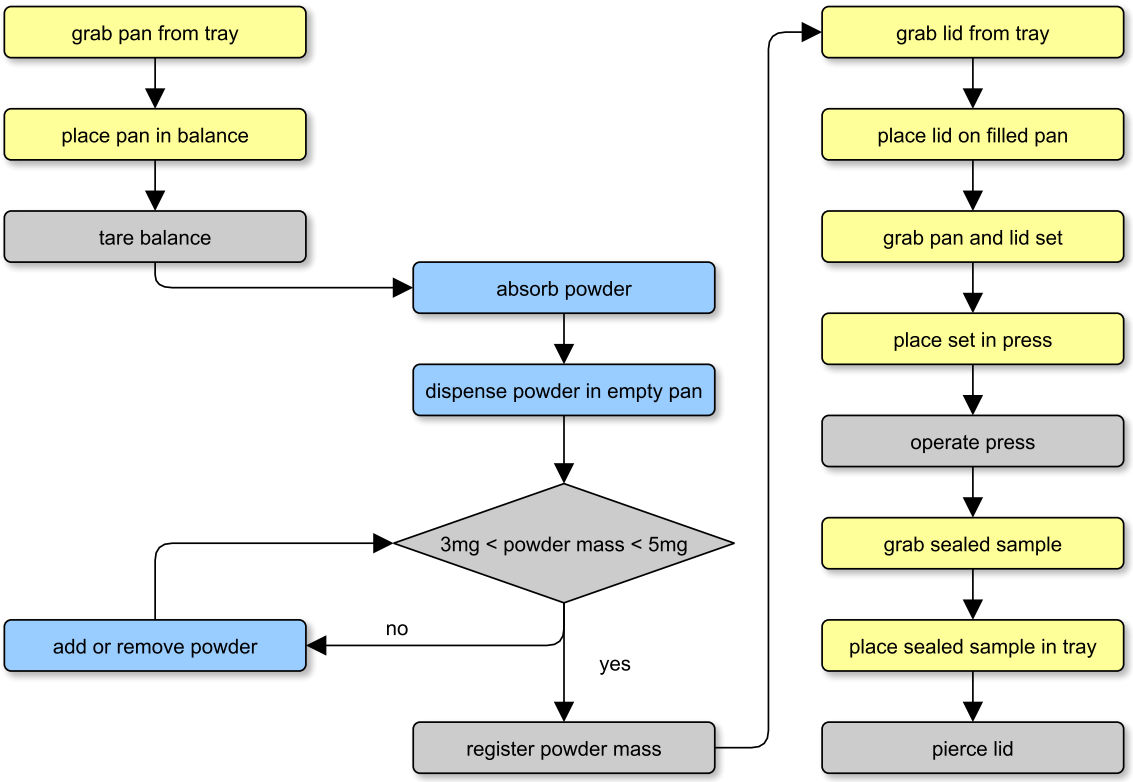

Figure 3.2: DSC sample preparation workflow for solution A.

The most important changes from the manual operation workflow are in the weighing of the sample. Now, the lid is only placed on the balance after the powder's mass has been obtained and it is placed on the filled pan, to avoid having to pick up the lid from the balance's flat surface. The filled pan and lid above it are then transported together to the press. The pressing and piercing sequence would vary depending on how those tools would be implemented.

As an initial workspace, the design represented in figure 3.3 was modelled. Some of the components are only representative of their modules.

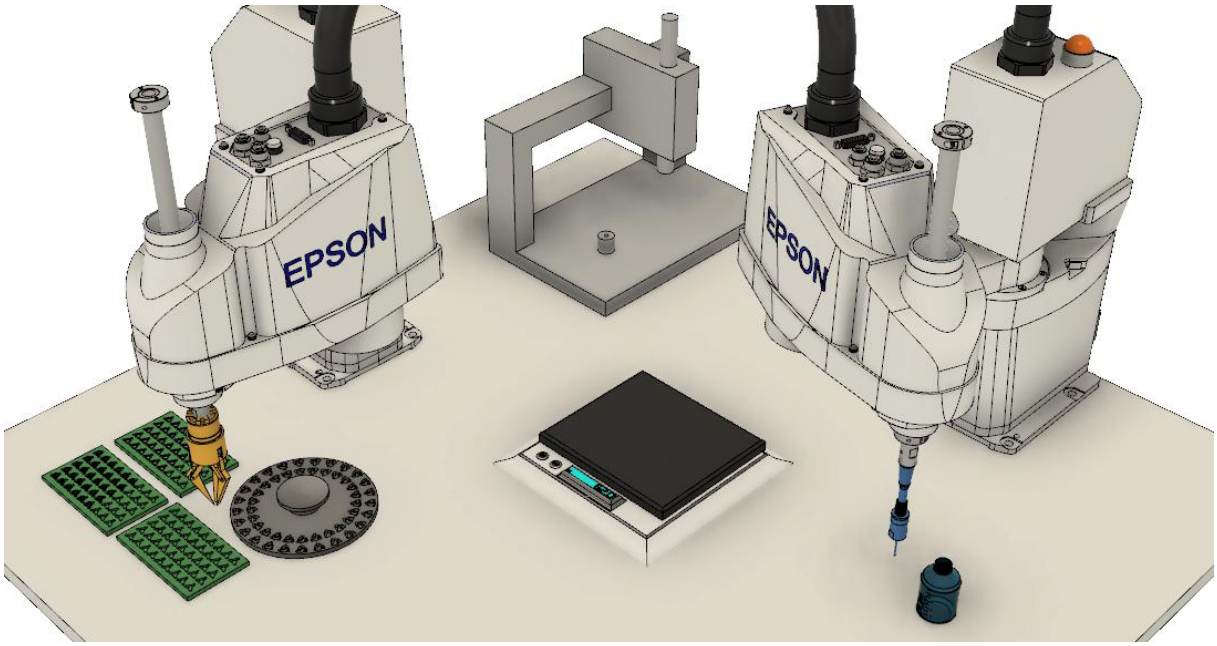

Figure 3.3: Modelled workspace A - the transport module is the robot with the gripper. Note that most components are only representative.

3.3 Workspace B – Carousel as Transport Module

Looking at the market turntable solutions, a different handling module was designed. The idea was to place the pans and lids in a carousel with slots like the ones in the DSCr's autosampler tray, instead of carrying them with the robotic arm. The balance would be integrated in a section of the carousel, and the dispensing robot would dispense powder to the pan in the slot over the balance. The outer row would have the pans and the inner row their respective lids. The piercing could be done beforehand by an external tool, moving up and down over the lid row. In a different section of the carousel from the weighing one (the one hanging over the balance), the press would cold-weld the crucibles, but it would require a firm base under the carousel to not bend it whilst pressing. The biggest caveat with this approach, however, is that implementing a balance in the carousel is quite a difficult task, given the relative dimensions and required weighing accuracy. This solution could also inhibit the flexibility, but it removes the need for the transport module's robot. The objective behind this setup is to avoid having to grab the pans with the gripper, since this can be challenging and slower than holding them in the described carousel. Despite that, it would still be necessary to pick up the lids and place them on the filled pan. However, this could be done by vacuum, using the dispensing robot to also work as part of the transport module. The suction power of the powder gun was tested, and the results were satisfactory, i.e., it can be used to pick and place lids.

The components that replace the transport module created for workspace A (robot and gripper) are:

- the rotating carousel, which matches the top of the original DSCr's autosampler, to be compatible with the DSCr after the batch of samples is prepared;
- a specifically designed part to place in the balance, that would allow the individual weighing of each pan.

The workspace overview of this alternative is shown in figure 3.4.

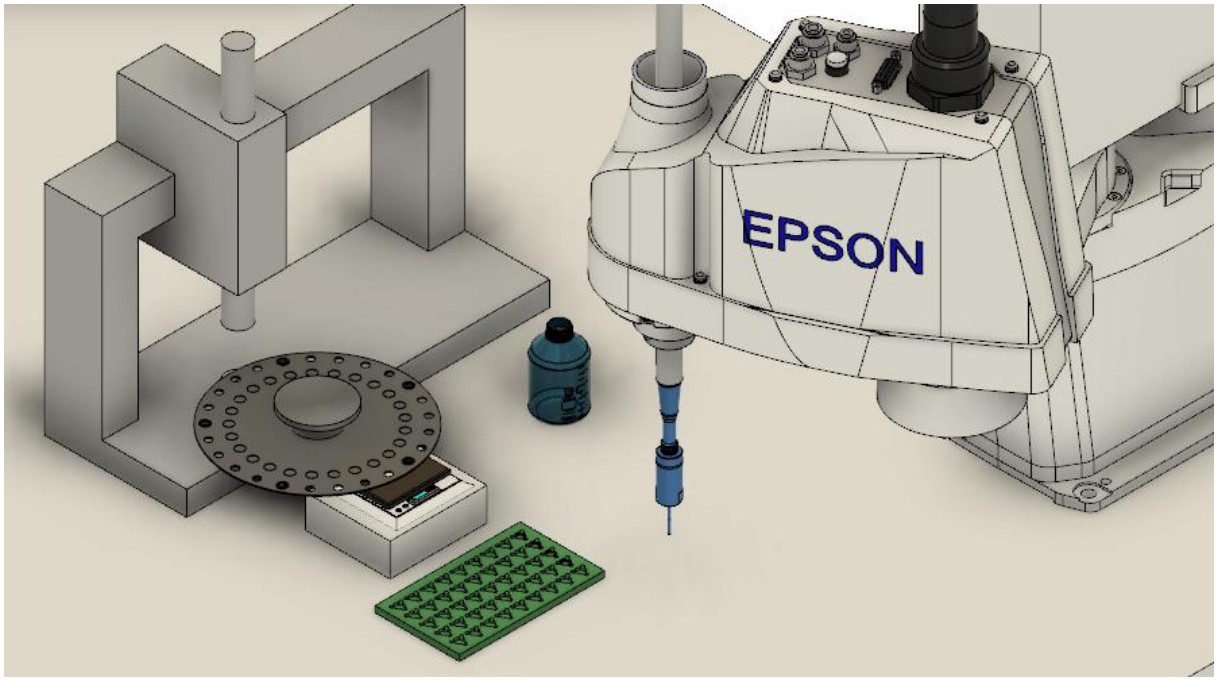

Figure 3.4: Modelled workspace B - the transport module is the carousel and in part the dispensing robot.

The dispensing module would have an extra task, i.e. carrying the lids, which could require a stronger vacuum. The optional press would also have to be adjusted to the new manipulation method, since the pans would not be removed from their positions in order to be pressed, i.e. the pressing would then be done with the pans still on the carousel.

3.4 Hardware components

In this section, the hardware components that constitute both workspaces are described. The master, the dispensing module and the weighing module (with a slight modification) are common to both workspaces, and have the same components. As stated previously, the transport modules are very different, referred to as A or B, and while they have common components, their implementation is not the same. Table 3.1 shows the modules and components used in each workspace.

Modules	Workspace A	Workspace B
Transport	SCARA robot, Arduino UNO, Stepper motor, designed Gripper, manufactured Trays	Arduino UNO, Stepper motor, designed Carousel
Weighing	MX5 balance	MX5 balance, manufactured part
Dispensing	SCARA robot, Vacuum Generator, Powder Gun	SCARA robot, Vacuum Generator, Powder Gun
Master	Raspberry Pi	Raspberry Pi

Table 3.1: Modules and hardware components used in each workspace.

3.4.1 Epson T3 SCARA robot

The robots used are from Epson, model T3 401S. It has three revolute joints and one prismatic joint and with its SCARA configuration means it has 4 degrees of freedom: position in X, Y and Z and rotation around Z. As important specifications, the load capacity is $1kg$ (nominal) and $3kg$ (maximum), the repeatability is $0.02mm$ (horizontal and vertical) and $0.02°$ (orientation) and the range is $400mm$ (horizontal) and $150mm$ (vertical). Other specifications for this component are listed in table A.1.

The direct kinematics is a function that determines the position and orientation of the end effector, with respect to a Reference Frame (RF), based on the joint coordinates, as written by B. Siciliano in [49]. This function is obtained using the homogeneous transformation matrix, which for a n-DOF robot is described by equation 3.1

$$T_n^0(q) = \begin{bmatrix} R_n^0 & p_n^0 \\ 0 & 1 \end{bmatrix} \tag{3.1}$$

Where R_n^0 is defined as the rotation matrix that gives the end effector reference frame with respect to the base reference frame, p_n^0 is the position vector of the origin of the end effector's RF with respect to the base's RF and q is a vector with the joint coordinates, with dimensions $n \times 1$. By attaching a coordinate frame to each link (0 to n) and defining a homogeneous transformation matrix as A_i^{i-1} for each pair of i and $i-1$ frames, as a function of the joint variables q_i, the direct kinematics function (nonlinear) can be written as:

$$T_n^0(q) = A_1^0(q_1)A_2^1(q_2)...A_n^{n-1}(q_n) \tag{3.2}$$

which for a robot with 4 links becomes

$$T_4^0(q) = A_1^0(q_1)A_2^1(q_2)A_3^2(q_3)A_4^3(q_4) \tag{3.3}$$

A systematic method to define the RF associated to each link and obtain the direct kinematics function is provided by the Denavit Hartenberg Convention (D-H), which is explained in detail in [49]. By following this method, the frames were attached to each link of the robot, illustrated in figure 3.5.

With these RF assigned and the real dimensions shown in figures A.1 and A.2, the D-H parameters were computed and are presented in table 3.2, where the θ's are the angles of rotation of each revolute joint, d_3 is the displacement of the prismatic joint and the l values are the lengths of each link.

Link	α (°)	r (mm)	d (mm)	θ (°)	Reference
1	0	$l_1 = 225$	192.3	θ_1	0
2	0	$l_2 = 175$	0	θ_2	0
3	0	0	d_3	0	L
4	0	0	0	θ_4	0

Table 3.2: Denavit-Hartenberg parameters for the Epson T3 SCARA robot. L is the distance from the end effector's tip to the mechanical stopper in the shaft and will depend on the attached end effector.

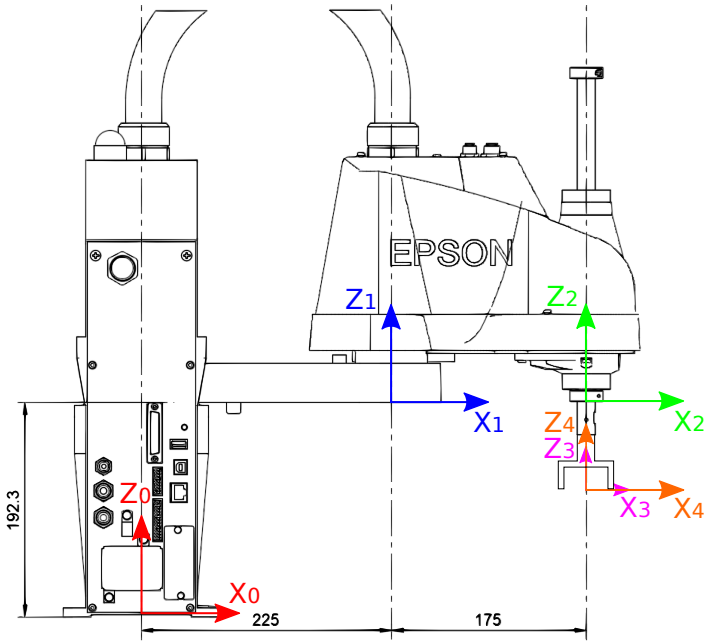

Figure 3.5: Epson reference frames using the Denavit-Hartenberg Convention.

Next, the inverse kinematics was obtained, in order to find the rotation or displacement of each joint based on the coordinates of the end effector. The inverse kinematics are, however, much more complex, being nonlinear problem and often having a not unique solution. Given its SCARA configuration, for every pose of the end effector, there are 2 possible robot configurations, one with the elbow to the left, and on with it to the right. This is important to control since it can result in collisions inside the Hotte where it will be installed.

To obtain the inverse kinematics solution, a way to start is by checking that the vertical position of the end effector (its Z coordinate) only depends joint 3, the prismatic joint, so:

$$z = d_3 \tag{3.4}$$

The x and y coordinates, meaning the position on the horizontal plane, depends only on the arm's first two revolute joints. By simple geometry, it is known that:

$$x = l_1 \sin\theta_1 + l_2 \sin\left(\theta_2 + \theta_1\right) \tag{3.5a}$$

$$y = l_1 \cos\theta_1 + l_2 \cos\left(\theta_2 + \theta_1\right) \tag{3.5b}$$

which combined gives,

$$x^2 + y^2 = l_1^2 + l_2^2 + 2 l_1 l_2 \cos\theta_2 \tag{3.6}$$

or, rearranging,

$$\cos\theta_2 = \frac{x^2 + y^2 - l_1^2 - l_2^2}{2\, l_1 l_2} \tag{3.7}$$

Knowing that

$$\sin\theta_2 = \pm\sqrt{1-\cos^2\theta_2} \tag{3.8}$$

and only if $-1 < \cos(\theta_2) < 1$, then θ_2 can be computed by:

$$\theta_2 = Atan2(\sin\theta_2, \cos\theta_2) \tag{3.9}$$

Next, solving equations 3.5 for θ_1 and using the same method as the one used for θ_2, one obtains:

$$\cos\theta_1 = \frac{(l_1 + l_2\cos\theta_2)\,x + l_2\sin\theta_2 y}{x^2+y^2} \tag{3.10a}$$

$$\sin\theta_1 = \frac{(l_1 + l_2\cos\theta_2)y - l_2\sin\theta_2 x}{x^2+y^2} \tag{3.10b}$$

which allows us to calculate θ_1 by:

$$\theta_1 = Atan2(\sin\theta_1, \cos\theta_1) \tag{3.11}$$

This leaves only the last revolute joint (joint 4), whose rotation only influences the angular orientation of the end effector. The angle in relation to the X_0 axis is $\alpha = \theta_1 + \theta_2 + \theta_4$ and since θ_1 and θ_2 were already computed, one can easily obtain:

$$\theta_4 = \alpha - \theta_1 - \theta_2 \tag{3.12}$$

As mentioned before, there are two possible combinations of joint variables for each end effector pose. From one configuration to the other, the prismatic joint will have the same displacement, while the joints 1 and 2 will have the symmetric value in their coordinates. The understanding of this concept is important when programming the robots' paths, so shoulder collisions with each other and with the Hotte's walls and window are avoided.

Figures A.1 and A.2 show the remaining dimensions of the T3 SCARA robot, which are relevant when assembling it in the Hotte (with dimensions of $1500mm$ width by $700mm$ length by $1500mm$ height), where the entire workspace must be installed.

3.4.2 Arduino UNO

To command the stepper motors with their integrated controllers, an Arduino UNO (shown in figure 3.6) was used.

As cited by J.Yoon in [50]: "Arduino is a tool for making computers that can sense and control more of the physical world than your desktop computer. It's an open-source physical computing platform based on a simple microcontroller board, and a development environment for writing software for the board.".

Due to its relative low price and open-source nature, it is widely used in automation, both for educational and commercial purposes, as referenced in [51]. Table 3.3 lists its specifications, where the main concern was the availability of enough I/O pins to communicate with the other components.

Given its availability and simplicity to implement, it was chosen to provide the communication be-

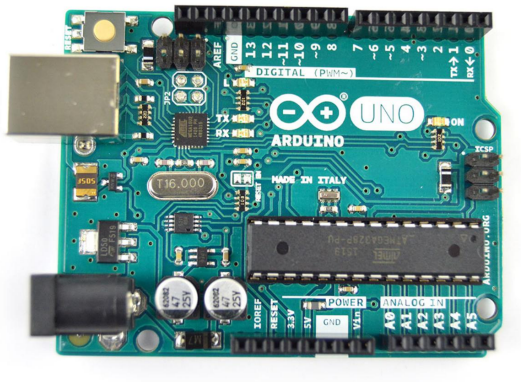

Figure 3.6: Arduino UNO used to control the stepper motor.

Microcontroller	ATmega328P
Operating Voltage	$5V$
Input Voltage	$7-12V$ (recommended) $6-20V$ (limits)
Digital I/O pins	14 (6 with PWM output)
Analog Input pins	6 (A0 to A5)
DC Current per I/O pin	$40mA$
Clock Speed	$16MHz$

Table 3.3: Arduino UNO specifications.

tween the stepper motors and other components, the transport robot in workspace A and the master in workspace B.

3.4.3 28BYJ-48 stepper motor

Due to the low forces, speeds and travel distances but high precision required for the desired tasks, a small stepper motor was adequate. Being incredibly cheap in relation to the precision it offers, a 28BYJ-48 stepper motor and ULN2003 driver board (figure 3.7) were used.

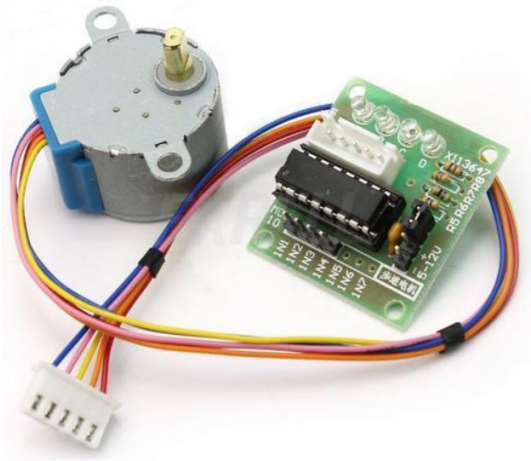

Figure 3.7: 28BYJ-48 stepper motor and ULN2003 driver board.

Their specifications are presented in table 3.4. The note are the *'step angle'* and the *'gear ratio'*, specifications that determine accuracy and give it a minimum shaft rotation angle of $0.176°$.

Motor Type	Unipolar Stepper Motor
Connection Type	5 wire connection to the driver board
Voltage	$5 - 12V$ DC
Frequency	$100Hz$
Step Mode	Half-step (recommended)
Step Angle	$11.25°/64$ in Full Step Mode
Gear Ratio	$64 : 1$ (specified) $63.68395 : 1$ (real)
Weight	$30g$
Voltage	$5 - 12V$ DC
Digital pins	4 (signal from Arduino)

Table 3.4: 28BYJ-48 stepper motor specifications.

3.4.4 Designed Gripper

For transport module A, a gripper was searched for and suppliers were contacted. However, their standard solutions were not adequate to the task of grabbing parts with such dimensions and shape. For this reason, a custom gripper had to be developed by the suppliers, which would require more time and capital invested. Due to this, a prototype of a gripper was created in-house to test the feasibility of the manipulation task. The modelled and later manufactured gripper is shown in figure 3.8.

A linear actuator could be used, but this means only one finger would move, which compromises the ability of the gripper to center the pans and lids, even with the presence of two other static fingers. A more complex option would be to have two or more moving fingers, but this could need more than one source of motion. Inspired in the gripper from Mettler Toledo's TGA sample robot [52], a planetary gear design was created. This would require only one revolute motion to move three fingers in a curved trajectory to the center, facilitating the centering and grabbing of the parts.

The revolute motion of the central gear is provided by the stepper motor which had to be fixed to a base that is then fixed to the gripper robot's shaft. A custom design of the fingers helps transferring the movement from the outer gears to a specific designed motion of the finger tips. The gears (ratio and number of teeth), the stepper motor and the finger design would determine the grippers precision. This is an advantage over using a pneumatic actuator, since it is possible to an infinite number of positions and to improve the accuracy , one can increase the gear ratio or use a stepper motor with smaller stride angle. The stepper motor used had a stride angle of $11.25°$ and included gear ratio of 64 (exact is 63.68395), which gives a minimum shaft step of $0.176653615°$. This minimum angle coupled with a gear ratio of 2 (the outer gear has double the teeth of the inner gear) and the length of the finger being the same as the outer gear's diameter, means every step of the motor is about $0.043mm$ of finger travel distance. This is around 1.3% of the radius of the parts to grab, which means it could cause slight deformations in the parts. However, for a proof of concept of manipulating the crucible around the workspace it proved satisfactory.

There is also a switch and a base to fix it in the left of figure 3.8, in gray. These has the function to serve as a reference for the gripper movement and will be explained in the section regarding the software of each module.

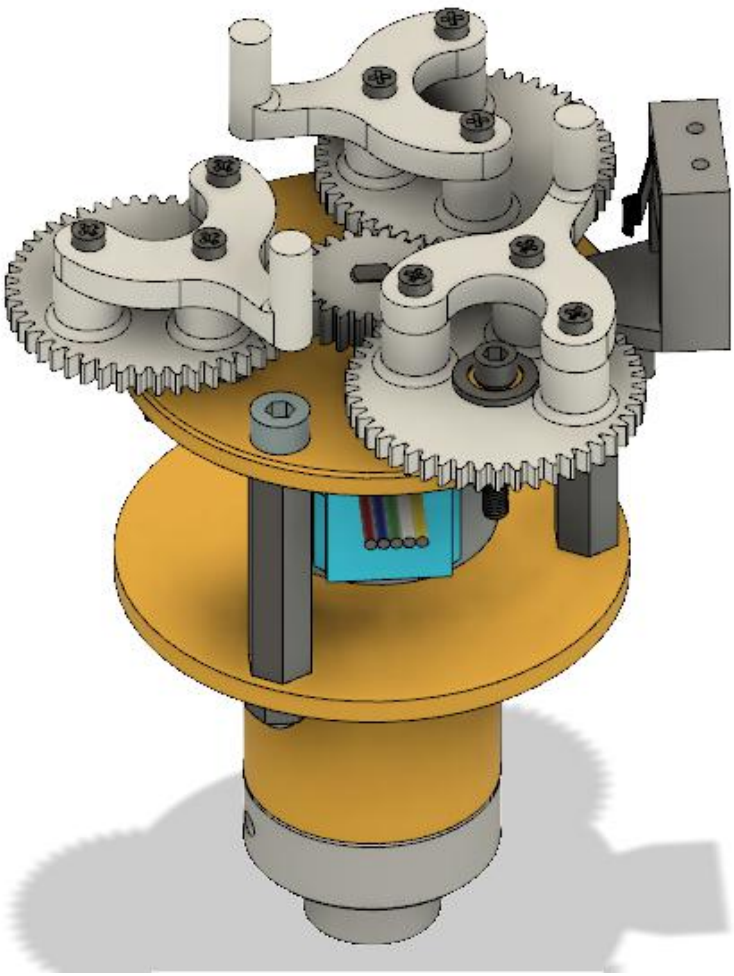

Figure 3.8: Modelled 3-finger gripper to be manufactured and assembled to the transport robot.

Finally, it was necessary to assemble the fingers, the gears system, the stepper motor, and the robot's shaft together. Starting with the fingers, these are attached to the outer gears by inserting their supports to the holes in the gears' bodies. Then the stepper motor is bolted to a base, and in this same base the axis for the outer gears are fixed, which was done with three equal sets (one for each outer gear) consisting each on one M3 bolt, two M3 nuts, one washer and one bearing. Additionally, this base was to be fixed to the robot's shaft, and for that purpose a top for it was built, with the upper section similar to the one in the adapter for the powder gun and the lower section to be connected to the base by M4 spacers. The gripper was finally assembled and fixed to the robot by M3 threaded rods and nuts.

3.4.5 Designed Crucible Trays

To avoid the need for the gripper to pick up the parts from a flat surface, which for the lids (having $0.2mm$ height), would require unfeasible vertical positioning, some trays were made by additive manufacturing. The design was inspired in the DSCr's sample plate, in which the slots for the pans have a specific depth and diameter to limit their movement while also allowing for some flexibility when placing them. It also has recesses compatible with the DSCr's gripper in a triangular layout, that align perfectly with the fingers and forward them to the pan.

The recesses of the manufactured trays have a slight curvature, so they are compatible with the gripper's non-linear finger movement and have slightly bigger width than the fingers' diameter, to account for any uncontrolled rotation or misalignment of the tray on the table. The slots have very exact diameters so that the part can never leave the slot but there is also enough clearance for the analyst to place them without trouble. The part will most likely not be exactly in the center of its slot, but since the gripper has 3 fingers, i.e. it's a self-centering gripper, the parts will be picked up in the center regardless. The depth of the slots and the recesses make it so both lids' and pans' rims are at the same distance from the workspace floor, meaning despite the different parts' heights, the robot can go to the same Z coordinate to grab empty pans, lids and filled pans.

Figure 3.9 shows the manufactured trays, with only 9 slots each since it was enough to test the implementation. However, on a bigger scale, they should be remade with more efficient dimensions and a better manufacturing method, to allow for more pans and lids to be stored.

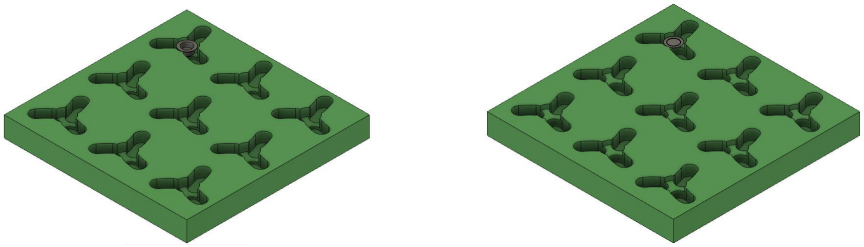

Figure 3.9: Tray to place pans (left) and tray to place lids (right).

3.4.6 MX5 balance

The weighing of the powder mass used in a DSC sample must be very accurate. For this reasoning, the microbalance from Mettler Toledo was used as the weighing module, since it was the smallest balance available with the required precision. This balance is shown in figure 3.10, where its separate units can be seen, characteristic that allows for some extra flexibility when physically assembling the system.

Figure 3.10: Mettler Toledo MX5 balance used as weighing module.

The specifications available are limited, since it was discontinued since 2008, but the most important are presented in table 3.5.

An important characteristic of the Mettler Toledo balances is the ability to control the door remotely.

Maximum Capacity	$5.1g$
Readability	11 µg
Repeatability	0.8 µg
Settling Time	$8 - 12s$
Free height above weighing platform	$55mm$
Dimensions	$128 \times 287 \times 113mm$ (weighing unit) + $224 \times 336 \times 94mm$ (communication unit)
Sensitivity (long-term stability)	$\pm 0.0001\%$
Linearization	Automatic

Table 3.5: Mettler Toledo MX5 balance specifications.

This allows the door to open, so the other modules can operate over the weighing compartment and once they have backed away, the door is close which makes the mass measurements much more accurate.

3.4.7 Powder Gun and Vacuum Generator

For both workspaces, there was a need for a powder dispensing tool and to join said tool with the robot. Given its immediate availably in the lab, the first tool tested for dispensing was a powder gun, model LM-14 by M&O Perry Industries, illustrated in figure 3.11.

Figure 3.11: Powder gun and LM-14 vacuum generator by M&O Perry Industries.

It is a pneumatic dispensing method that provides an adjustable dispensed volume and dispensing 'force'. The dispensing range is from $2mg$ to $10g$ (depending on the powder gun's size) and the operating pressure is below 1 bar, so some pressure regulators were used to reduce the laboratory's $8bar$ to $0.5bar$.

This tool is used for capsule filling, drug containers with dimensions similar to the crucibles', and it is connected to a vacuum generator. This system converts compressed air into vacuum to absorb powder until a switch is pressed, which makes the compressed air by-pass the Venturi system and thereby forcing air out. The amount of time that this switch is pressed determines the interval of time of this by-pass, meaning the amount of time that the powder gun is forcing air out instead of taking it in.

The manual foot switch was disassembled and replaced by a relay, which would be activated electrically, giving the same effects as the manually operated mechanism but with much higher precision

regarding the time interval for the compressed air to flow and dispense the powder.

The powder gun itself is composed of two parts with thin hollow tubes at their tips, with very close diameters, and a nut, that helps fix the relative position between these two parts. At the end of the smallest tube, a filter is inserted, to let air through and not powder. This smaller tube is then inserted in the larger tube, creating a chamber with only one inlet. The powder is sucked inside the larger tube until it hits the filter (that essentially makes the inner tube not hollow). The amount of volumes stored inside the larger tube is a function of the distance between the two thin tube tips, (basically adjusting the height of a constant diameter cylinder, changing its volume). To facilitate the understanding of this tool, figure A.3 is provided.

Both parameters are adjustable but the time interval for the air being outputted is a lot easier to automate since it is just a numerical value that could be changed in the programmed routine. The time of air blast and the amount of times it is activated could depend on the properties (viscosity, hygroscopicity) of the powder. The idea is to keep the volume of tip's inner compartment, since automating this change would be very challenging and respond to the range of powder density in a different way. However, depending on the mass desired for the application, this volume could be manually adjusted (e.g. if this module was used for the creation of a different type of sample and analysis, where more than $3mg$ was needed).

The pressure of the compressed air fed to the powder gun is changeable with its incorporated screw-like pressure regulator, as well as the vacuum pressure (although a removal of the generator's outer shell is necessary). However, different pressures could be provided to the generator, and these could be controlled by an electric device remotely activated, such as a digital pressure regulator.

An adapter was designed and manufactured by additive manufacturing in order to fix the powder gun to the robot. This adapter had to be compatible with the pipe attached to the powder gun and also be used to fix the powder gun to the robot's shaft. Figure 3.12 illustrates this adapter, connecting the powder gun to the robot. In the upper section (in white) the pipe that is tightened to the powder gun via a nut is also shown, as the ability to rotate it and connect the air to the gun is mandatory to utilize this dispensing method.

Its lower section design makes good use of the powder gun's thread by only occupying half of said thread and allowing the other half to be attached to the nut present in the ending of the air pipe.

The upper section simply has a through hole so a M3 bolt is used to first align the adapter with the shaft and then also to support its weight when tightened.

To increase the reliability of the dispensing, two smaller components were added to this module. They here implemented just by adapting their manual usage to the robotic workplace. An anti-static ring that minimizes static electricity with small discharges, to reduce the amount of powder that could be spread across the workplace. A paint brush was used as a sieve, to remove excess powder from the tip of the powder gun. The robot trajectory would simply cross this brush a few times before or after dispensing in order to clean any powder that stuck to the outside of the powder gun.

Figure 3.12: Powder gun and shaft adapter used in the dispensing module.

3.4.8 Raspberry Pi

In terms of communication in the workspace, there would be a master that dictates the tasks to run during the sampling. There are two main options for the master-slaves setup.

One is to use one of the components to behave as the master, possibly the transport robot in workspace A or the Arduino that controls the carousel in workspace B, since they control the position of the sample and determine which tasks should be performed by the other components (that would act as slaves). This removes the necessity to buy an extra device just for coordinating the sample operation.

The other alternative is to have an external device that would create the link between all the slaves, possibly even connected to the DSCr. The advantage of this approach is that it has more flexibility to communicate with new components and that its status would be easier to monitor by the user, in case a Human-Machine Interface (HMI) was implemented for supervision. Additionally, one could have limitations regarding limited ports and I/Os when using the robot as a master, which this option prevents.

Since flexibility was the main concern for the master, the option to have a separate device acting as master was chosen. Within this option, the most commonly used hardware are a Raspberry Pi and a Programmable Logic Controller (PLC). A Raspberry Pi has chosen due to its lower price, given the nature of this implementation being a proof of concept for automatic sampling. The acquired component is shown in figure 3.13. However, for a final application, a PLC would provide a more powerful solution,

with more room for expansion and communication with sensors and other components.

Figure 3.13: Raspberry Pi 3 model B+ used as master.

Chosen as master for the workspace slaves, the Raspberry Pi is responsible for the coordination of the different machines involved in the sampling automation. Its functions are better explained in a later section, where the software implementation is explored.

The specifications for the Raspberry Pi 3 Model B+ are listed in table 3.6. The important specifications are the high number of I/O pins and diverse ports, since it must communicate with many different modules.

System on Chip	Broadcom BCM2837B0 quad-core A53 (ARMV8) 64-bit $1.4GHz$
GPU	Broadcom Videocore-IV
RAM	1 GB LPDDR2 SDRAM
Networking	Gigabit Ethernet (USB) 2.4 GHz and 5 GHz 802.11b/g/n/ac Wi-Fi
Bluetooth	Bluetooth 4.2, Bluetooth Low Energy
Storage	Micro-SD
Ports	HDMI, 3.5 analogue audio-video jack, 4x USB 2.0, Ethernet, Camera Serial Interface, Display Serial Interface
Dimensions	$82mm \times 56mm \times 19.5mm$
Weight	$50g$
I/O Pins	40 Pin GPIO Header
Voltage	$5V/2.5ADC$ Power Input

Table 3.6: Raspberry Pi 3 model B+ specifications

3.4.9 Designed Carousel

The DSCr compatible carousel was designed to transport the pans in small holes, with a specific diameter that makes them hold the pans by their rims and not their bottoms, and is shown in 3.14.

The movement of this carousel is provided by a stepper motor controlled by an Arduino, is a similar setup as the one used for moving the gripper but removing the transport robot. Some parts were 3D printed in order to couple the motor to the workspace base and the to carousel. The complete module can be seen in A.4. The idea of this carousel is that it can be transported directly from the sampling workspace to the DSCr, thereby replacing the DSCr's disk-shaped autosampler. For this reason, the

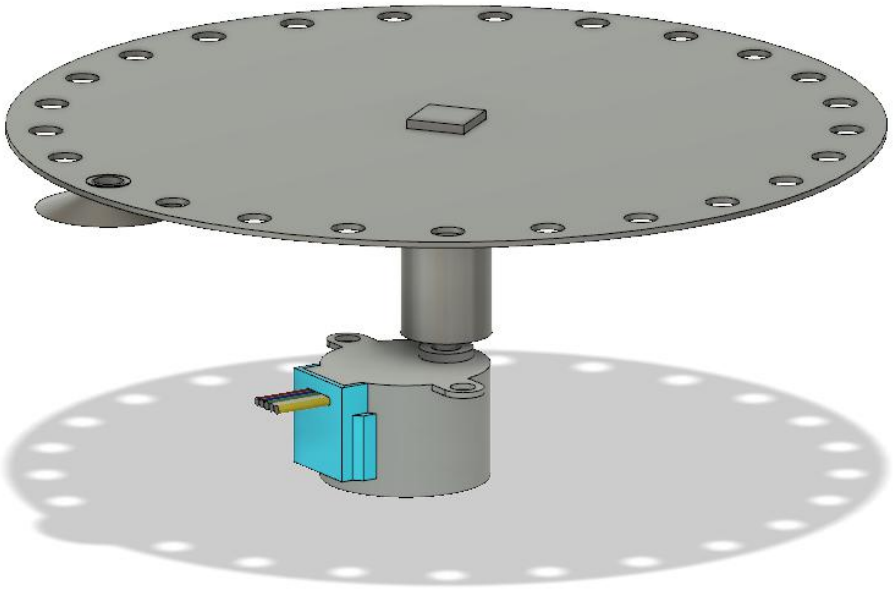

Figure 3.14: Modelled and manufactured carousel used in transport module B. On the left and under a modelled pan, the conical part that was manufactured and placed on the balance, to allow individual sample weighing.

dimensions of the manufactured carousel are the same as the autosampler's, except for the thickness, which is smaller, allowing pans to be protruding out of its bottom. This carousel would then be placed on a compatible disk-shaped bottom and combined have the DSCr's autosampler's dimensions.

The objective of having the pans protruding out of the carousel's bottom, is to be able to push them up slightly when passing over the balance's weighing platform. This was done with a specifically designed part (also visible in figure 3.14, on the left), that was manufactured and polished, to smoothly raise every individual pan as it goes over the balance, and allowing each of their masses to be measured. However, for this measurement to be valid, some conditions must be true. First, the pan must slide and not jam or be damaged while being pushed up. Related to this, the pan must also be supported only by the piece over the weighing platform, since any unwanted support from the carousel would give an inaccurate mass. Finally, the hardest condition to control is the air flow over the platform, since one cannot close the weighing compartment, as could be done for workspace A. All these factors can significantly influence the powder mass measured.

3.4.10 Hermetic lids and Standard lids

An important alternative to the workspace was the use of a different kind of lids, instead if the hermetic ones. Figure 3.15 illustrates this type of lid and a hermetic one for comparison.

These are called the standard lids and have a different usage and behavior when closing the pan. For start, they are not hermetic, so they are equivalent to a pierced hermetic lid in that regard. However, using hermetic lids, the user has the option to make the sample hermetically closed, by not piercing it. The purpose of having this alternative is in the DSC analysis objectives, where it might be desired to release the solvents or not.

By the fact that they are not hermetic, they do not need such a large pressure to be closed, since there is no cold-welding. The matrix used in the manual press is different, and the maximum force it

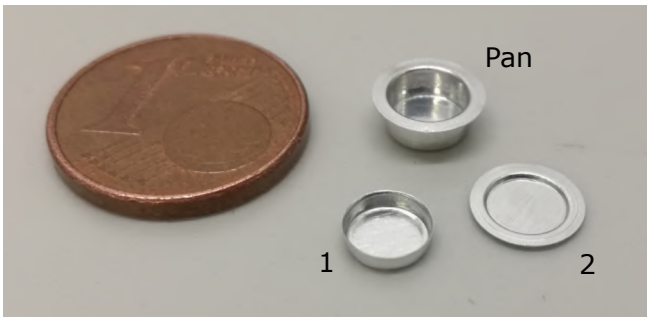

Figure 3.15: A standard lid (1) and a hermetic lid (2). Both used with the same pan but for different sample types.

creates is about $3kg$, which is the same as the T3 SCARA robot's payload. It also does not have a very complex shape, being basically a metal cylinder attached to a spring. This gave the option to use the dispensing robot as a press, by applying force with the powder gun's tip on the lid placed on top of a filled pan. The described pressing method was tested, and the sample was properly closed and the powder gun not damaged. Another test made was to pick up these lids with the vacuum, with the objective of checking if they were compatible with workspace B. The results were positive, i.e. the dispensing module can be used to transport the standard lids as accurately as the hermetic lids.

Another advantage is the fact that they sink into a filled pan, instead of just sitting on top of it, resulting in a uniformization of the powder during the closing of the samples This is due to their dimensions, with a smaller diameter than the inner diameter of the pans, which comes at a cost. By having such small dimensions, they are a bigger challenge to handle by the transport module A, and are even more fragile when grabbed by the side, due to their shape. Another disadvantage was the fact that by sinking into the pan, they result in a sample with smaller volume, allowing less powder to be in it. This could be a concern if the powder that is to be sample has a very low density, meaning the volume might not be enough to contain the desired $3mg$. As a conclusion, depending on the user's desired results (hermetic sample or not), the system implementation (workspace A or B) and powder properties, one can choose which lid to use. It would be easy to create a variable for the lid type that could indicate the master which tasks the slaves would do. Could the dispensing robot press the sample, or would another instrument have to press it and perhaps pierce it? How much the gripper would have to close to grab the lid and where would the transport robot move to pick it up? The number of possible combinations of workspaces, lid types and hermetic/non-hermetic analysis results in a plethora of possible implementations. The most commonly used lid was the hermetic one (possibly because it enables a late choice for hermetic or non-hermetic analysis) so the tools and routines implemented were designed with these lids in mind, although flexibility to change was always a concern.

3.5 Software Architecture

In this section, the algorithm for each module is explained and the sequence of operations for the automatic sample preparation is presented. Since transport module B works over the balance, which is the only sensor available, its performance can directly influence the weighing and dispensing modules' operations. On the contrary, transport module A, is easy to isolate and any failures do not compromise

the ability to evaluate the other modules in the system. To improve experiment validity when testing the complete system, the master-slaves architecture implemented in the laboratory was the one designed for workspace A. For this reason, the presented algorithms and flowcharts are the ones respective to this workspace and transport module. As an added advantage of this module, it is more flexible to be used for other sampling containers, just by adjusting the gripper step values. The most alterations between A and B regarding algorithm are in the master's routine, since the communication with the carousel's Arduino and the Gripper Robot must be different as are the commands sent to them. Despite this change in the coding and, in part, the sequence of tasks, the other modules work is the same way and the sampling tasks are very similar. Another small difference would be in the lid transportation, done by the gripper (workspace A) or by the dispensing module (workspace B), meaning the command would be sent to a different module, although in the same sequence.

The components that are attached to the robots only need to communicate with them and not with the master, since they are only activated when the robots are in specific positions. In a cascade setup, the robots are in the layer below the master and the other components below them, as depicted in figure 3.16, where the type of communication implemented is indicated.

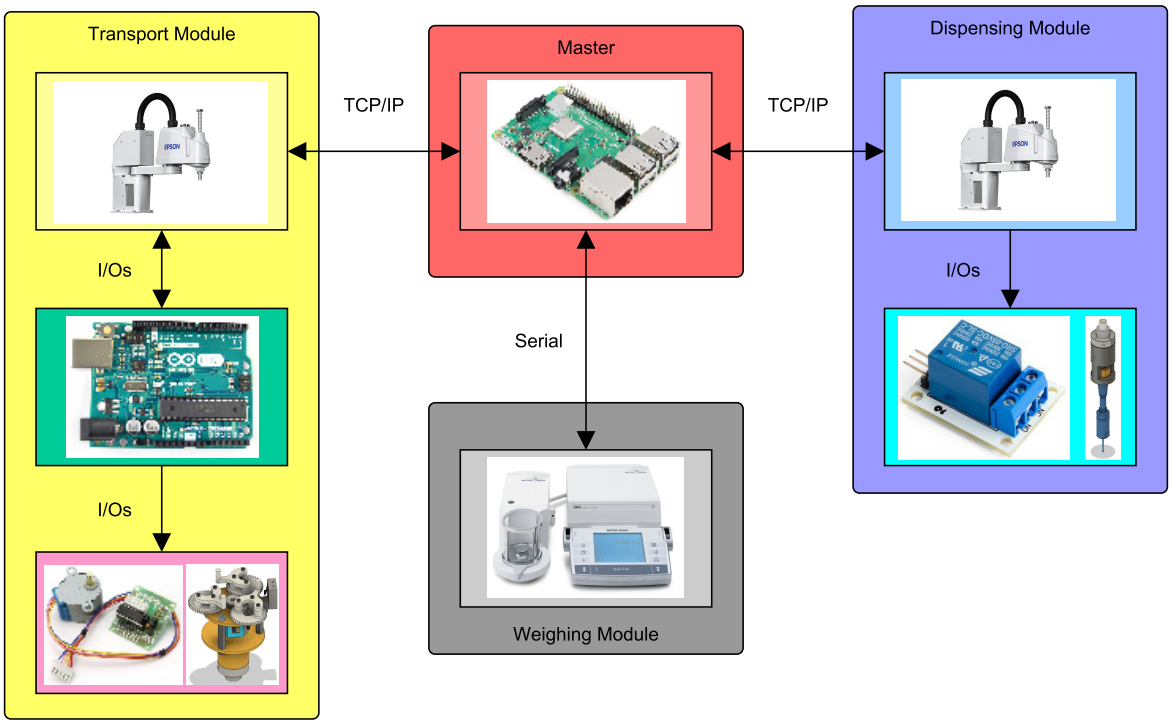

Figure 3.16: Master-Salves setup. The cascade setup allows for an easier module separation and the simplification of the master's algorithm.

This cascade methodology makes it easier to separate each module for testing and to increase complexity. The dispensing robot controls the relay that inverts the vacuum generator described in the dispensing module. This is done by using the robot's hand I/Os. The gripper robot communicates with the Arduino by means of its hand I/Os which then controls the stepper motor in the same way. This is also applied to the transport module in workspace B, where the master only communicates with the

Arduino, and not with the stepper. To note are the colors used for each component, which are used in the below presented flowcharts accordingly, for an easier understanding of the involved components in each step.

3.5.1 Weighing Module

Starting with the simplest module, the MX5 balance is composed of two units, a measurement unit and a communication unit. The communication unit is connected via serial and operates in MT SICS programming language. This is the module with the simplest software design. The communication settings were set manually in the balance's display and when connected to the master, a bidirectional communication is established. The master sends commands in the form of strings and the balance responds with other strings. The main commands used are the order to zero the balance, the order to tare the balance and the order to return the mass measured in the weighing unit. The other commands to be used are to open and close the weighing compartment.

3.5.2 Master

The master's program was coded in Python 3 language and imported to the Raspberry Pi. The main goal of the master is of course to coordinate the top-level slaves present in the workspace. As mentioned in the introduction, the presented setup is the one used for workspace A, being the more complex one but also the more powerful and flexible.

Firstly, the master establishes a serial communication with the weighing module and sets a TCP/IP server to host the 2 robot clients. It then verifies if the balance is at zero ($|mass| \approx 0$) and if not, it sends the order to zero the balance. While the balance is zeroed, the master waits for the two robots to connect and sends them to their home position. As soon as it receives the *'at home'* state from the two robots, the sample preparation is ready to start. These steps compose the startup tasks, as shown in figure 3.17, and the master can now start the sampling routine.

After the initial setup, the master starts to coordinate the sample preparation, following a sequence of tasks that the different modules will be ordered to perform. This sequence is illustrated in figure 3.18, where some 'STOP' conditions occur, which in the current implementation mean human intervention.

The master commands the gripper robot to get a pan and waits for it to complete its task. The master now sends the command to the balance to measure the mass. If the weigh obtained is the expected pan mass, m_{pan}, within a 10% interval, the master moves to the next routine. If not, it means that most likely the gripper robot did not grasp the pan, or it was dropped during the trajectory to the balance. In this case, the master is stuck in a loop where a new command to get a pan is sent to the gripper robot, and another mass check is made after the robot has given the indication that it has placed a pan in the balance. This loop is performed until a pan is actually placed in the balance (and the master moves to the next step) or the order to stop the automation process is given, either by manually stopping it or by setting a limit of failed attempts.

Once a pan is confirmed to be in the balance, the master commands the gripper robot to move to its rest position and orders the dispensing robot to perform its task. This is the beginning of the dispensing routine. With the information from the robot that the dispensing was completed, the powder mass is

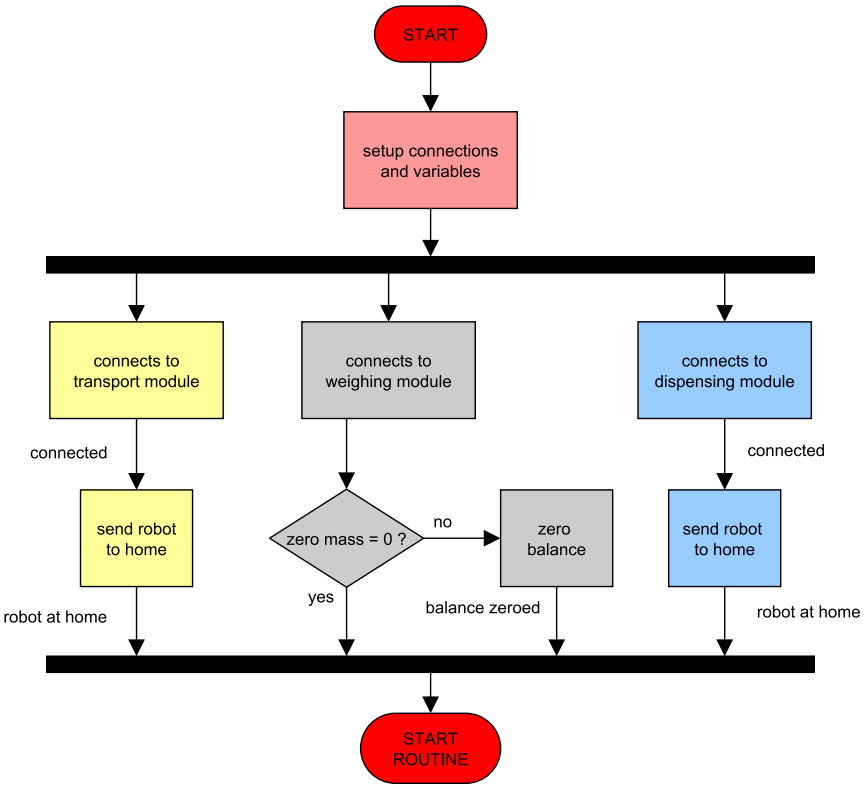

Figure 3.17: Flowchart for the master - communication establishment and components startup.

obtained by sending the command to the balance. If the powder mass is in the desired range, between m_{min} and m_{max}, the dispensing routine is completed successfully. If it is lower than the minimum allowed, a new dispensing to the same pan takes place, and a new weighing occurs, until $mass > m_{min}$. If it is above the maximum allowed, the pan is considered overloaded, and the sample must be discarded and the whole sampling operation must be redone. The master orders the dispensing robot to go home and the gripper robot to remove the overloaded pan from the balance and take it to a position defined as trash. It registers the sample as invalid and increments the counter for failed powder dispensing operations. If this counter is over a certain value, the automated sampling should stop and the system should be checked by the user, because it could mean a critical failure of the dispensing module. If its lower than the defined value, the master orders the gripper robot to change the pan and lid coordinates to the ones of a new cycle (meaning the next positions on the tray, that were expected to be used for the next sample). The master also orders the dispensing robot to adjust its powder source coordinates, so it does not try to absorb powder from the same position as the previous run. If the dispensing was successful and the right amount of powder is in the crucible, the master proceeds to the lid routine, in which the dispensing robot is commanded by the master to move to home, and the gripper robot receives the order to get a lid. It takes the lid to the balance and signals the master when it is done. A new mass is obtained from the balance and if it is an invalid mass, a similar loop to the one in the pan routine takes place. If the mass returned is equal to $m_{lid} \pm 10\%$, it means the lid was in fact placed in the balance properly and the gripper is ordered to take the complete set, i.e. the filled pan and its lid.

The final routine starts when the gripper robot takes this set, places it in the *'next location'* and

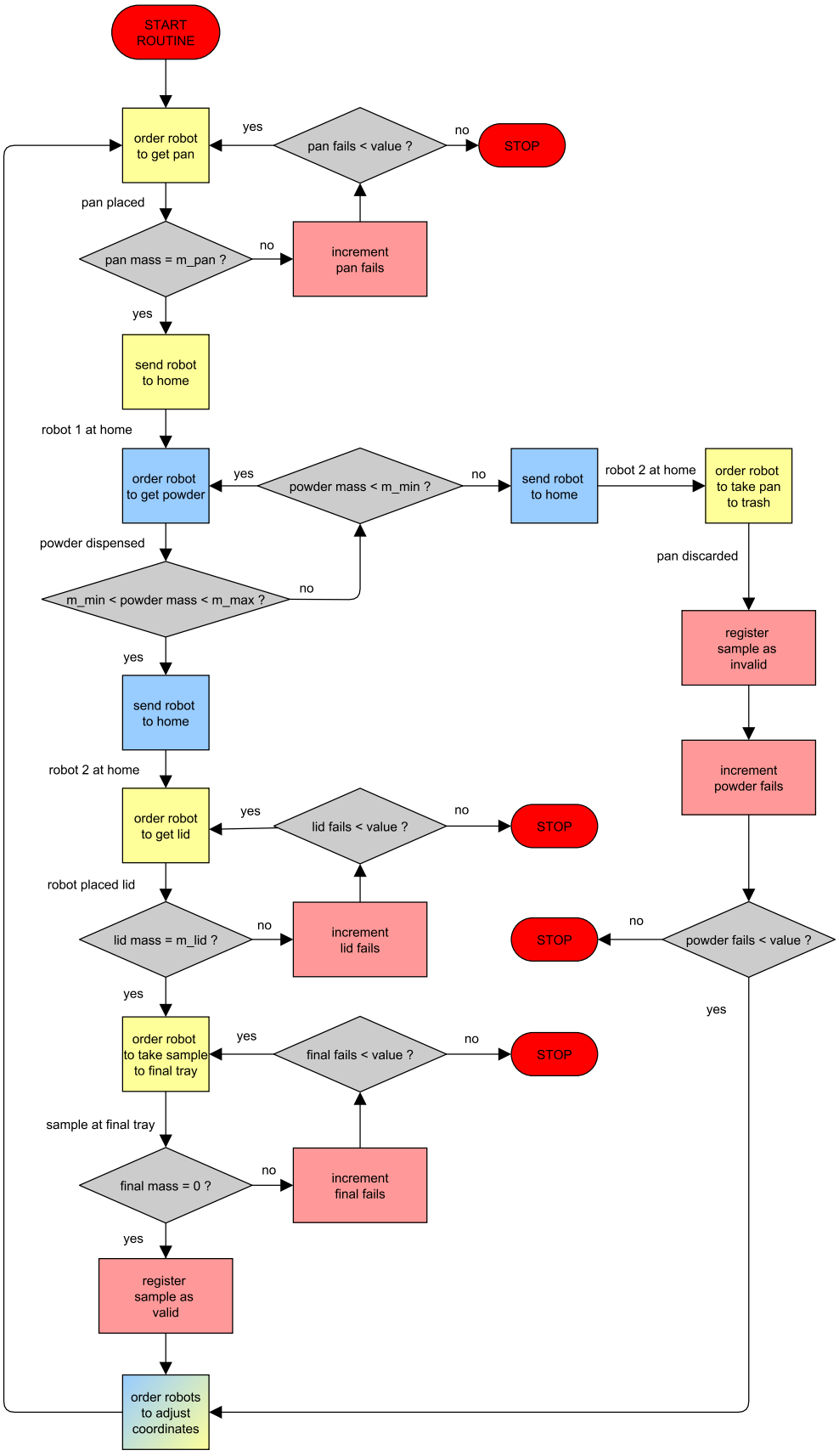

Figure 3.18: Flowchart for the master - sampling routine coordination.

a weighing is done to check if the final mass in the balance is zero. If it is very different from zero ($mass >> 0$), the set was not properly grabbed, and the master orders the gripper robot to take it again. This loop is performed just like the one described for the pan and lid routines, meaning until a certain value of failed tasks is reached, after which the operations stop until the user intervenes. If, however, the mass is zero, the sample is considered valid. If the mass that remains in the balance is close to but not zero (e.g. less than $0.5mg$), this probably indicates that some powder missed the pan during the dispensing, and it is sitting on the weighing platform. Since it would be very difficult to remove this powder with the tools available, a different strategy was opted for. First, the remaining mass is subtracted from the powder mass obtained during the dispensing routine, so the recorded powder mass is accurate and valid for a DSC analysis. Second, the occurrence of the powder dispensed outside of the pan is accounted for, by incrementing a *'powder inaccurately dispensed'* counter, which after a certain threshold should stop the operations or warn the user. Last but not least, for the next sample to be created, the remaining weight in the balance platform is set as tare, so it does not influence the decisions made in the next cycle (if masses are valid for each routine). After these three steps, the master runs as if the remaining mass was zero, the case where the completed sample is flawless, which was previously described. For readability, these steps are not represented in the master's flowchart, since it is just a simple addition to the final mass' *'if...then'* loop.

Regarding the *'next location'* above mentioned, for this implementation, it refers to the position where the finished samples would be stored in. As stated before, the scope of the thesis only contemplated the transport and dispensing operations, but the communication with a press is easily implemented in the master's script, with the gripper robot taking the sample to it and removing it after the closing is achieved. This means it would only be necessary to add the press' coordinates to the robot's database and order it to place the sample there. Afterwards, it would take the sample to the finished tray so the process sequence is maintained, only having an extra task before the final sample is stored.

For the present case, once the sample is in the final position and considered valid, the gripper robot is commanded to alter the container coordinates to the ones of the next cycle (the same command that is given when a pan was overloaded with powder). The dispensing robot also slightly adjusts its powder flask coordinates but this necessity to move around the powder source is further explored in the experiments section. At this stage, the master saves the obtained masses and outputs them, for the user to monitor if desired and possible to be used by the DSCr equipment if connected to the master. A new sample can now be created, as soon as the order to get a new pan is given by the master.

3.5.3 Dispensing Module

The dispensing module communicates with the master via TCP/IP. The software used in the robot is the EPSON RC+7 which is written in SPEL+ programming language. The initial procedure sets the variables such as speed and acceleration, as seen in the top portion of the flowchart represented in figure 3.19. The module then waits for the queue from the master to start the dispensing.

The robot takes the powder gun to the powder bottle and takes in powder. After dipping inside the anti-static ring, it moves into the brush, crossing it three times to remove the excess powder that could

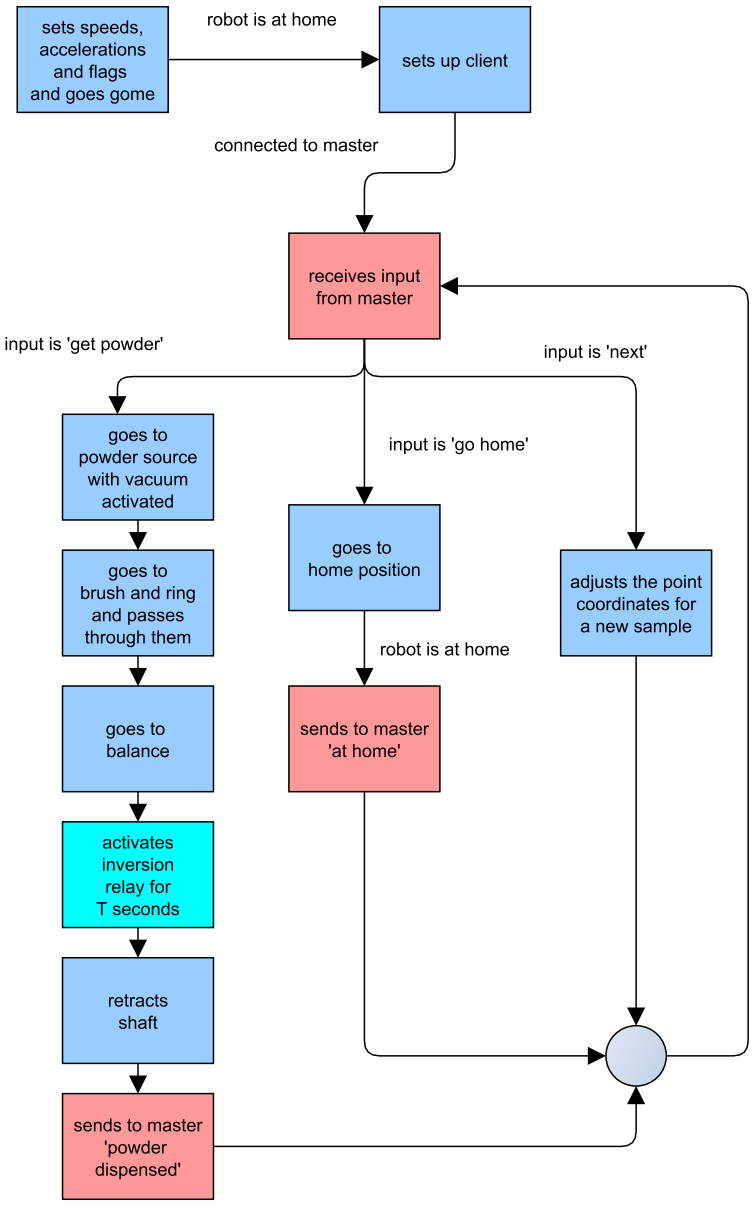

Figure 3.19: Flowchart for the robot used in the dispensing module.

have adhered to the outside of the probe, although this part of the trajectory can be changed to take place after the dispensing. The robot moves to the balance and once the powder gun is lowered close to the pan, the robot activates the relay with a $5V$ output signal by a certain time duration (whose value will be studied in the experiments), closing the inversion circuit and making the vacuum generator output compressed air instead of vacuum. This makes the powder leave the tip of the gun and be dispensed into the pan. After retracting the shaft, the robot waits for the master to respond if the powder dispensed is over the minimum required value. If not, another dispensing run takes place, as mentioned in the master's algorithm. To reach a mass of $3mg$, the dispensing module usually runs five to eight times, depending on the powder's density.

The usual sequence ends with the robot travelling to its home position, if the master signals the task as completed, once the powder mass is enough. In spite of the simplicity of the presented flowchart,

the dispensing routine was iteratively improved in terms of powder absorption, as will be extensively explained in the experiments chapter.

3.5.4 Transport Module A

The robot establishes communication just like the one from the dispensing module, and goes through a similar setup. The way it is programmed makes the robot stay in a loop and depending on the task ordered, it goes to different positions in the workplace such as the pans tray, lids tray, balance, finished samples tray and trash, with the possibility to add the aforementioned position for the sealing press. All the routines depending on the master's input are shown in figure 3.20.

Another command, labeled as *'next'* orders the robot to adjust its tray coordinates, corresponding to another set of pan and lid. The last option is to move to home position, which is used to give space to the other robot during the dispensing and, therefore, avoid collisions. For each position within a task, the robot has two sets of coordinates, one with $Z = 0$, with the shaft retracted at the maximum height and one with the Z coordinate that makes the gripper fingers reach the parts to grab. During these tasks, the robot sends outputs to the Arduino to command the gripper to open or close.

The Arduino UNO runs a script written in Arduino language, which is merely a set of C/C++ functions. The program initializes by importing the stepper library in order to have the ability to easily control the stepper motor. The step variables are given values (steps per revolution and steps for each gripper position), other variables such as counters and thresholds are initiated, and the input and output pins are defined. The setup routine, presented in the beginning of figure 3.21, basically calibrates the gripper, by making the stepper's shaft rotate in one direction until the finger activates a switch.

Once this switch is pressed, the rotation direction is inverted and when it is no longer pressed, the gripper stops. The gripper is at its home position and the steps from home are, of course, zero. It is now known how many steps the stepper must take, so the gripper's fingers are at the desired positions, since the steps between each position and the home position are constants defined in the setup section described above. The Arduino is now in an *'if. . . then'* loop in which the voltages in the analog input pins sent by the robot are read and if one and only one of them is at certain value, this indicates the robot is sending a command to move the gripper to a specific position. If this input position has the same number of steps from home as the current one, it means the gripper already has the desired distance between the fingers and the gripper does not move. If it the input position is different than the current one, the difference between the steps from home of the two positions is calculated, and the stepper is commanded to rotate by that number of steps. This ensures the gripper never open or closes excessively even if the robot sends multiple identical commands.

3.5.5 Transport Module B

The DSCr's disk-shaped autosampler plate has 55 positions in 3 rows, 25 of them in the outer most one. The manufactured carousel has then 25 holes (where the pans will be located) around its $360°$, in its outer row, at the same distance from the carousel's center as the outer positions in the DSCr's autosampler. The idea is to divide the 25 positions by the steps per revolution of the stepper used, resulting in the number of steps between two neighboring positions: $steps_{next}$. Depending on the desired

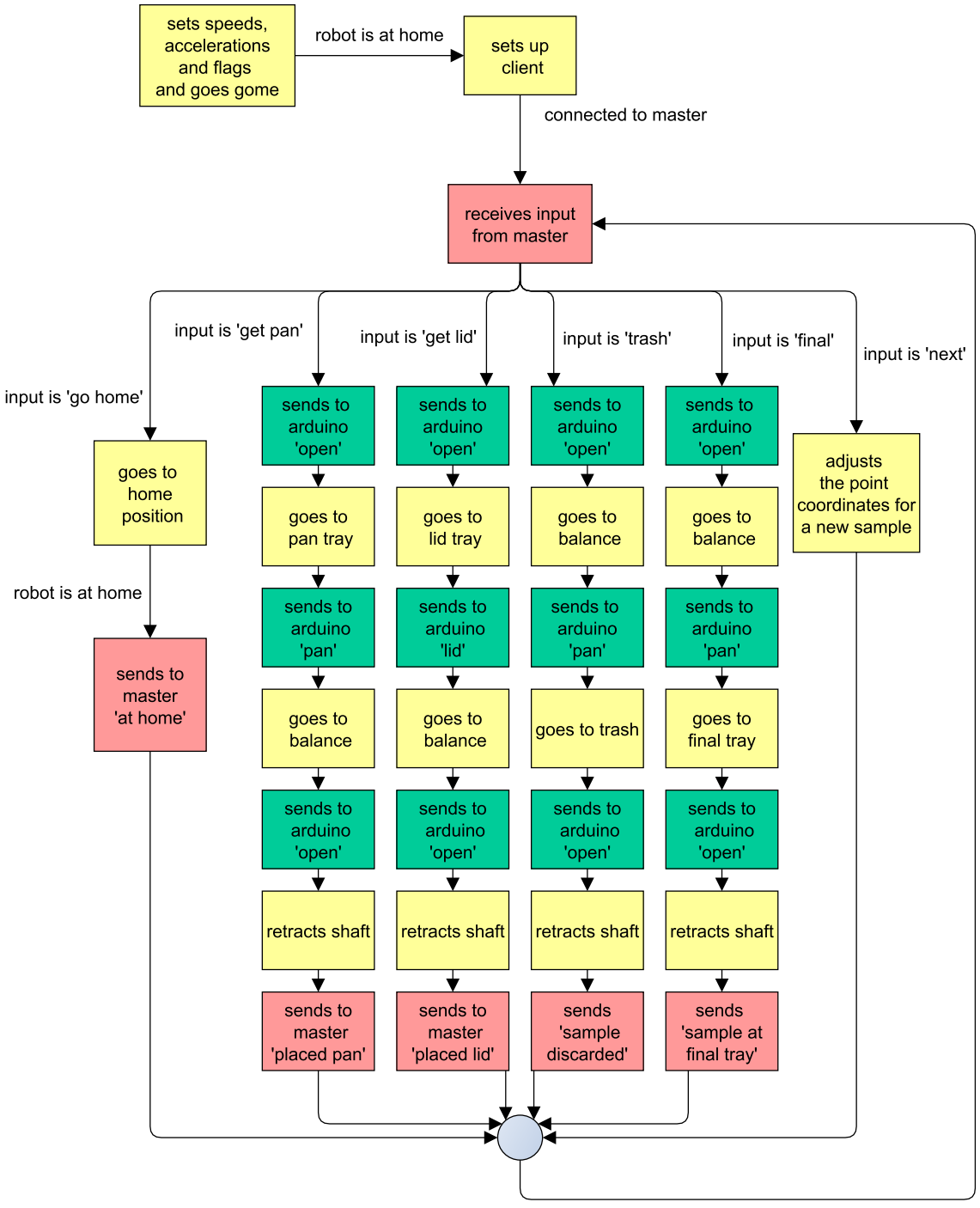

Figure 3.20: Flowchart for the robot used in transport module A.

position for the sample, the master informs the Arduino, and the Arduino commands the stepper to take a certain number of steps. The Raspberry Pi to Arduino communication is established by serial and the commands sent to the stepper by the Arduino are via I/Os.

The programmed routine is quite simple. The setup is similar to the one used for the Arduino used to control the gripper, i.e., the pins and variables are defined, and the communications established. The carousel assumes its original position as reference, meaning position 0. Regarding the loop, the Arduino listens for an input from the master which can be either a specific numbered position, *'next'* or

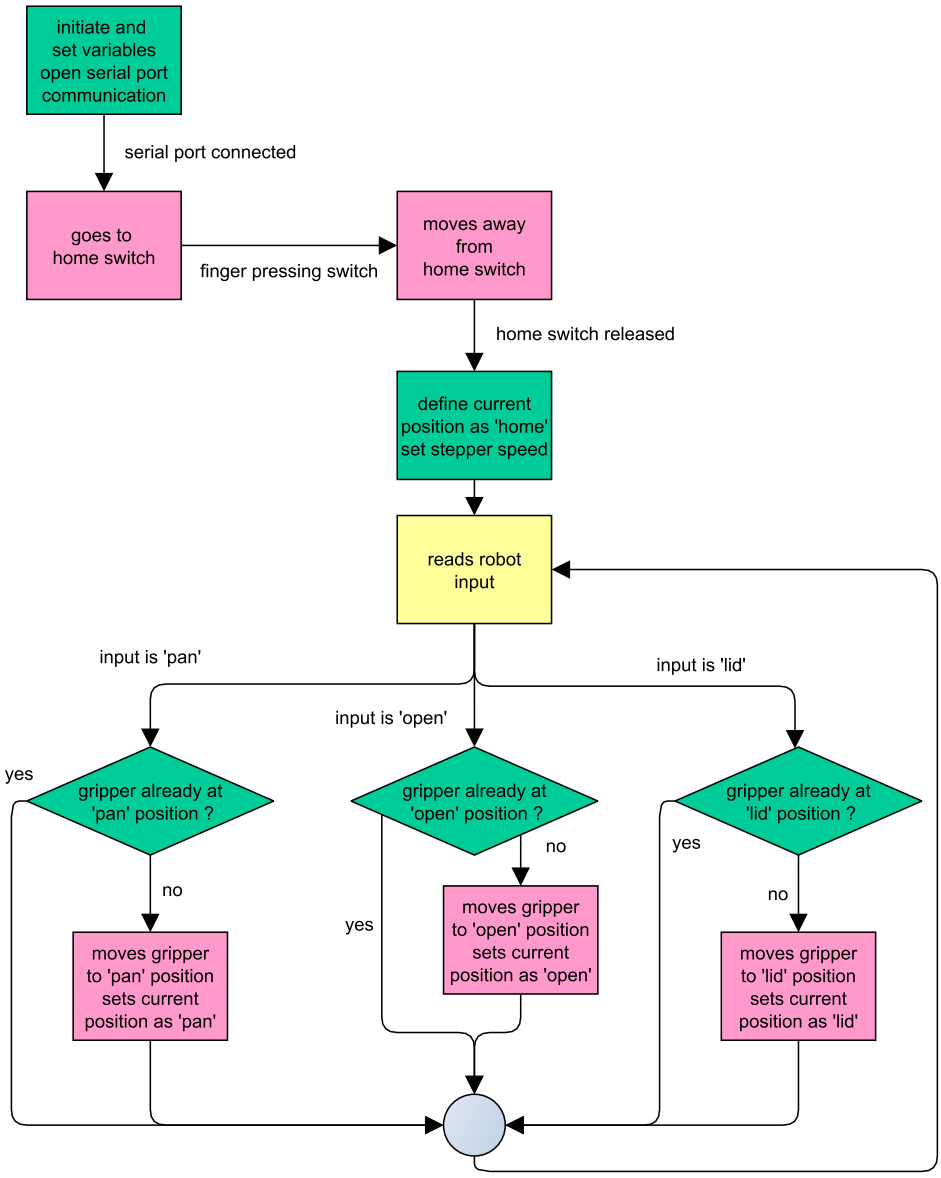

Figure 3.21: Flowchart for the Arduino controlling the gripper used in transport module A.

'previous'. For the two latter cases, the Arduino commands the stepper to take $+steps_{next}$ or $-steps_{next}$ (respectively) and registers its new current position. For a specific numbered position given as input, e.g. position 5, the Arduino checks its current position (say 7) and determines how many positions away it is from the input position. In this example, it would be $5 - 7 = -2$ positions away from the desired position. The stepper is then commanded to move $-2 * steps_{next}$ steps.

As a side note, it is important to mention how the Arduino sets its original position for reference. After every rotation, the stepper program registers its new current position by saving the number of steps to the origin it has travelled. Since this step counter is a variable in the program, it is important to note that if the carousel is not at the reference position when it is shut down (e.g. the Arduino is shutdown while at position number 10), it will assume this last position as the new origin, upon turning back on. This means the stepper should be taken to the origin after its rotations, before shutting it down. One could

implement a similar approach as used in the gripper, by adding a home switch to the carousel, but this could prevent the stepper from performing a full rotation.

3.6 Global coordinates to robot coordinates

In order for the robots to move to the desired locations, it was necessary to transform the workspace's global coordinates of these locations to the coordinates of each robot.

In order to illustrate the described coordinate transformation, figure 3.22 with the three RFs is given. The bases where the robots stand were manufactured and the real assembly is very similar to the modelled workspace, with the small inaccuracies inherent to manufacturing and assembling in the Hotte. The equations and algebraic transformations used in this section are based on the chapter 'Kinematics' in [49].

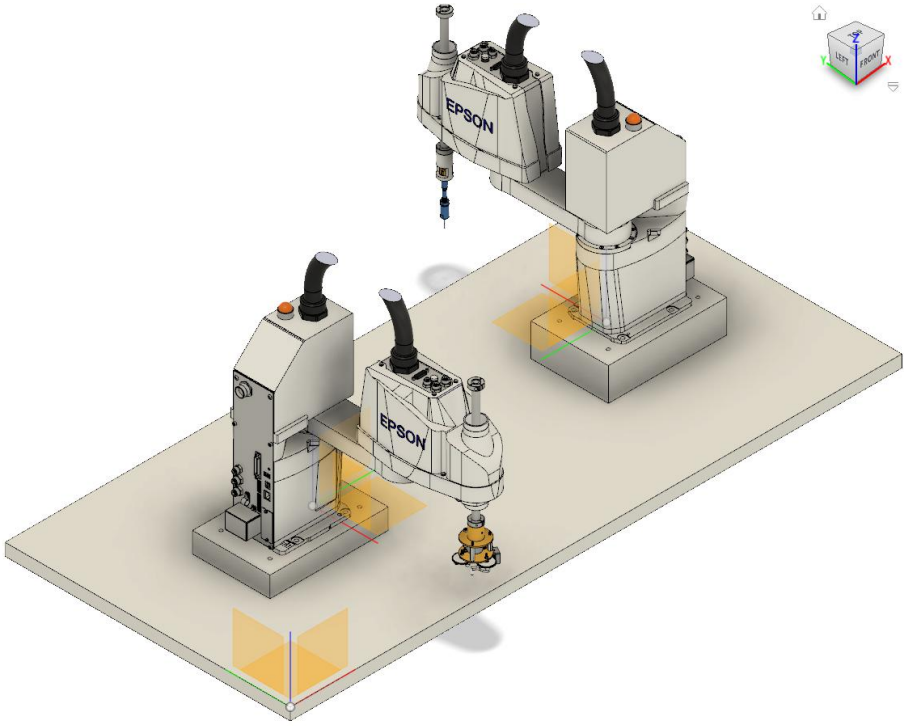

Figure 3.22: Relative orientation of the robots' reference frames and the global reference frame.

p_{robot} and p_{global} will be defined as the position vectors of a certain workspace component (e.g. the balance), with respect to one of the robot's RF and with respect to the global RF, respectively. To relate p_{robot} with p_{global}, the following expressions can be used:

$$p_{global} = o_{robot}^{global} + R_{robot}^{global} p_{robot} \tag{3.13}$$

$$p_{robot} = -R_{robot}^{global^T} o_{robot}^{global} + R_{robot}^{global^T} p_{global} \tag{3.14}$$

Where R_{robot}^{global} is the rotation matrix that aligns the global RF with the robot's RF and o_{robot}^{global} is the position vector of the robot's RF origin with respect to the global RF.

For both robots, since the Z axis are all parallel, and therefore all rotations are with respect to this axis, the rotations matrixes can be calculated with:

$$R_z(\theta) = \begin{bmatrix} cos(\theta) & -sen(\theta) & 0 \\ sen(\theta) & cos(\theta) & 0 \\ 0 & 0 & 1 \end{bmatrix} \tag{3.15}$$

For the gripper robot (located on the left of figure 3.22), the angle of rotation is $\theta = -\pi/2$ so the resulting rotation matrix is:

$$R^{global}_{gripper}(-90) = \begin{bmatrix} cos(-90) & -sen(-90) & 0 \\ sen(-90) & cos(-90) & 0 \\ 0 & 0 & 1 \end{bmatrix} = \begin{bmatrix} 0 & 1 & 0 \\ -1 & 0 & 0 \\ 0 & 0 & 1 \end{bmatrix} \tag{3.16}$$

The position vector is (according to the modelled workspace):

$$o^{global}_{gripper} = \begin{bmatrix} 405 \\ 350 \\ 50 \end{bmatrix} \tag{3.17}$$

In the same way, for the dispensing robot (right of figure 3.22, using $\theta = \pi/2$ (since the rotation is symmetric), the rotation matrix and the position vector are easily obtained as:

$$R^{global}_{dispensing}(90) = \begin{bmatrix} cos(90) & -sen(90) & 0 \\ sen(90) & cos(90) & 0 \\ 0 & 0 & 1 \end{bmatrix} = \begin{bmatrix} 0 & -1 & 0 \\ 1 & 0 & 0 \\ 0 & 0 & 1 \end{bmatrix} \tag{3.18}$$

$$o^{global}_{dispensing} = \begin{bmatrix} 1125 \\ 350 \\ 80 \end{bmatrix} \tag{3.19}$$

Note the different X and Z values but the same Y value between $o^{global}_{dispensing}$ and $o^{global}_{dispensing}$ as was predicted with the observation of figure 3.22.

It is now possible to determine any position's robot coordinates from any global coordinates set as p_{global} by using 3.14 and either $R^{global}_{gripper}$ and $o^{global}_{gripper} or\ R^{global}_{dispensing}$ and $o^{global}_{dispensing}$. As an example, taking the balance's weighing platform global coordinates:

$$p^{balance}_{global} = \begin{bmatrix} 800 \\ 400 \\ 100 \end{bmatrix} \tag{3.20}$$

and the coordinates for each robot are computed by using:

$$p_{gripper}^{balance} = -R_{gripper}^{global\ T} o_{gripper}^{global} + R_{gripper}^{global\ T} p_{global}^{balance} = \\ = -\begin{bmatrix} 0 & -1 & 0 \\ 1 & 0 & 0 \\ 0 & 0 & 1 \end{bmatrix} \begin{bmatrix} 405 \\ 350 \\ 50 \end{bmatrix} + \begin{bmatrix} 0 & -1 & 0 \\ 1 & 0 & 0 \\ 0 & 0 & 1 \end{bmatrix} \begin{bmatrix} 800 \\ 400 \\ 100 \end{bmatrix} = \begin{bmatrix} -50 \\ 395 \\ 50 \end{bmatrix} \tag{3.21}$$

and,

$$p_{dispensing}^{balance} = -R_{dispensing}^{global\ T} o_{dispensing}^{global} + R_{dispensing}^{global\ T} p_{global}^{balance} = \\ = -\begin{bmatrix} 0 & 1 & 0 \\ -1 & 0 & 0 \\ 0 & 0 & 1 \end{bmatrix} \begin{bmatrix} 1125 \\ 350 \\ 80 \end{bmatrix} + \begin{bmatrix} 0 & 1 & 0 \\ -1 & 0 & 0 \\ 0 & 0 & 1 \end{bmatrix} \begin{bmatrix} 800 \\ 400 \\ 100 \end{bmatrix} = \begin{bmatrix} 50 \\ 325 \\ 20 \end{bmatrix} \tag{3.22}$$

As expected, the balance's coordinates are different for the two robots' RFs even if they were calculated from the same global coordinates. The values reached are also in accordance to the layout of the RFs in figure 3.22.

The same procedure was performed for every other component in the workspace and for both robots, arriving at an list of coordinates. This made possible the definition of the robots' trajectories during the sampling operation. If more modules are added, the same computations can be done for their position coordinates, so this method provides a systematic way to quickly program the robots to travel to the desired locations. Is is also important to detect collision risks by using the robots' software, avoiding them in the real workspace and therefore promoting safety in the laboratory.

3.7 Final implementation

As stated in the beginning software architecture section, the setup installed in the laboratory was workspace A, since the performance of its transport module (i.e. the gripper robot) would only influence directly the success of other modules if it inaccurately placed the pan in the balance. Since this is easier to identify and correct than the influence of the carousel on the weighing, workspace A would provide more trustworthy results. These assumptions showed to be correct during the tests to each module, as will be seen in the experiments chapter. Based on the performances of the two transport modules, it was concluded that, in its current state, the carousel transport did not provide reliable weighing, which could negatively impact the validity of the samples created. Since the gripper showed great results in handling hermetic lids, while also demonstrating enough precision and flexibility to grab standard lids, and speed was not a major concern, this transport module was considered best to implement for an end-to-end test. The samples to be made are non hermetic, but since the most common practice was to use pierced hermetic lids and not standard lids, this was the part diameter value set for the gripper. This meant the lids had to be previously pierced and the samples manually pressed after the automatic operation. The gripper taking a hermetic lid from the tray can be seen in figure 3.23.

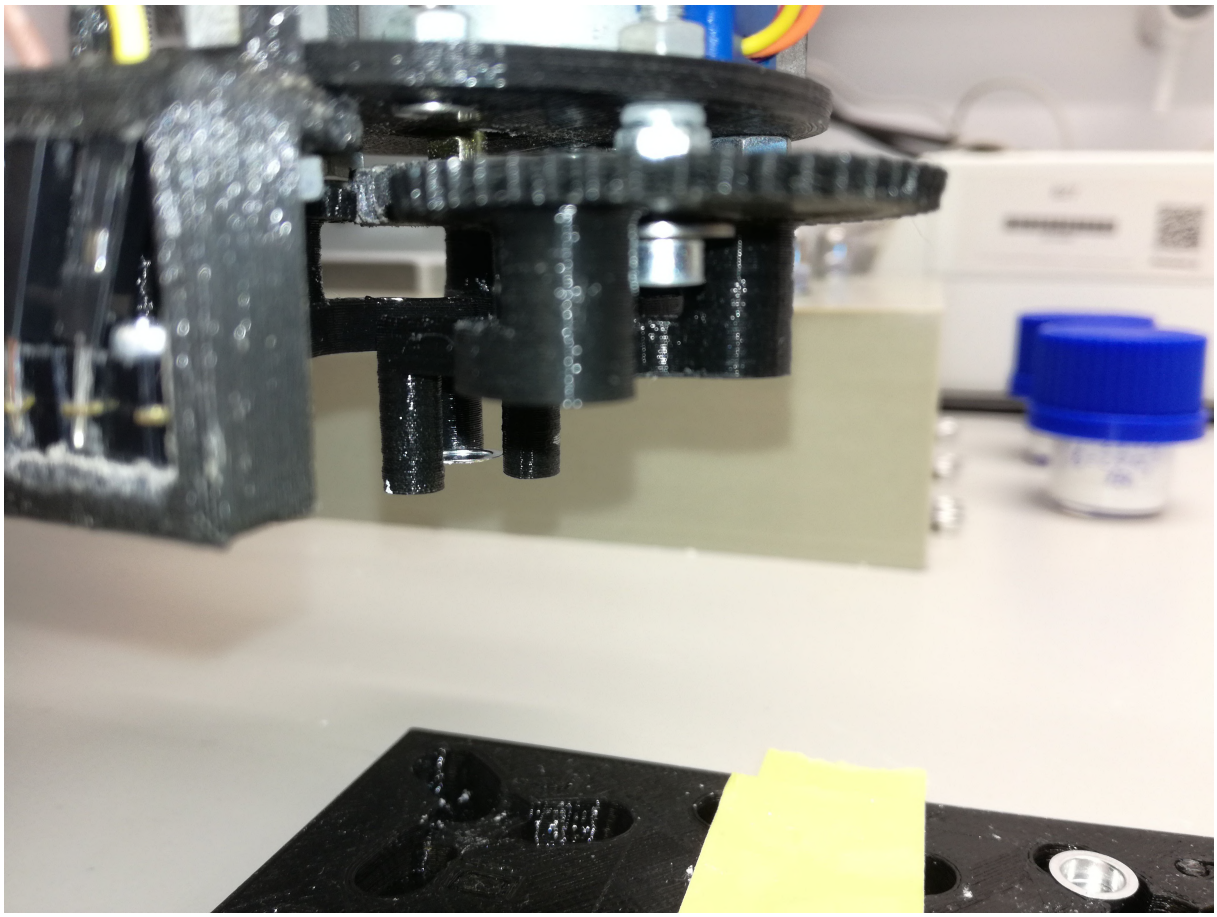

Figure 3.23: Gripper grabbing a hermetic lid from its tray.

The final setup installed is presented in figure 3.24 and the following components identifiable:

- **Transport Module A:**
  - SCARA robot
  - Arduino
  - stepper motor
  - designed gripper
  - manufactured crucible trays with 3 pans and 3 lids
- **Dispensing Module:**
  - SCARA robot
  - powder gun and manufactured shaft adapter
  - vaccum generator and pressure regulators
  - an anti-static ring
  - a brush and a container to catch brushed powder
  - many flasks as powder sources
- **Weighing Module**: MX5 balance

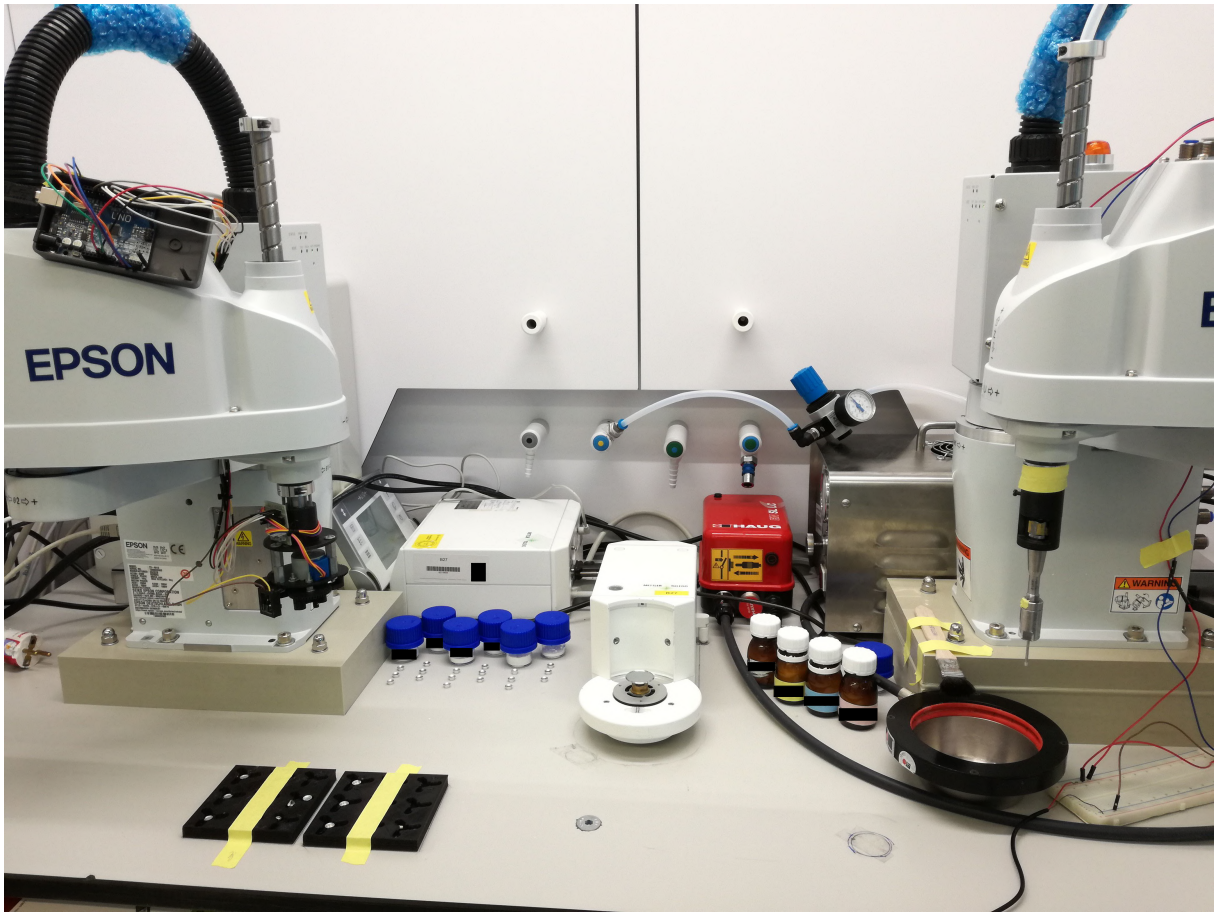

Figure 3.24: Setup implemented in the laboratory and used for the full system experiments.

Chapter 4

Experiments and Results

In this chapter, the experiments carried out and the results obtained are presented. The discussion of these results is done after each experiment, since they influenced the posterior tests' design. First, the two transport modules are evaluated. The gripper, regarding the repeatability of its movements and how reliable it is when handling the pans and lids. The carousel, in terms of how accurate it allows the weighing to be, given is position over the balance.

Then, the dispensing module is tested in several ways. To start, the source of powder is studied, regarding what properties of the powder surface that are more influential on the module's performance. Secondly, the adjustable parameters (compressed air time interval, compressed air pressure and distance from powder gun to pan) are explored, to check how their values are impactful on the accuracy of the dosing. Lastly, the routine or path that the powder gun follows to absorb powder from the flask is iteratively improved, to be more powder efficient and robust.

To further test the implementation, a full sampling system test took place, to quantify throughput and overall functionality. Additionally, the samples obtained in this experiment were analyzed in the DSCr to evaluate their validity.

4.1 Gripper Handling

To evaluate the effictiveness of the transport module from workspace A, the performance of the gripper was tested. First, the gripper was opened and closed repeatedly 6 times, to check if the finger tips would stop in similar locations and if the finger's centerpoint was the same when open and closed. This would give an indication of the precision of the finger trajectories and the ability to center the part to grab. The finger tips were moved in a horizontal plane just $0.2mm$ above the workspace floor, where a millimetric paper sheet was placed with several reference frames drawn on it. Correction fluid dots were drawn in the finger tips and their locations registered in the paper, by touching the finger tips on the paper sheet. To enhance the markers visibility, the dots were posteriorly marked with a pen. The tips' locations were marked for both *open* and *closed* gripper positions. Then, for every observation, the coordinates of those marks in relation to the respective reference frame were taken and the centerpoint coordinates were calculated by:

$$O_x = \frac{A_x + B_x + C_x}{3} \tag{4.1a}$$

$$O_y = \frac{A_y + B_y + C_y}{3} \tag{4.1b}$$

Where A, B and C are the vertices of the triangle (points where the fingers were positioned) and O is the center of the triangle (point were the fingers would meet, or where the center of the part grabbed would be). The points were labelled as shown in figure 4.1, with O being the center of triangle A, B, C and o the center of triangle a, b, c.

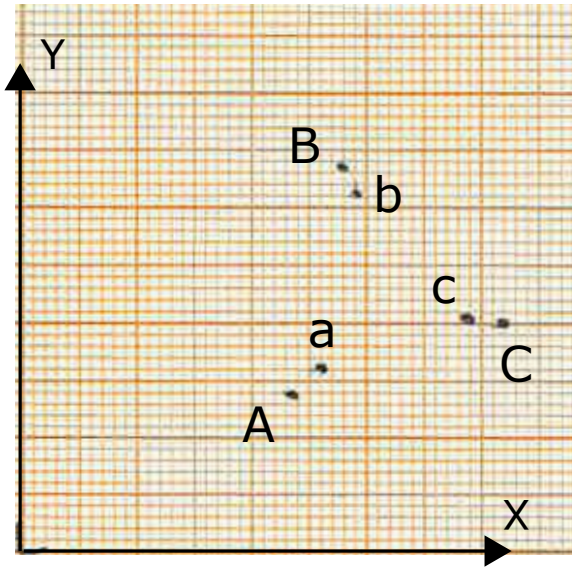

Figure 4.1: Labels used for the gripper points. *A,B,C* is the triangle corresponding to the *open* position and *a,b,c* the one corresponding to the *closed* position.

If the gripper is accurate, the centerpoint coordinates (O_x, O_y) and (o_x, o_y) should be the same, for each reference frame (or each observation) and the distances between the points registered should be similar for all the reference frames (across all observations). The results were very similar for all 6 observations, with the millimetric paper resolution and marking method not being enough to verify any obvious misalignment of the centerpoints. Figure 4.2 shows the experiment observations and table 4.1 lists the obtained coordinates.

Coordinates (mm)	**Observations**					
	1	**2**	**3**	**4**	**5**	**6**
A_x	25.0	25.5	25.0	23.5	24.0	25.0
A_y	14.0	14.5	13.0	14.0	13.0	13.5
B_x	28.5	29.5	29.0	28.0	28.0	28.0
B_y	35.0	33.5	33.0	33.5	33.0	34.0
C_x	43.5	42.5	42.5	42.0	41.5	42.5
C_y	20.0	19.5	19.0	20.0	19.0	18.5
a_x	27.0	27.0	27.0	26.0	25.5	27.0
a_y	17.0	16.0	15.5	16.0	15.0	15.5
b_x	29.5	30.5	30.0	29.0	29.0	30.0
b_y	31.5	30.5	31.0	31.0	30.0	30.5
c_x	40.0	39.5	39.0	38.5	38.0	39.5
c_y	21.0	20.5	19.5	20.5	19.5	19.5

Table 4.1: Gripper fingers trajectory test registered coordinates for all 6 observations, in (mm).

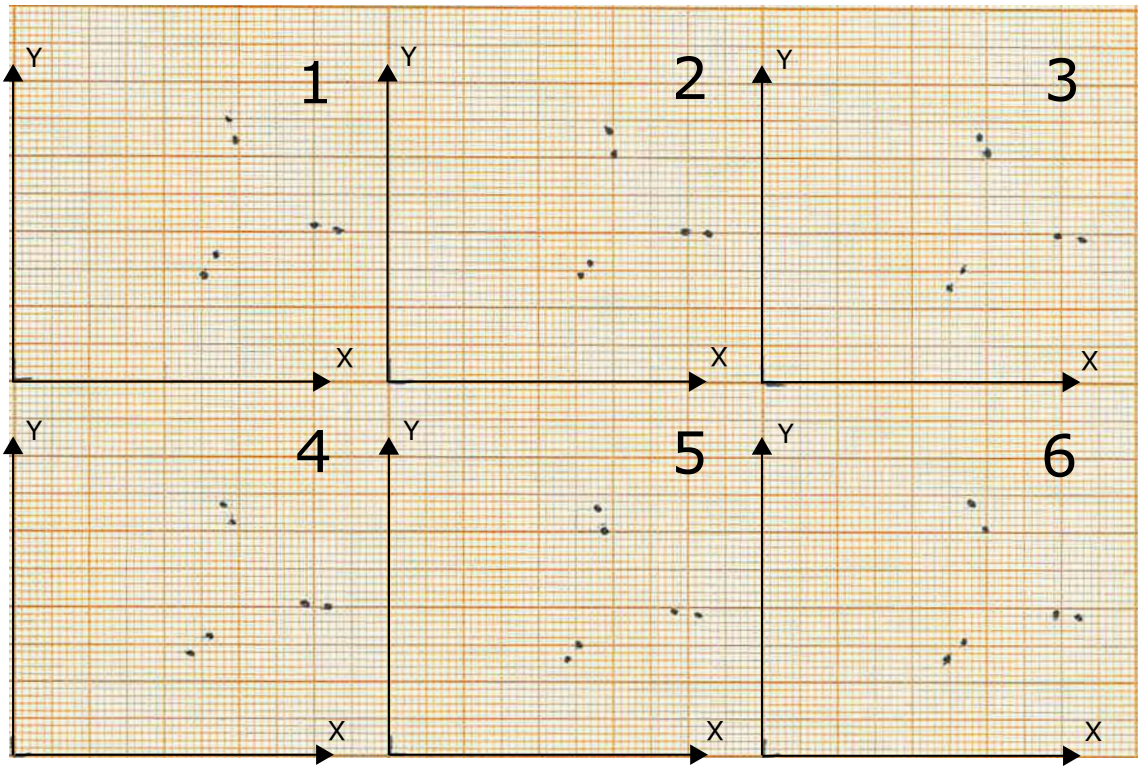

Figure 4.2: Gripper fingers trajectory test observations. Note: the positions change between every observation due to the human error when aligning the paper sheet.

By taking the coordinates of the vertices from table 4.1 and using equation 4.1, (O_x, O_y) and (o_x, o_y) were calculated are listed in table 4.2.

Coordinates (mm)	**Observations**					
	1	**2**	**3**	**4**	**5**	**6**
O_x	32.3	32.5	32.2	31.2	31.2	31.8
O_y	23.0	22.5	21.7	22.5	21.7	22.0
o_x	32.2	32.3	32.0	31.2	30.8	32.2
o_y	23.2	22.3	22.0	22.5	21.5	21.8

Table 4.2: Gripper fingers trajectory test obtained centers for all 6 observations, in (mm).

Then, the coordinate difference between the centers O and o were obtained, to check for self-centering accuracy of the gripper. Additionally, the distances between the center and the a, b, c triangle vertices were calculated, to check if the spacing between the fingers when in the *closed* position were similar for all observations. The computed distances and difference between maximum and minimum distances registered across all observations are presented in table 4.3.

The results indicate that the repeatability of the gripper movement towards the center is smaller than $0.5mm$, which is enough to guarantee the centering of the part to grab. The precision of the finger's positioning is smaller than $1.5mm$ which is sufficient for the current task of grabbing pans and lids with $7mm$ diameter, although leading to some uncertainty regarding the damaging of the samples. Both of these values were also influenced by the human error when registering finger positions, so there could be some variation due to the position marking method used.

Distance (mm)	Observations						Max. Difference (mm)
	1	2	3	4	5	6	
$\overline{Oo}$	0.2	0.2	0.4	0.0	0.4	0.4	-
$\overline{oa}$	8.0	8.3	8.2	8.3	8.4	8.2	0.4
$\overline{ob}$	8.7	7.5	8.1	8.4	7.5	7.6	1.2
$\overline{oc}$	8.1	7.8	7.8	6.9	6.9	8.2	1.3
$\overline{ab}$	14.7	14.9	15.8	15.3	15.4	15.3	1.1
$\overline{ac}$	13.6	13.3	12.6	13.3	13.3	13.1	1.0
$\overline{bc}$	14.8	13.5	14.6	14.2	13.8	14.5	1.4

Table 4.3: Gripper fingers trajectory test distances between points and maximum differences for all 6 observations, in (mm).

The second tests performed were to evaluate the reliability of the gripper in pick-and-placing the crucibles. The same routine was executed 20 times, and the position of the placed pan and lid were evaluated. A circle with the pan's diameter was drawn in a millimetric paper sheet placed on the workspace's floor, and the objective was to check if the gripper robot could place the pan exactly in this position, as well as the lid on top of the pan, and finally pick up the crucible set and return it to a tray.When placing the parts, the gripper was opened when the fingers where $2mm$ over the targets, a distance representative of the ones present during the stages of the sampling routine. Any attempt where any part was not grabbed, dropped or damaged was considered a failed task. Then, for every observation, the distance from the pan to the drawn target was measured in order to quantify the handling accuracy. This is an especially important output, because the position of the placed pan influences not only its posterior grabbing, but the powder dispensing success since the dispensing module will aim not at the pan, but at a set position, i.e. the target drawn (independent of the gripper's accuracy). The possible misalignment of the lid with its pan was evaluated by checking if the completed crucible set could be picked up by the robot without external help, being also a qualitative result. Finally, it was important to place the complete sample set in its destination, i.e. the tray for the finished samples. This was evaluated using the pan tray, by taking the set to the pan's original position and checking if it was correctly placed in the slot.

For all 20 observations, no part was dropped, no damage was detected and all complete sets (pan and lid) were taken to their slot in the tray. Figure 4.3 is one of the 20 almost identical results, where the target drawn and the pan placement are indiscernible. The points surrounding them are the markings done to record the positions with the gripper at *home* position and *closed* position (which have a much larger distance between them than the one in the previous experiment) and are used to obtain the centerpoint location while also verifying the accuracy of the fingers throughout their maximum range trajectory.

Since the results were very satisfactory, it was attempted to create a worse scenario for the gripper. To simulate an alteration of the balance or trays height, the previous test was repeated 5 times but now with the parts being dropped from $5mm$ and not $2mm$. This gives more risk of error since the part has a larger distance to fall and there is also a possibility of it bouncing upon contact with the floor. Still no parts were damaged and the lid still landed on top of the pan accurately enough that the couple was picked up. The most notable difference was in the misalignment of the pan and the target, which is due

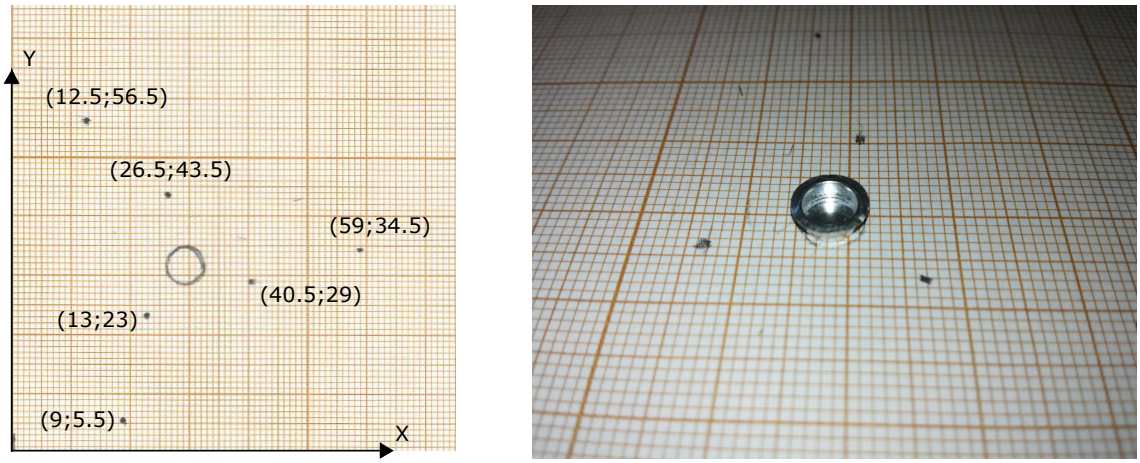

Figure 4.3: Gripper handling test results when placing the parts $2mm$ from the target surface.

to the 2 factors mentioned above. Figure 4.4 shows the worst case observed, in which the pan missed the target by about $2mm$. While this is enough to influence the powder dispensing accuracy, the error obtained was still small enough that the sampling could still happen without major problems.

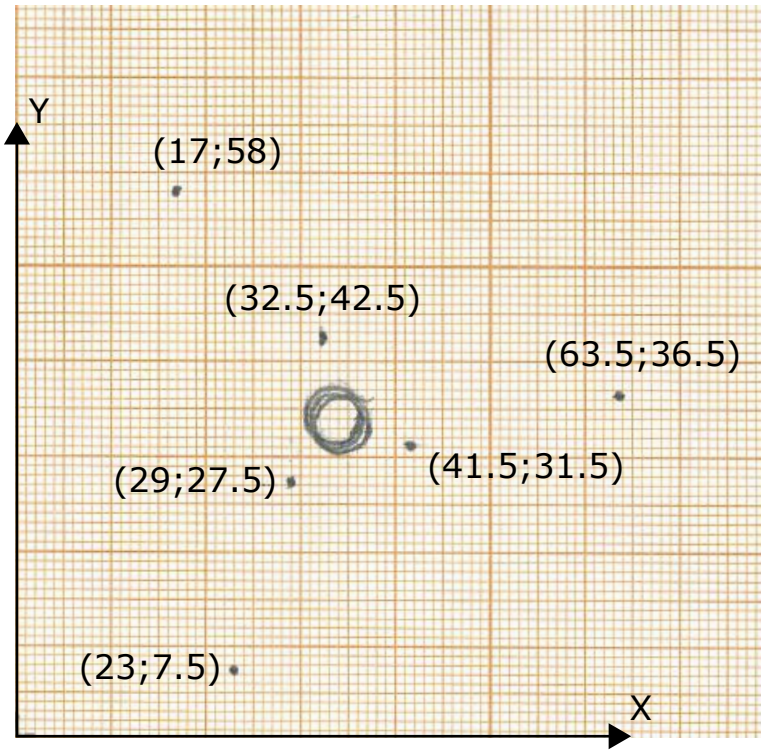

Figure 4.4: Gripper handling test results when placing the parts $5mm$ above the target surface. There is some observable difference between the target and the pan's position.

In both of the above scenarios, the shown coordinates for the triangle vertices were used to compute the distances between the centers. The resulting values were still below $0.5mm$, $0.2mm$ for the $2mm$ experiment and $0.4mm$ for the $5mm$ experiment, despite the larger distance between *home* and *closed* positions in comparison to the distances present in the first gripper experiment.

It must be noted, however, that for all gripper experiments the methodology used has some limitations regarding the position marking. For more reliable conclusions, another method such as laser position

sensors could be used, to mitigate human error and variations resulting from the marking tool.

After these tests, the conclusions drawn indicated that the gripper was sufficiently reliable to be used in a full system test. When testing both modules simultaneously, the gripper's performance, if poor, could negatively influence the dispensing accuracy, due to pan placement variations. Given how accurate it has shown to be, the module was considered successful and able to reliably place the pan in the right position for the dispensing module and transport the samples around the workplace with precision.

4.2 Carousel Transport

To evaluate the workspace B transportation method, an experiment was carried out to check if the weighing of a protruding crucible was precise and repeatable. 4 pans were placed on different positions in the carousel simultaneously and the stepper was ordered to move those pans to the position over the balance, so a mass was measured.

First, the pans were placed with 3 empty positions between each pan position. After all 4 pans' masses were measured, the stepper was ordered to perform a full rotation clockwise and another 4 measurements were registered. Another full rotation clockwise was made and 4 mass measurements were registered, and the slight misalignment of the pans with the balance were beginning to show effects on the weighing precision. The carousel was rotated to its reference position (by rotating the stepper counter-clockwise twice) and another 4 measurements were taken. The 2 rotations and 8 measurements were performed again, now for anti-clockwise direction and the misalignment was notable. The masses obtained are show in table 4.4. For reference, the average mass obtained for the pans in the balance without the carousel is around $41mg$.

Mass (mg)	**Rotations**						
	None	**1 Clockwise**	**2 Clockwise**	**None**	**1 Counter-c.**	**2 Counter-c.**	**None**
Pan 1	41.2	42.2	22 to 23*	41.2	44 to 46*	23 to 25*	38 to 43*
Pan 2	41.3	41.3	25 to 26*	41.1	41.1	24 to 26*	41.2
Pan 3	41.4	41.3	34 to 35	41.3	41.3	26 to 27*	41.4
Pan 4	41.2	41.0	24 to 26*	41.1	31 to 34*	25 to 27*	41.2

Table 4.4: Pan masses measured (mg) during the carousel weighing test with 3 empty slots between pans. It is easy to note the loss of precision even after only 1 full rotation. *Masses are displayed as ranges because the balance could not stabilize.

Note that some measurements have a wide range due to the unstable mass value measured by the balance. This instability was created by the tilted pans due to the misalignment with the part placed in the weighing platform. It can also be resulting from the bending of the carousel or the tilting of the motor's shaft, making the carousel not stay perfectly horizontal and touch the weighing platform.

The same experiment routine was repeated, now with no empty positions between each pan, i.e., with all 4 pans in 4 consecutive positions, as illustrated in figure 4.5, where the sliding of a pan on the piece placed on the balance's weighing platform can be seen.

The measurements are shown in table 4.5 with similar negative effects of the 2 full rotations clearly showing.

After some basic observation of the results, it was clear than Pan 1 was slightly deformed or damaged

Figure 4.5: A detailed view of a protruding pan sliding onto the part placed in the balance. This is the method designed for sample weighing if using transport Module B.

Mass (mg)	**Rotations**						
	None	**1 Clockwise**	**2 Clockwise**	**None**	**1 Counter-c.**	**2 Counter-c.**	**None**
Pan 1	41.2	41.3	23 to 25*	41.2	43 to 47*	25 to 29*	41.3
Pan 2	41.2	41.2	24 to 28*	41.3	41.1	24 to 27*	41.3
Pan 3	41.3	41.3	25 to 26*	41.3	41.3	26 to 28*	41.2
Pan 4	41.1	41.0	40.9	41.2	40.2	31.2	41.0

Table 4.5: Pan masses measured (mg) during the carousel weighing test with no empty slots between pans. The loss of precision due to full rotations is still present. *Masses are displayed as ranges because the balance could not stabilize.

and it was providing poor results even after changing its position in the carousel. For this reason, the pan was discarded.

For a final experiment, the 3 remaining pans were placed with 5 empty positions between each of them. Then, 3 lids (each with about $10mg$) were placed on top of them to check if they would have much influence on the weighing precision. The same routine was performed (2 rotations clockwise and 2 rotations counter-clockwise) and the masses registered are shown in table 4.6. The most noticeable effect was the visible sliding of the lids out of the pans due to the ramp shape of the part placed in the balance. It made the pans tilt when going over it which was enough to shift the lids slightly out of place. This effect could compromise the ability to press-join the set, but it was not tested since the pressing operation was not implemented.

Mass (mg)	**Rotations**						
	None	**1 Clockwise**	**2 Clockwise**	**None**	**1 Counter-c.**	**2 Counter-c.**	**None**
Pan+Lid 2	51.6	52 to 54*	31 to 33*	51.7	48 to 51*	29 to 34*	51.6
Pan+Lid 3	51.6	51.8	35 to 39*	51.6	53 to 55*	34 to 39*	51.7
Pan+Lid 4	51.2	50.8	40 to 43*	51.3	51.4	34 to 36*	51.5

Table 4.6: Masses measured (mg) during the carousel weighing test with 5 empty slots between pans and with a lid on top of each pan. The effects of misalignment due to rotations are even more noticeable. *Masses are displayed as ranges because the balance could not stabilize.

It was concluded that in order to implement this transport module effectively, the carousel would have to return to its original position (with no rotations done in relation to the starting position), or a new stepper with higher precision should be used to rotate the carousel. In addition to that, the carousel itself, the parts that couple it to the stepper shaft and the part placed in the weighing platform would

have to be manufactured with a more precise method than 3D printing and using a new material, so there would be minimal bending or deformations that influence the weighing accuracy. One could even recommend a surface finish, to the pans are better held in the slots and their movement when going over the weighing platform is as smooth as possible.

4.3 Dispensing Module

To test the dispensing module some powders were acquired, whose components' names are confidential, so they are labelled from A to C. Their properties are factorized and quantified in relation to substance A. These properties are representative of powders that are commonly sampled and analyzed in laboratory and were gathered from [53] and other related but confidential sources. The substances and their relevant properties, meaning the ones that likely influence flowability, are listed below:

- Substance A (used as reference) has a wide PSD resulting in diameters between $0.1mm$ and $1mm$, which are rather large. The density of powder is $0.6g/cm^3$ when in bulk and $1g/cm^3$ when tapped, making it the heaviest powder used. Its powder form is considered cohesive.
- Substance B is characterized by a PSD that results in an approximate particle size range of $0.05mm$ to $0.2mm$. In terms of density, the relative values are $0.47g/cm^3$ (bulk) and $0.77g/cm^3$ (tapped). Some forms might have lower powder density.
- Substance C shows a narrow PSD with diameters between $0.05mm$ and $0.065mm$. It has a powder density of approximately $0.34g/cm^3$ when in bulk and about $0.48g/cm^3$ when tapped. It is described as a relatively free-flowing powder despite how fine and light it is.

4.3.1 Powder Surface condition

Before choosing the best parameters for the dispensing of the powder, it was important to check how consistent is the powder absorption done by the powder gun, depending on the condition of the powder in the flask. With the use of a very fine powder, substance C, 4 powder conditions were tested. These conditions represent possible changes and inconsistencies present in the pre-sampling processes, i.e. the powder source.

- The flask containing the powder could be full or almost empty, depending on the amount of powder available for sampling.
- The powder could be normally sitting in the flask or it could have been compacted due to bad handling or long idle time, making its density turn from bulk to tapped density.
- The powder surface could be flat or on an angle, with some powder adhered to the flask wall.
- Finally, the powder gun could create a hole after a certain number of times it absorbed powder from the same position and this lack of powder would probably change the reliability of powder handling. For this reason, the influence of this factor was also tested, by having the powder gun grasp powder from slightly different positions, avoiding the creation of a hole and then from the exact same position, forcing the creation of said hole.

To further test the worst-case scenarios, the dispensing task was performed with more than one of the described conditions present at the same time, for example, having small amounts of powder and it being compacted into the flask's bottom.

The output measured was the mass dispensed, not particularly its absolute value (since it would depend on density), but which of the following cases happened:

- the powder was not absorbed at all;
- the powder was absorbed and compacted in a way it created a slug in the powder gun, that could only be removed manually;
- the powder was absorbed in excess and a lot of it adhered to the outside of the powder gun's tip (i.e. it was stuck to outside walls) making cleaning it necessary;
- the powder was properly absorbed inside the powder gun's tip and did not create a slug, and it was properly dispensed.

Since it was somewhat complex to control the conditions of the powder, 5 observations were made for each combination of conditions to mitigate any unwanted variations that could occur when preparing the powder source. The objective of this experiment was not to optimize any parameters or absorption methods, but to find which of the powder surface states are important to keep as regular as possible, i.e. check if any of the described favorable conditions are requirements for the powder source.

After several observations, some factors were clearly more relevant than others. The volume of powder in the flask did not influence its absorption, as long as there was enough powder height to absorb before reaching the flask's bottom. About $1mm$ of powder was enough to absorb without having contact with the flask.

The slope of the powder surface had very little impact, since the diameter of the powder gun's tip is very small when compared to the change in height created by the angle present in the surface. The only true problem was if this slope made it so all the powder went to one side and the above-mentioned minimum powder height was not present, meaning low volume and slope could become a difficult powder condition, possibly resulting in no powder being absorbed.

Powder compaction was not an issue (with the tested powder and as long as it was a reasonable level of compaction) for absorbing some powder since it was always lifted and sucked into the tip regardless. However, it made slugs more likely and these are a huge difficulty in pneumatic solid dispensing. They can ruin the powder gun's effectiveness at pushing the powder out of it and, consequently, fully disable the dispensing module. This factor is then better to be kept at standard, i.e. not too compact but not too fluffy either, although it depends not only on the flask handling and the time it is kept open but on the powder properties themselves.

The hole created by successive runs had a major influence since it resulted in the intake of no powder at all, having similar effects to a low volume and slope condition, i.e., the gun has no product to absorb before reaching the glass. Also, by lowering the powder gun successively, trying to reach more product, some powder particles were adhering to the outside of the gun, since the created hole had a

similar diameter to the tip's outer wall. This meant it would be desirable to keep changing the absorption location for successive runs, to avoid reaching the flasks bottom without reaching the $3mg$, especially if there was few powder volume available.

To summarize, the conditions considered as requirements are:

- the powder should not be too compact to avoid the creation of slugs, so handling the flask with care is favorable
- there should be enough powder height, and not only mass in the flask, to create a sample with $3mg$ (or multiple $3mg$ samples if that's the objective)
- the powder gun should not try to absorb powder from the same point in the flask in successive runs

4.3.2 Dispensing Design of Experiment

Now that it is known which absorption conditions are important, some tests were performed to evaluate the consistency of the dispensing using the powder gun and its vacuum generator. It is therefore assumed in this experiment that the powder flask has enough powder height and the compaction is not present. As will be discussed later in this chapter, an optimum absorption pattern will also be searched for, in order to avoid picking powder from the same place and creating the unwanted hole in the powder surface.

An important objective was to quantify the amount of variability in mass dispensed depending on the parameters defined by the user: compressed air pressure, air blast time interval and distance from the powder gun's tip to the pan, for different powders. The interval of time for compressed air must be enough to create enough pressure inside the tip to dispense the powder, but too much time only promotes the splashing of the powder that is already inside the pan. The air pressure fed into the system directly influences the flow rate of air when the relay is activated, which can also cause splashing if it is too high. On the other hand, too low pressure might not even allow the dispensing to occur due to the forces that the powder particles apply on the wall (especially if the powder is cohesive and conducive to creating slugs). The tip cannot be too far from the pan, since it allows powder to spread during its descent. However, if this distance is too short, it promotes splashing of the powder already in the pan, and this effect is more noticeable if the pressure is high. A one factor at a time method was considered but given the possibility for large variations due to a certain combination of factors, a different Design of Experiment (DoE) was searched for.

A 2-level factorial design was used to evaluate how much of an influence in the dispensing these 3 factors and their correlations have. This would provide information about which factors are more relevant and in what ranges of values they should be at. It also provides a reliable way of finding optimum operating conditions for these 3 variables. Finally, it could show how robust our dispensing method is by quantifying the outputs variation in relation to the input factor changes, that is, how sensitive the system is to relatively small parameter changes [54].

A factorial design was chosen because "Factorial designs are efficient and provide extra information

(the interactions between the factors), which cannot be obtained when using single factor designs" [55]. For the mentioned factors, it is easy to understand that for smaller tip-to-pan distances, the effects of higher pressure or longer compressed air time interval will be more significant than if the tip is far from the pan. This combined effect of factors, called interaction effect, is reliably quantified by a factorial design.

For each powder, 8 combinations of parameters were used with the individual factors as low or high. For each combination, the total powder mass dispensed was recorded as well as the mass of powder that missed the crucible and was dispensed onto the balance weighing platform itself (i.e. particles that landed outside of the pan).

The reason for a full factorial is, since there are only 3 factors with 2 levels each, the amount of combinations is 8. Even with 3 repetitions of every combination, that means 24 observations for each powder, which is not excessive for this specific experiment. The option to use a 3^3 design (3-level) was considered but with a number of combinations equal to 27, it meant 81 observations for each powder, even running each combination only 3 times, which could be unnecessary for the purpose of our experiments. Besides the mentioned observations, centerpoint runs were performed, one at the start, one every 8 observations, and another at the end. These centerpoints are used to verify that similar results are obtained for replicated conditions [54] and to provide a measure of process stability and inherent variability while also checking for curvature. [55]

To guarantee that the changes in recorded mass depend only on the dispensing and not the powder absorption, before every observation the powder bottle was shaken to create a new flat surface with no compact power or hole left by the powder gun. This was done as best as possible to remove the variable present in the powder source, to have valid results in the experiments with the dispensing itself, in other words, the expelling of the powder from the powder gun into the pan.

Other factors such as air flow, temperature and humidity were kept constant as much as possible, since the implementation of this method of dispensing is to be done inside a Hotte, where ambient conditions are maintained. Furthermore, the robot's trajectory, balance, pan and flask position were kept the same for every observation. Another important parameter is the volume of powder that can be contained in the powder gun. This volume is regulated by moving the lower part of the powder gun up and down in relation to its central part (by tightening the thread) which effectively changes the powder gun tip's Z position. For this reason, and because it does not influence dispensing consistency, only absolute mass dispensed, this factor was kept constant. It was set by an expert in powder gun usage for approximately $4mg$ of the most common powder and locked via the powder gun's nut. To further mitigate the effects of these factors, all observations were done in a randomized order and done in the smallest time period possible. One last factor that should be mentioned it the condition of the filter that is placed inside the powder gun. In the manual usage of this tool, the filter is changed every 20 to 100 runs depending on the powder, because with every absorption, some powder gets lodged in it, letting less air through and effectively changing the amount of pressure loss it creates. The influence of the filter's condition is very difficult to remove, but by doing the observations in a random order, the effects of the filter usage should be minimized.

To summarize, this factorial design is characterized by:

- 3 process, quantitative, controlled factors each with 2 levels (inputs):
  - compressed air pressure referred to as ‘pressure’
  - compressed air blast time interval referred to as ‘air time’
  - distance from tip to pan referred to as ‘distance’
- 7 uncontrolled factors, intended to be kept constant:
  - Temperature,
  - Humidity
  - Air flow
  - Powder gun tip volume
  - Powder surface condition
  - Pan position in the balance
  - Filter Condition
- 2 regular, quantitative responses (outputs):
  - powder mass dispensed referred to as ‘dispensed mass’, with optimum as $4mg$ and with the lowest variation possible
  - powder mass that missed the pan referred to as ‘wasted mass’ that should be minimized, so as close to $0mg$ as possible

After some initial testing of the dispensing mechanism, it was experimentally determined the values that would be used as standard for each factor.

For pressure, since the vacuum generator’s operating compressed air pressure ranges from $0.1bar$ to $0.3bar$, the values used were $0.15bar$, $0.2bar$ and $0.25bar$, to avoid limit conditions but still have some significant variation.

For air time, to be able to create enough force to push the most compact powder, the circuit had to be inverted for at least $0.2s$ approximately, meaning compressed air should be acting on the powder gun’s tip for that minimum time in order to have reliable and generalized dispensing capability. To avoid excessive air blowing which could disperse the powder after it already has landed in the pan, this interval should not be larger than 1 second. The value set for low was $0.3s$, for centerpoint was $0.5s$ and for high it was $0.7s$.

Regarding the distance, having the tip too far from the pan would only increase the chance of missing the pan, since the powder would have more height to spread, so $10mm$ above the pan was considered maximum. The relay was actuated and the powder gun lowered into a pan with a very light powder, with a very high pressure ($0.4bar$). The powder started splashing around $Z = -57mm$ so this was the shafts Z coordinate that resulted in the minimum distance possible without blasting powder out of the pan, even when setting the value of pressure as high. After measuring the Z coordinate corresponding to touching

the pans base, set as $Z = -62mm$, one can compute $5mm$ as the minimum distance (from the pan's base to the tip) for that powder to be blown out of the pan. The distances defined as low and high were then, $6mm$ and $8mm$ respectively, resulting in a standard distance of $7mm$, for a range of $1mm$.

Table 4.7 shows the created Design Matrix, using typical DoE notation: -1 means low, 0 means standard (for centerpoint runs) and $+1$ means high. The combination column is used for sorting, but the order of the observations will be randomized. However, the centerpoint run order is not randomized as they are there as guardians against process instability [55].

Combination No	Distance	Pressure	Air Time
0	0	0	0
1	1	1	1
2	1	1	-1
3	1	-1	1
4	1	-1	-1
5	-1	1	1
6	-1	1	-1
7	-1	-1	1
8	-1	-1	-1

Table 4.7: Design Matrix for the dispensing experiment.

The masses measured were registered and means, standard deviations and coefficients of variation were calculated for each powder. The data was then graphically represented in DoE scatter, mean and standard deviation plots. The DoE scatter plots allow for a quick identification of outliers in the experiments, very useful in the current implementation to detect samples with masses much smaller than $3mg$, a good indication of a slug occurrence. These plots also give a general idea of the response variation, i.e., if it is obvious that a level of a specific factor leads to a lot of mass outside the pan, then that level should be avoided in future implementations. The DoE mean plots are useful to check which factors have the most significant impacts on the responses. With them, it is possible to exclude some of the factors in a redesigned model, in favor of spending resources fine tuning the more important factors. It is valuable tool in the studied case since it can prove that, for example, the pressure of the compressed air does not influence the response, which removes a requirement from the installed system – keeping the pressure from $0.1bar$ to $0.3bar$. They can also be used to easily quantify and compare the amount of powder dispensed outside of the pan, giving an indication of the best parameters to increase dispensing accuracy. The DoE standard deviation plots are used to check how much variation occurs in the process result depending on the parameter value. This is especially important when trying to evaluate variation in powder dispensed, which is desired to be as low as possible.

4.3.3 Absorption Routine

While evaluating the dispensing of powder into the pan, it was important to establish a pattern or path of the powder gun's tip inside the product source that would reliably absorb the right volume of powder and without compacting it.

The first powder tested was substance B, an easy to handle powder and with a full flask, so to avoid

any influence of having a low powder volume available. The dispensing module would run normally, taking powder in, passing through the brush and the anti-static ring, activating the inversion relay at the balance and returning to the flask. Figure 4.6 shows the scatter plot of masses dispensed using the single absorption and dispensing approach, and the large variations in mass are clear. The number of samples with masses not between $3mg$ and $5mg$ is quite high, independently of the levels chosen for the parameter. Figure B.1 demonstrates that the standard deviation of masses dispensed is never smaller than $1mg$, which is not satisfactory. The mass dispensed outside the pan, illustrated in figure B.2 is also frequently higher than $0.2mg$.

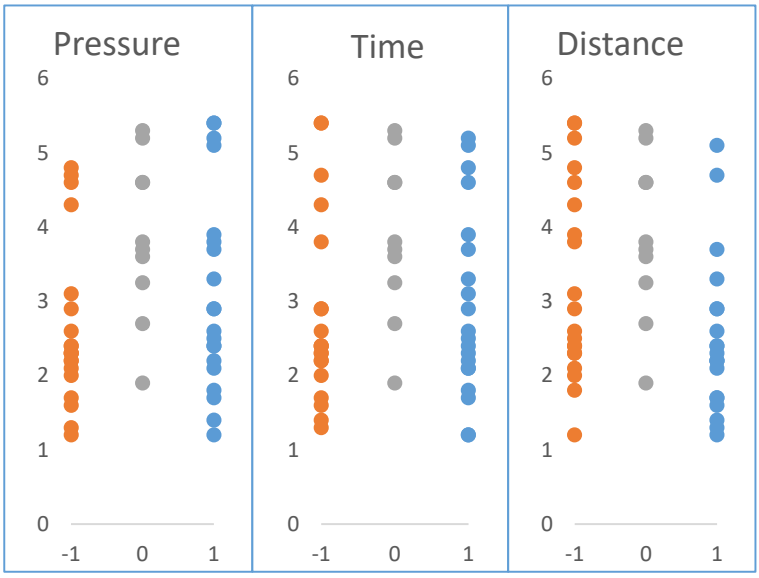

Figure 4.6: Substance B total masses dispensed (in (mg)) DoE scatter plot. The very wide range of powder masses is obvious, meaning this method cannot guarantee samples with valid mass.

This meant that it would be impossible to ensure a precise dosing of powder, regardless of how much fine-tuning was done to the parameters, and a new dispensing approach should be used.

The powder gun tip height was shortened, making the volume smaller and now with an average mass of about $1mg$. Instead of a single dispensing routine dosing $4mg$ of powder, the routine was run multiple times, taking approximately $1mg$ of powder to the balance per run. This meant the master would stay on a loop until the mass measured by the balance was over $3mg$ and it would order the dispensing module to performs its task repeatedly until this target mass was reached.

To avoid the creation of the hole in the powder after some dispensing runs, the tip of the gun should not always absorb powder from the same coordinates. Therefore, a pattern was thought of and implemented in the robot routine. The first pattern tested was a simple square motion in the XY plane at a certain Z value, which would decrease (the shaft would go lower) with every repetition of the routine. Some powder would be absorbed every run, and depending on its mass, the powder gun would travel a different Z value:

- $mass < 1mg \Rightarrow Z_{delta} = 0.5mm$
- $1mg < mass < 2mg \Rightarrow Z_{delta} = 0.2mm$

- $2mg < mass < 3mg \Rightarrow Z_{delta} = 0.1mm$

The test was performed 10 times, and each time the robot would perform multiple dispensing routines until $3mg$ were reached. The parameters set for air time, pressure and distance were kept standard (labelled as '0', centerpoint runs). An important note to add, the first Z value was set to $Z = -111.5mm$, and the bottom of the flask was at $Z = -113mm$. This meant there was only $1.5mm$ height of powder available. The mass measurements of the experiments are shown in table 4.8, as well as the final Z coordinate (to have an idea of how much powder it was still possible to absorb).

Sample No	**Iterative Mass (mg)**					**Z_{final} (mm)**
1	1.0	1.2	2.2	3.7		-112.0
2	1.7	2.1	2.7	4.1		-111.9
3	0.6	2.0	3.3			112.1
4	0.3	0.9	**5.1**			112.5
5	0.0	0.2	**6.3**			112.5
6	2.6	2.8	2.9	3.4		111.8
7	1.0	1.0	1.1	2.9	4.1	112.2
8	1.8	1.9	2.8	3.2		112.0
9	1.6	1.7	3.0			111.9
10	1.5	2.4	2.9	3.9		-111.9

Table 4.8: Powder masses (in mg) using the iterative dispensing method used to narrow the powder mass range in each sample. The final Z coordinate shows how far the tip was from the bottom of the flask, which is related to the amount of powder absorbed. The highlighted masses correspond to overloaded pans.

It was clear that $0.5mm$ for Z_{delta}, occurring when the mass was smaller than $1mg$, was too large, since the runs where the shaft had lowered $1mm$ ($Z_{final} = -112.5mm$) created overloaded pans (with $mass > 5mg$). Disregarding those runs, the samples created had valid mass, so this XY pattern + Z change method had potential. One thing that was observed and not quantifiable, was that after filling up, the powder gun tip would continue to travel along the pattern and it would push some of the powder to the sides of the flask, making that powder impossible to grab on the next runs.

To increase the amount of powder reachable for each Z value, the pattern was changed to a circular pattern with the diameter of the flask, allowing the powder gun's tip to reach further and also minimizing the powder pushing effect described previously. Any powder pushed inside could be absorbed during a posterior run, by reducing the diameter of the trajectory's circle. Another change made was, instead of having discrete intervals for mass measurements and three different values of Z_{delta} ($0.5mm$, $0.2mm$, $0.1mm$), the robot would now calculate its Z_{delta} depending on the mass dispensed using equation 4.2:

$$Z_{delta} = \frac{3 - mass}{10} \tag{4.2}$$

This method and the changes made were used for substance C, which has different handling properties. The same full fractional design was used, 3 factors with 2 levels each, 8 combinations each observed 5 times, 6 centerpoint runs, same values for standard, high and low, measuring mass dispensed and mass outside of the crucible. The only difference from the experiment with substance B is that, due to the new iterative method, every mass is registered, from the first run until the last, where

the mass reached $3mg$. One should also mention that because only $1mm$ of powder height was in the flask, the initial Z value was set to $-112mm$, to avoid initial zero mass runs (expected if the starting Z was kept at $-111.5mm$).

All 46 resulting samples had powder masses between $3mg$ and $5mg$, as is shown in figure 4.7, and the minimum Z value ($-113mm$ i.e. the bottom of the flask) was only reached once, so all created samples were valid and the method was powder efficient. The masses recorded outside of the pan were so small that for all 8 combinations and centerpoint run combined, the measurement was always smaller than $0.2mg$.

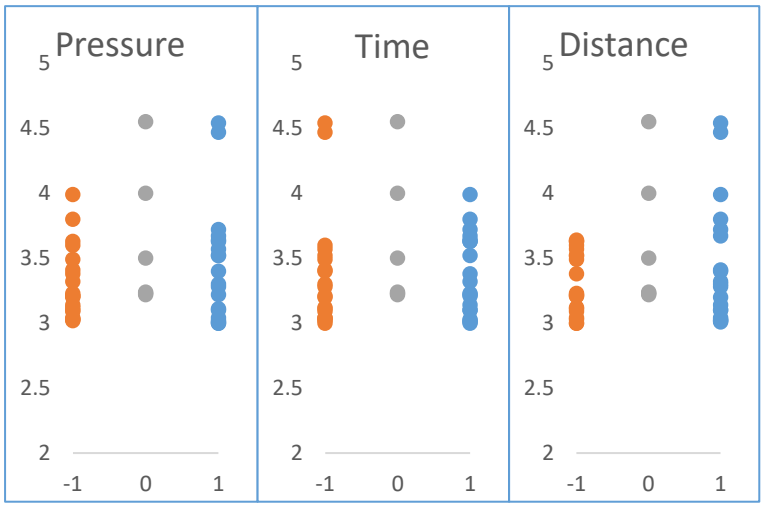

Figure 4.7: Substance C dispensed powder masses (in mg) DoE scatter plot

Despite this apparent success, this method had a major flaw due to the sliding of the tip on the powder surface during the circular trajectory. It had as a requirement a frequent filter change, in this case once after every 9 observations (right before every centerpoint run) because some powder would start to accumulate in the filter and the powder gun would lose its suction power. Since the filter change could not be automated easily, the system could not run overnight without human intervention, so a new absorption routine had to be came up with. This experiment however, proved that the iterative dispensing idea was successful and that even with changes in the parameters, the system was robust enough to avoid large variations in the mass dispensed to the pan.

To try to minimize the clogging of the filter due to rubbing on the powder and to avoid pushing the powder to the flask walls, a new absorption technique was implemented. Instead of having the trip travel in the XY plane with a constant Z and only iterating this Z value in between runs, the tip would go to a specific (X, Y, Z) point and not move around the powder surface. First, it would go to the center of the flask (standard X and Y values) with a certain Z coordinate. The next run, the X value would change to $X_{original} + X_{delta}$, where X_{delta} is the radius of the circle used in the trajectory of the previously described experiment. On the next run, the value of Y also changes to $Y_{original} + Y_{delta} * 0.5$ and X becomes $X_{original} + X_{delta} * 0.5$. These coordinate adjustments go on 8 times, meaning 8 points around the center, describing a square shape with length of $2 * X_{delta} = 2 * Y_{delta}$, thereby creating 9 small holes for each Z value. After these 9 runs on the same Z coordinate, Z_{delta} is applied, and the powder gun

returns to ($X_{original}; Y_{original}$) with a lower Z value, obtained by $Z = Z_{original} + Z_{delta}$ (where Z_{delta} is negative and could be customized depending on the powder's density).

This pattern provides the benefits of moving around the surface with a constant Z, by making the most out of the available powder, while avoiding the issues observed previously due to the brushing of the tip across the surface. The biggest issue expected with this method would be the conducive compaction of the surface since the tip would have to sink slightly to absorb the powder. In an attempt to avoid this predicted outcome, the vacuum generator was opened and manually set to maximum vacuum power. This would allow the powder gun to absorb powder from a greater distance, minimizing the risk of powder compaction under the tip's rim.

This method was first used with a mixture of substance A as a mock API and substance B as the polymer, labelled as powder AB. The same 8 combinations of parameters were used, the ranges kept constant but some standard values changed. To help the removal of all the powder inside the tip, to minimize the risk of creating slugs, instead of one air blast, three air blast where used, with the same $0.5s$ as standard. After some initial runs, the standard distance to the balance was also changed. It was increased by $2mm$ (from $7mm$ to $9mm$) to compensate for the higher number of air blasts. Without having the tip further from the pan, the compressed air could make a larger volume of powder splash. However, there is no correct universal setting for this distance, since it depends heavily on the powder and its condition. The optimum distance that reduces splashing to a minimum, while maintaining the pressure, will change considerably with powder properties, so a compromise value was the best that could be reached. The pressures used stayed the same, with the standard of $0.2bar$ and a range of $\pm 0.05bar$.

Each of the 8 combinations was observed 3 times and 4 centerpoint runs were made. Of the performed 28 observations, presented in figure 4.8, all samples had valid powder mass (i.e. from $3mg$ to $5mg$ of powder) and only in 2 observations Z was decreased, meaning the majority of the samples was created with less than 10 routine runs (the 9 holes were made on the same surface and Z stayed constant).

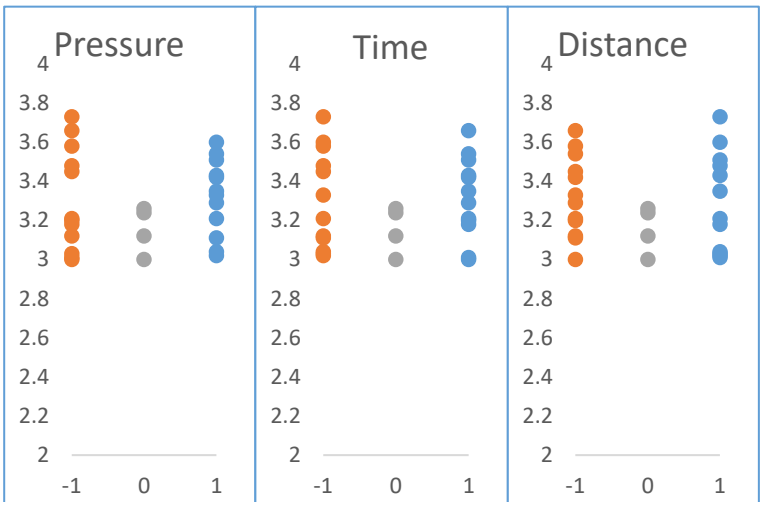

Figure 4.8: Powder AB dispensed masses (in mg) DoE scatter plot

This shows how powder efficient and effective the absorption method is. The samples created also had very similar masses, as seen from their small standard deviations (figure B.4, meaning this method could be used with a narrower range (e.g. from $3mg$ to $4mg$)

Regarding the filter status, it was cleaned after 18 runs (after 2 repetitions of the 8 combinations) and it did not seem clogged with powder, so its cleaning was possibly unnecessary.

The biggest unsatisfactory result was in the powder mass that missed the pan (illustrated in figure B.5), averaging about $0.08mg$ per full run (after all iterations to reach $3mg$), which although not problematic, showed some room for improvement in the dispensing itself. One can observe from the graph that, while pressure does not have a significant impact on the powder dispensed outside the pan, having a short air blast time and less distance between the tip and the pan improve dispensing accuracy.

The same exact experiment was performed for another product, with substance A as mock API and substance C as the polymer, labelled as powder AC.

The results were not as satisfactory as with powder AB, since 5 of the 28 samples created (over 17%) had less than $3mg$ of powder in them, whose worst cases can be seen in figure 4.9 as outliers.

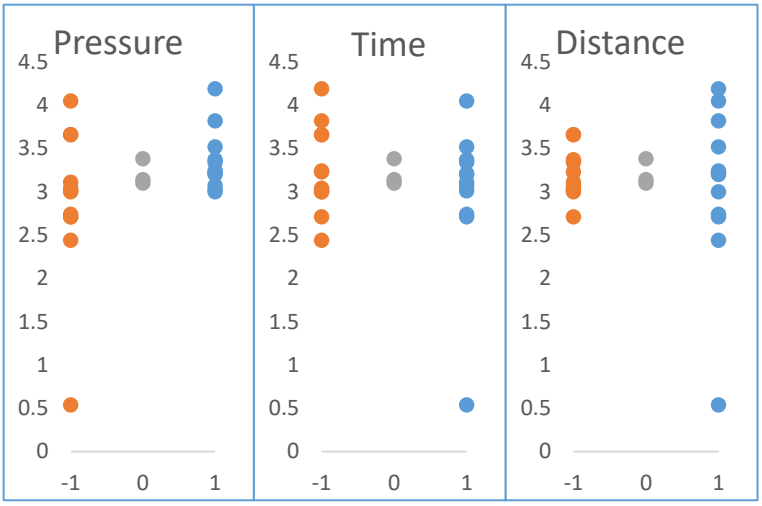

Figure 4.9: Powder AC dispensed masses (in mg) DoE standard deviation plot

These uncompleted dispensing routines were due to occurrence of slugs of powder inside the gun, whose removal lead to the need to stop the module. Some slugs removed from the tip and a slug that was dispensed to the pan, can be seen in figure 4.10.

This frequent slug occurrence could be due to substance A being heavy and cohesive, which required the tip to get too close to the powder surface, sometimes even dipping in it. Since substance C has a smaller minimum particle size, this explains the increased clogging of the filter. This combination of compacted powder inside the tip and the higher pressure loss due to a clogged filter, made it so the pressure of the air blast was not enough to release the powder. The powder gun would jam and stop dispensing, leaving the pan with less than $3mg$ of product.

In addition to this slug frequent occurrence, there was also the need to change the filter 3 times, making the idea of running the system without supervision impossible in practice, since it how be very difficult to implement an automatic filter change for this dispensing tool.

Figure 4.10: The figure on the left shows some powder slugs manually removed from the powder gun's tip when it jammed. Even after being dropped, some keep their cylindrical shape due to how compact they are. On the right, a slug that was pushed out of the gun during an air blast and stood vertically in the pan. It can compromise posterior dispensing and lid placement.

The resulting masses left to the balance's platform were also larger than with powder AB (shown in figure B.6, averaging about $0.2mg$ per dosing of $3mg$, meaning over 6% of the powder dispensed.

Using the results for these 2 representative powders, the best parameters were chosen. The standard deviation of final mass was computed for each combination, and the smaller it was, the more robust the dispensing would be. The mass wasted outside of the pan was also to be minimized, so a simple metric 4.3 was used to evaluate each combination of parameters:

$$metric = 0.5 \cdot mass_{wasted} + 0.5 \cdot \sigma_{finalmass} \tag{4.3}$$

The combination that gave the best results for the powder with substance C (powder AC) and second best for the one with substance B (powder AB) was (-1,-1,1), meaning short air blast time ($0.3sec$), shorter distance to the pan ($8mm$) and higher pressure ($0.25bar$). In spite of this result, by analyzing the entirety of the DoE plots, one can conclude that the variability caused by which powder is dispensed and by the dispensing routine is more significant that the one resulting from parameter changes. This is a favorable output, since it demonstrates that the dispensing repeatability, using the absorption method arrived at, is quite insensitive to alterations of these 3 input factors.

4.4 Full Sample preparation

These parameter values and the *'9 holes'* absorption pattern were used in a full system test, where the master orchestrated the two robots and the balance, to create 3 samples of a given powder without human intervention. 3 pans and 3 lids were placed in their trays at the start and the powder flask set in its determined position. The objective was to create a total of 12 samples, using 4 different powders and only changing the flask every 3 samples and providing new pans and lids, to evaluate the overall functionality of the implemented workspace.

To note, the available product in each flask was not the same, so the height of the powder surface was different for every 3 samples. To avoid having to change the initial Z coordinate for the dispensing robot to get powder from, an extra routine was programmed in the dispensing module and the master. To put it simply, for the first sample of each powder, after the pan was in the balance, the master would

order the dispensing robot to find powder, meaning instead of running the above mentioned developed patterns, it would just go to the center of the flask, try to absorb any powder mass and then dispense it. If no powder was measure in the balance, it meant the powder surface was not reached and the Z coordinate would decrease, so the powder gun would go even lower. This loop is repeated until some powder is absorbed and dispensed, and the master would then start sending the *'get powder'* order, making the robot perform the designed absorption pattern.

Workspace A was used simply because it is the one where the transport module has less influence on the sample weighing, which is what is used to check if the powder dosages were valid, especially important with the programmed iterative dispensing runs. Since there is no carousel over the balance and the transport is done by the gripper, it is easy to detect any failure with the dispensing module.

The powders used were similar to the ones used in the dispensing module tests, but with known proportions of mock API and polymer, listed in table 4.9.

Powder	Mock API	Polymer
1	substance A (5%)	substance B (95%)
2	substance A (15%)	substance B (85%)
3	substance A (10%)	substance C (90%)
4	substance A (15%)	substance C (85%)

Table 4.9: Powders used for the full system experiment, where the proportions are relevant for further analysis.

The results were somewhat expected due to the previous results with these same powders. 3 samples of both powder 1 and powder 2 (the ones with substance B) were obtained, with minimal mass dispensed outside of the pan. For powder 3, only 2 samples were valid, with the last one having only $2mg$, due to the creation of a slug that jammed the powder gun. As for powder 4, no sample was created, since all attempts resulted in a jammed gun, possibly due to the higher percentage of substance A or due to an already used filter. The same full system test was attempted, with a new filter and with the reverse order (starting with powder 4 and ending with 1), and after 3 slugs in the powder gun without a single sample successfully created, it was confirmed that substance C and substance A together were not dispensable with the current vacuum and compressed air pressures. This meant new changes had to be made in order for the system to be able to dispense cohesive and sticky powders without jamming.

With the aid of a flow sensor, the air flows during vacuum and compressed air actuation were measured, with the powder gun without filter, with a new filter and with a used filter. It was observed that even with the powder gun plugged, the air flow was not zero. This meant there were leaks in the pneumatic system. The pressure loss was due to wear in the nut that connects the powder gun with the air pipe and it was solved with the use of an O-ring. Since most samples would be prepared when the filter has already been used, the optimum pressures for the desired flow during that condition were searched for. Vacuum was set in the generator to maximum and the compressed air regulated to create a flow of $0.1l/min$, value that was enough to push most plugs of powder out, while not making very light powders splash excessively. With these values of pressure set and the other parameters set as the best values obtained from the experiments done previously, a new full system test took place. This time again start-

ing from powder 4 to powder 1 and then continuing with powders AC and AB, just to widen the range of formulations. This meant a total of 18 samples of 6 different powder combinations with no filter change or human intervention to clean or unstick the powder gun.

Figure 4.11 shows the 18 samples created and table 4.10 the masses of powder measured, which are all valid. The last column has the mass of powder left in the balance after the creation of the 3 samples of each powder. In other words, it is the sum of the masses inaccurately dispensed after 3 runs, registered with less decimal places since it is only used as an indication of the amount of powder wasted from each flask.

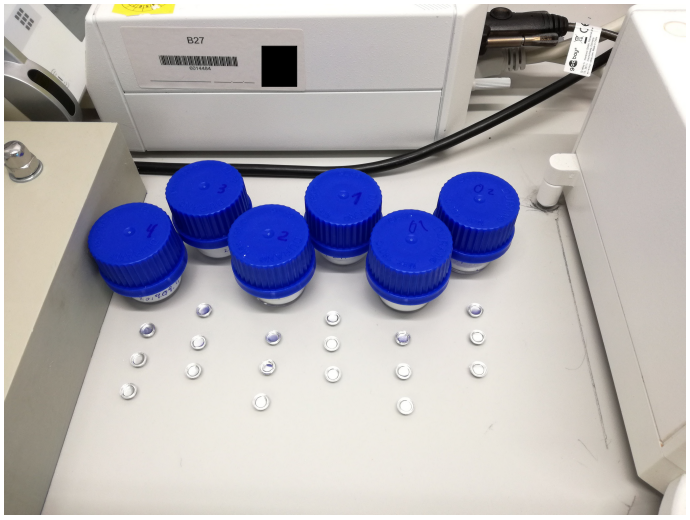

Figure 4.11: 18 samples created with final implementation: dispensing parameters, absorption routine and flux adjustment

Powder	Sample	Sample Powder Mass (mg)	Total Mass Wasted (mg)
1	a	3.02	0.4
	b	3.79	
	c	3.84	
2	a	3.45	0.3
	b	3.42	
	c	3.18	
3	a	4.88	0.1
	b	3.32	
	c	4.74	
4	a	3.82	0.1
	b	3.74	
	c	4.92	
AC	a	3.37	0.2
	b	3.41	
	c	3.43	
AB	a	3.22	0.2
	b	3.49	
	c	3.07	

Table 4.10: Powder masses (mg) for the 18 samples created with final implementation during the full system test. As can be seen, all samples have valid masses and the mass dispensed inaccurately is small for all powders.

These results were very positive but not without flaws. The most relevant issues were the amount of powder that landed in the pans rim and not it's bottom and the influence of the dispensed powder's height when placing the lid (which influences the posterior pressing), both of which are not easily quantifiable.

The system ran for less than 3 hours, giving an average of 10 minutes per sample prepared. Note that the first sample of each powder always takes longer (between 5 and 15 minutes, depending on the powder volume in the flask), since the dispensing robot must find the powder surface. The master has the dispensing module run its *'find powder'* routine a few times before absorbing any powder, slowing down the process. Compared to the average time of a manual sampling, about 5 minutes, the other 2 samples of each powder take about the same time made by the system as the ones made by the analyst. The average 5 minutes are mostly due to the iterative process of getting enough powder, although the robot's speed is set quite low, for safety, and could be increased.

This means that manually, an analyst working exclusively in sample preparation, can create about 96 samples in the 8 hours of work every day. Since the system can work 24 hours per day, it can provide 144 samples in that time. This means that, even though the system takes longer per sample, it has a higher throughput overall, because it can run during non-working hours. This is even more noticeable when dealing with potent products, which require a lot more time for the human to get prepared before performing the operations, and has no impact in the robots' routine.

If a sensor to detect the proximity of the powder gun's tip to the powder surface was added, the throughput would increase significantly and be less dependent on the powder volume in the source. Supposing the powder surface was the same and there was no need to iteratively find it, the system would have the same speed as the analyst, but with triple the availability, further increasing the gap in throughput.

It must be mentioned, however, is the lack of the pressing task in this implementation, which could add about 1 or 2 minutes to each sample.

4.5 DSC analysis of prepared samples

Of the created samples during the full system experiment, the 12 from the powders with known substance proportions (powders 1 to 4) were analyzed in the DSCr, to evaluate their validity. A sample of each powder was prepared manually by an analyst and were also analyzed in the DSCr. The resulting plots from the DSC analysis of the prepared samples were evaluated by the analyst, and the plot resulting from the manually created sample was quite similar to the ones resulting from the sample prepared with the autonomous system. This can qualitatively show the repeatability of the automatic sample preparation, since for the same powder, the samples created provided very similar results and those results were close to the ones used as reference, i.e. the ones obtained from manual preparation.

After this subjective comparison, the relevant temperatures were studied, i.e. T_g and melting temperature, since these were the main values obtained from a DSC test. Knowing the T_g's of each of the substances that constitute the samples and their proportions in each powder, it is possible to estimate the T_g's of the powders used for sampling. The known substance T_g's, obtained from [53] and shifted by a value K, are the following:

- substance A: $31°C$ to $38°C$
- substance B: approximately $182°C$
- substance C: $125°C$ to $128°C$

Given the proportions mentioned in table 4.9, one can estimate the expected T_g's of the mixture powders, although their values are not always exact weighed averages of the T_g's of their components, since it depends on the interactions between substances. Assuming they were however, for simplicity, the T_g's of the sampled powders were computed and are presented in table 4.11.

Powder	Substance A (%)	Substance B (%)	Substance C (%)	Estimated T_g (°C)
1	5	95	0	174.6
2	15	85	0	159.9
3	10	0	90	117.3
4	15	0	85	112.7

Table 4.11: Expected T_g's of the powders sampled during the full system experiment, in $°C$.

From the graphs obtained from the three samples of each powder, the experimental T_g's (shifted by the same K value) were computed, using the DSCr's software. The obtained values are presented in table 4.12, where the previously estimated T_g's are shown for comparison.

Powder	Sample a T_g (°C)	Sample b T_g (°C)	Sample c T_g (°C)	Estimated T_g (°C)
1	172.9	172.0	169.3	174.6
2	158.0	158.5	159.3	159.9
3	117.1	116.6	116.5	117.3
4	115.2	114.5	112.6	112.7

Table 4.12: Experimentally obtained T_g's from the samples prepared by the robotic system, in $°C$.

Comparing the values in the table, it is clear that the T_g's values are very similar and even someone who is not an analyst could determine which powder corresponds to which graphs. Further improvements such as the uniformization of the powder and a more optimized cleaning process will only improve the quality of the samples, making them even more reliable for analysis.

The melting peak temperatures appearing in the DSC analysis graphs are also close to the ones taken from [53], both of which were shifted by a constant value. The values taken from [53] are listed below, for the two substances that have a melting temperature.

- substance A: $167°C$
- substance C: $140°C$

Powder 1 graphs show melting peaks at approximately $161°C$ and powder 2 shows $164°C$. Both are very similar to the melting temperature of substance A ($167°C$) with powder 2 showing values closer to it, since it has a higher percentage of substance A. Powders 3 and 4 show two melting peaks. A large peak

at around $140°C$, that corresponds to substance C, and a very small one between $150°C$ and $160°C$, close to the value of substance A.

This further indicates that the DSC samples created by the implemented solution are valid and reliable enough to make decisions about the substances and proportions in the produced powders, improving the quality and speed of the drug manufacturing process.

Chapter 5

Conclusions

In this thesis, the concept of Pharma 4.0 was explored as a game-changer for the pharmaceutical industry, with the main opportunities for improvement indicating that automation could provide many benefits. The problematic of solid dispensing was studied, regarding both the physics behind it and its automation. A brief but thorough report of dispensing tools and market sampling platforms led to the conclusion that there is still no reliable end-to-end platform adaptable to all solid dosing applications.

The primary goal of this project was to implement a bulk solid dispensing and sampling platform with enough versatility to be used in other applications were product in powder form is handled. To achieve this objective, the assembled solution was modular, with each module performing its tasks in such a way that allowed for them to be used in a different environment.

The dispensing module implemented displayed the possibilities of using a pneumatic dosing method to fill DSCr crucibles but also for other containers where larger volumes of powder are to be dispensed and less accuracy is required. The absorption routine and the input settings arrived at presented great results in achieving the desired powder mass after few iterative dispensing runs. The accuracy of the dispensing, however, was not sufficient to guarantee that there was no cross-contamination. The experiments and discussed results provided ideas to improve the dispensing module, constituting important steps towards a reliable tool for small dosage of solids.

Both transport modules showed promising results in the handling of small fragile sample containers. The gripper robot transport had a very good performance at picking and placing the crucibles. With a better manufacturing technique, other larger and heavier containers could also be carried using this module. This transport approach provides admirable flexibility regarding origin and destination of the parts to carry, proving it can be adapted to other operations. The carousel has shown to be less independent as a module and have less adaptability to other applications. However, for this specific sampling task, the achievable speed and simplicity is much higher than with the pick-and-place approach. Although it was proven to be possible to hold the crucibles by their rims and weigh them by pushing them up individually, in order to this module to be effective, very precise dimensioning is necessary.

The Raspberry Pi used as master to orchestrate the diverse modules functioned as expected, causing no issues during the full system experiment. The cascade master-slaves methodology was successful at coordinating all the components, since the first end-to-end test only showed less satisfactory results caused by the dispensing module, which was readily fixed.

In the second iteration of the experiment, the system was able to create 18 valid samples without human intervention (with the exception of providing different powder sources and new sample containers, i.e. the system's input materials), meaning it displays good repeatability. The masses of both the

crucible and the powder were registered and outputted, letting the user specify how to handle the data. The system ran for 3 hours, and it was able to continue if necessary, demonstrating that it could function unsupervised. Since it has maximum availability, it evidenced a higher throughput that an analyst, even at lower robot speeds. Its robotic nature means its performance is not influenced by dangerous powders, making it a great tool to reduce the staff's exposure to them.

Concluding, the work developed achieved a fully automated system for crucible handling and powder dispensing, with fair dosing accuracy and good flexibility for new tasks. With the addition of more external tools and sensors, the repeatability and robustness of the implemented platform would rise and the complete automatic DSC sample preparation would be possible.

5.1 Future Work

After a thorough analysis of the results encountered during the experiments, it becomes clear that many improvements could be made to the implementation. Even to the most successful modules and methods, performance can always be improved with a few alterations. These changes and enhancements are thereby listed here.

- **Transport module A**

  To start, the gripper could be made more robust with the addition of induction sensors, since it would not need the balance confirmation that a part was taken from its origin and placed properly, reducing the master's algorithm complexity. The sensor could provide a direct feedback to the stepper and inform it to keep rotating and closing the gripper until the part was in fact grabbed. They would also detect if a part was dropped during the robot's movement, an important information for fine-tuning velocities and trajectories.

  As another improvement, building the gripper with a more durable material and adding a better position control (since the thin home switch could deform after some uses), would make the gripper perform well for longer without wear. Additionally, this would allow the fingers to be longer and thinner, giving them a better reach when working around the workspace's stations and permitting the usage of trays with more pans and lids per area.

  One request was to make it 'dust proof' so it would not become contaminated after several samplings. As it is build, smaller powder particles could be flicked across the workspace and soil the insides of the gripper, making it harder to avoid cross-contamination.

- **Transport module B**

  For future implementations, the carousel needs to be manufactured with better dimensioning in order to reach its full potential. It must be made of a rigid material that does not suffer from bending, factor especially important if other tasks such as pressing are to be implemented to work beside it. This and the usage of a higher quality stepper motor allows the carousel to stay perfectly horizontal, which will improve the accuracy of the weighing. If the assembly is very precise, the module's simplicity can prove to be the most ideal handling method for the specific DSC sampling task.

- **Dispensing module**

  To increase robustness, it would be desirable to add a way to determine if the powder was absorbed and not dispensed (i.e. the powder got stuck inside the tip in the form of a plug), so the false 'no powder was absorbed' information given by the balance was avoided. Added to this sensor, a way to command the robot to remove said plugs and clean the outside of the powder gun's tip.

  A proximity sensor would also improve the speed of the dispensing routine, by avoiding the iterations to find the powder surface. This was the major inhibitor of a higher throughput and a solution to it would be easy to implement.

  Another possible alteration is to replace the vacuum generator with a 3-position valve, connected to the vacuum and compressed air lab utilities and two electrical pressure regulators. This in conjunction with flow feedback from a bidirectional sensor in the powder gun's feeding tube, could provide means to maintain the air flow despite the filter degradation.

  To improve accuracy, a funnel shaped disposable object could help dispense the powder into the pan's bottom and not the rim or the balance. Of course, this adds another component to change this funnel after each dispensing.

  To avoid cross contamination, the tip could be washed and dried with nitrogen between samples and a more complex filter could be used to make sure no particles contaminated the next samples.

  All these improvements would be made to maintain a pneumatic dispensing method. However, the system could be tested with a completely different tool, using volumetric dispensing.

- **Master and global workspace**

  The major improvements to the master would be in the communication with more sensors other than the balance (the ones described above) and in the implementation of more complex feedback control loops. The addition of these control routines could make the different tasks faster and with less failed attempts, while providing more reliable automation and less need for supervision. If more modules are implemented, new communication channels and routines must also be added.

  A cleaning system could be added not only to the dispensing tool as mentioned, but to the balance and to the transport module, using vacuum to remove particles spread around the workspace and therefore minimize cross contamination.

  The addition of a press and a piercing tool would also be necessary to complete the automation of the entire sampling process. This would require a bigger workspace and a more complex master-slaves structure. After this is implemented, a fully automated system for DSC sample preparation can be achieved.

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Appendix A

Hardware Components

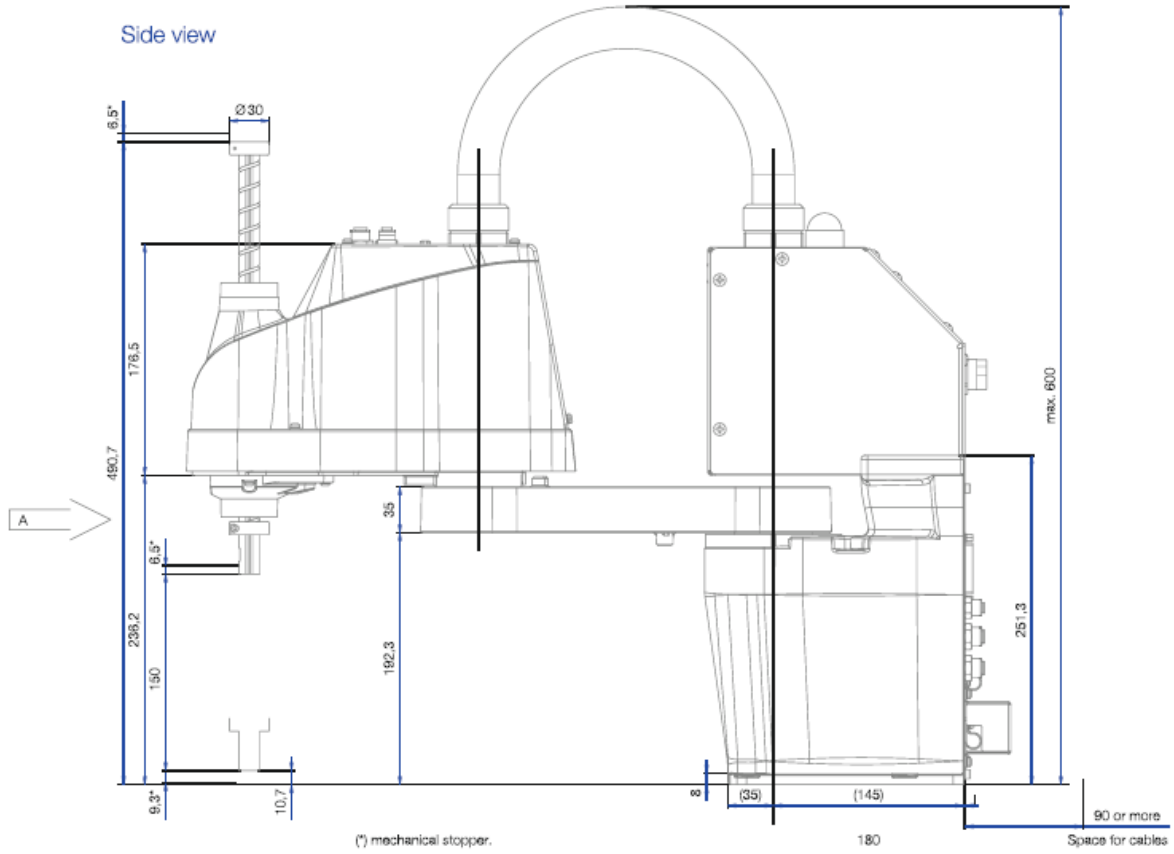

Figure A.1: Epson T3 SCARA robot dimensions side view.

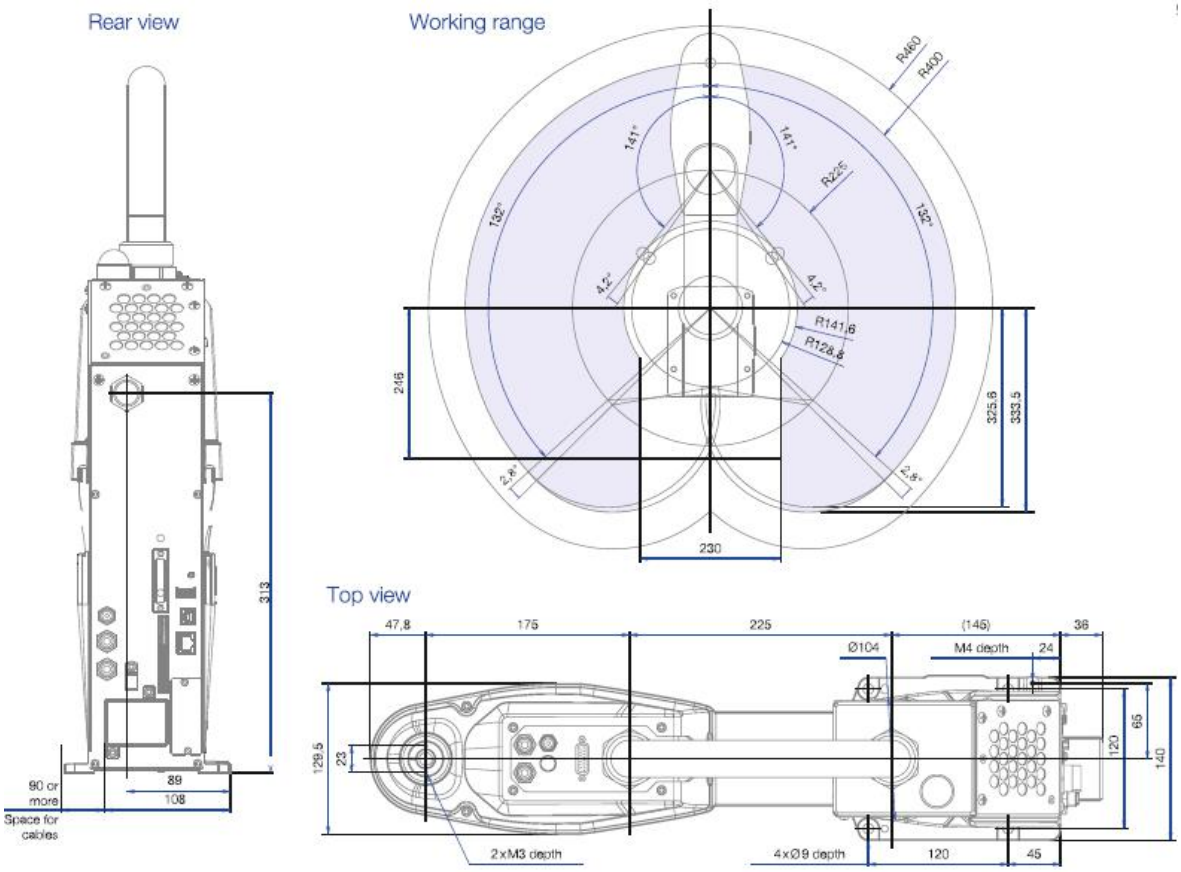

Figure A.2: Epson T3 SCARA robot dimensions top view.

Load capacity	1/3 kg
Horizontal range	400 mm
Vertical range	150 mm
Arm length	J1 225 mm + J2 175 mm
Orientation range	J4 +/- 360 °
Horizontal repeatability	J1, J2 +/- 0.02 mm
Vertical repeatability	J3 +/- 0.02 mm
Orientation repeatability	J4 +/- 0.02 °
Max. working range	J1 +/- 132 °, J2 +/- 141 °, J3 150 mm, J4 +/- 360 °
Max. axial speed	J1, J2 3,700 mm /s , J3 1,000 mm /s, J4 2,600 °/s
Mass moment of inertia	0.003 / 0.01 kg.m²
Power ratings	AC 100 V to AC 240 V
Weight	16 kg

Table A.1: Epson T3 SCARA robot specifications provided by Epson.

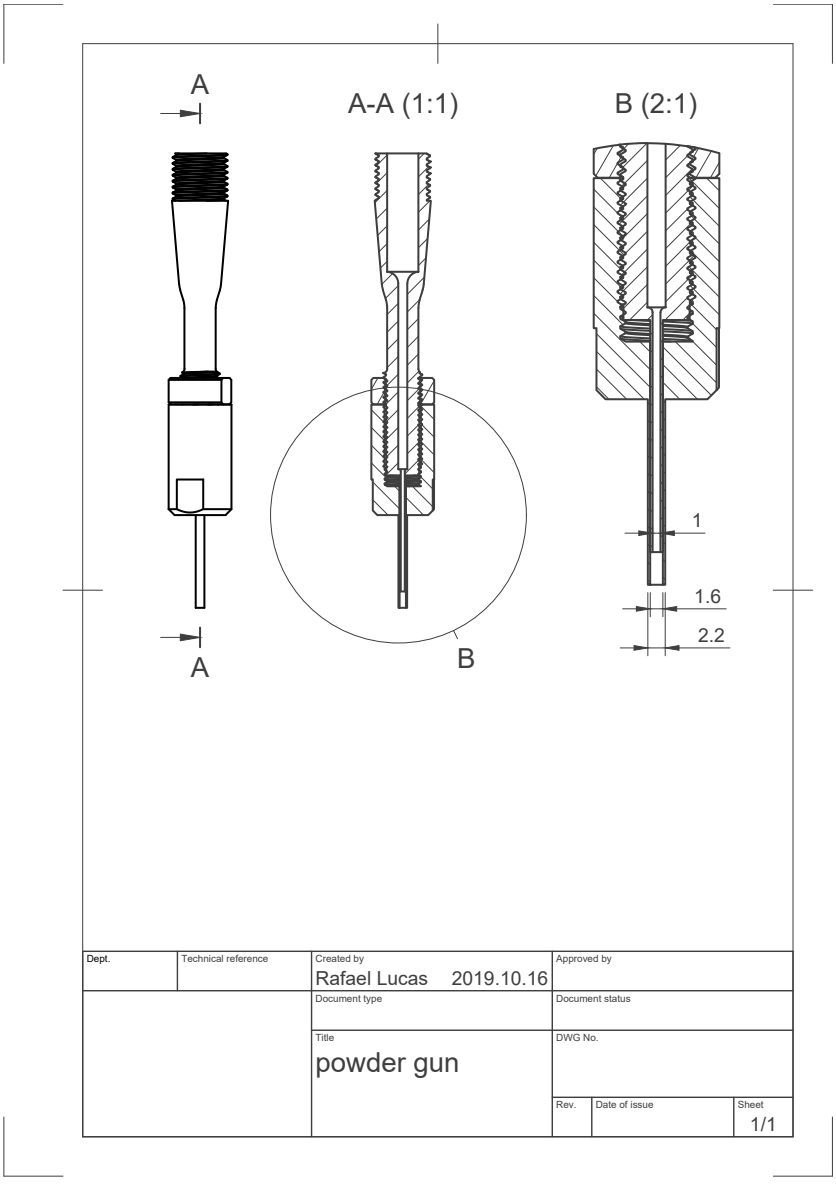

Figure A.3: Powder gun 2D drawing with a cross section view and a detailed view of the tip. Dimensions are in mm.

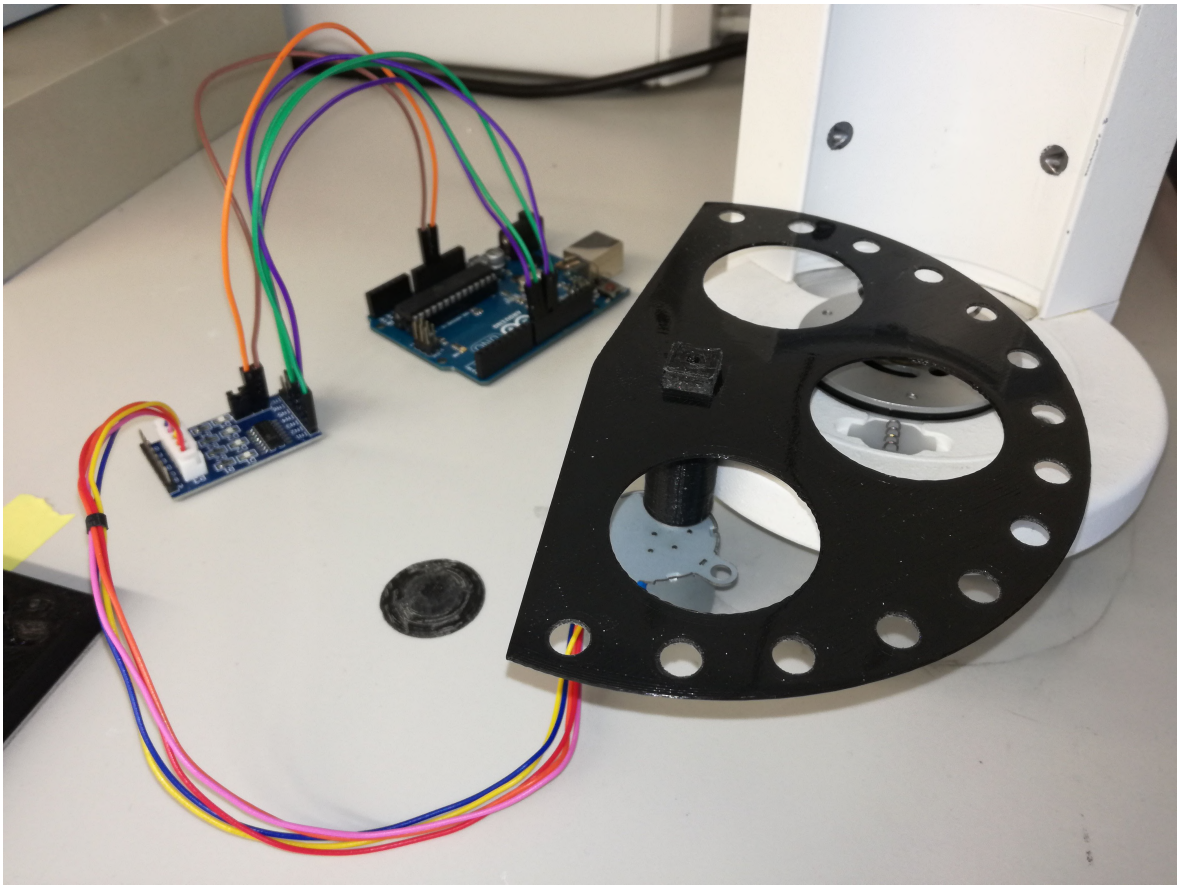

Figure A.4: The complete Transport Module B. The Carousel, the stepper and the Arduino to move it, the conical part to place on the balance and some parts to couple the different components.

Appendix B

Dispensing Experiment Results

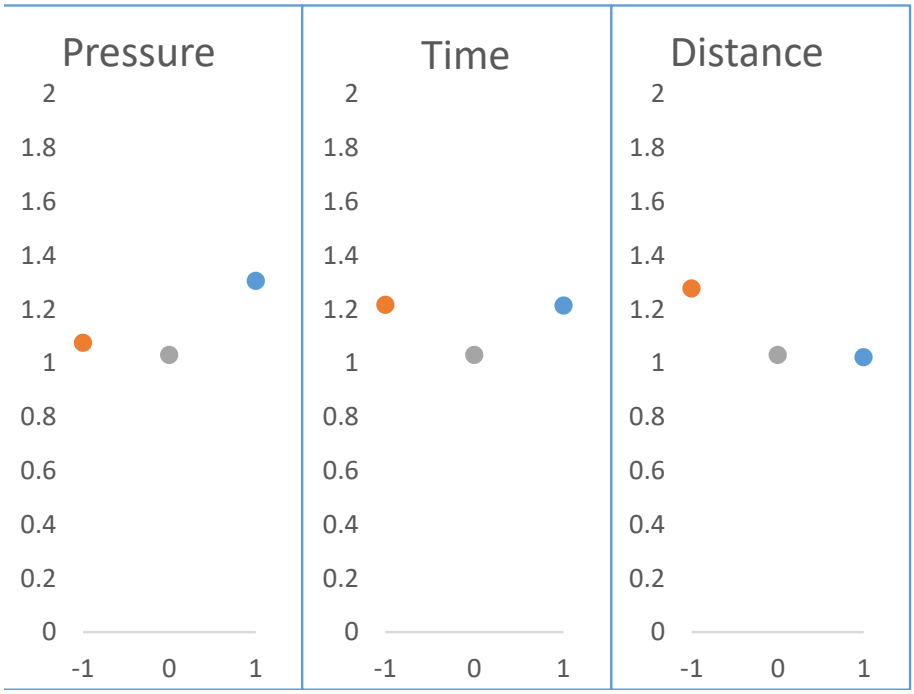

Figure B.1: Substance B dispensed powder masses DoE standard deviation plot.

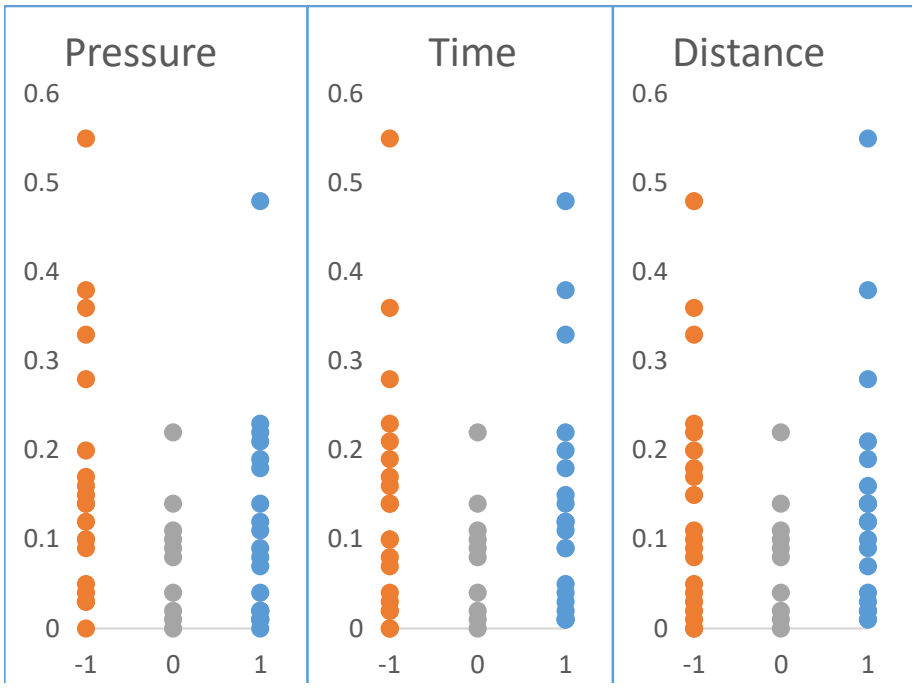

Figure B.2: Substance B inaccurately dispensed powder masses DoE scatter plot.

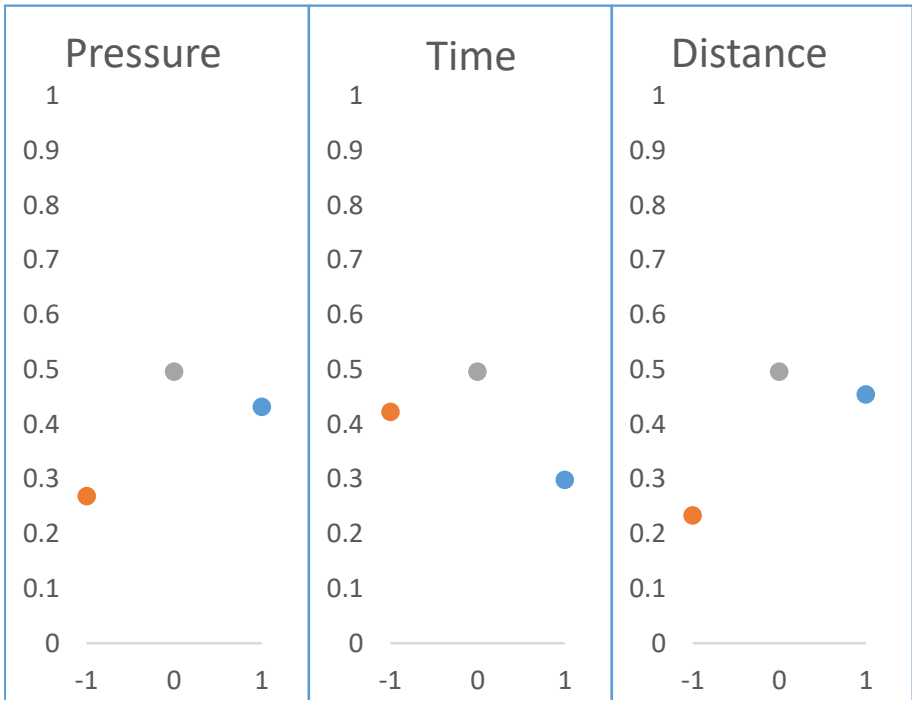

Figure B.3: Substance C dispensed powder masses DoE standard deviation plot.

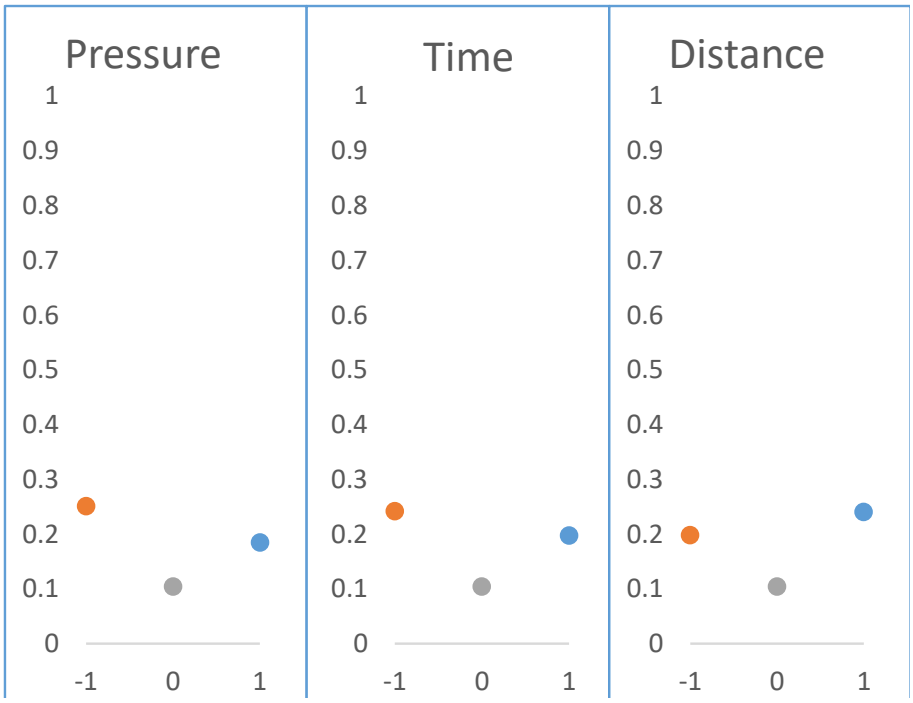

Figure B.4: Powder AB (Substance A + Substance B) dispensed powder masses DoE standard deviation plot.

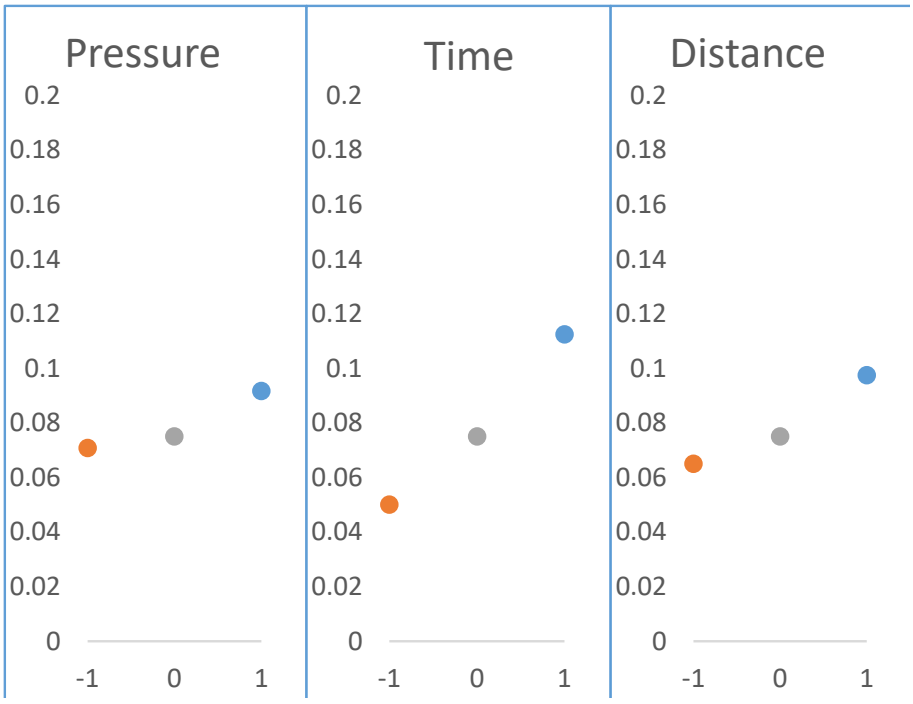

Figure B.5: Powder AB (Substance A + Substance B) inaccurately dispensed powder masses DoE mean plot.

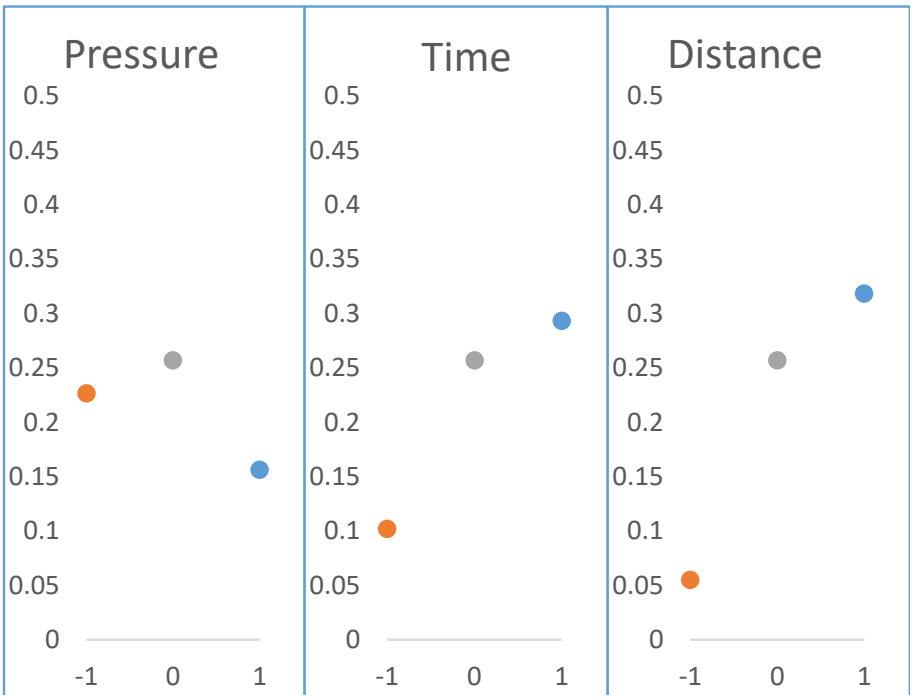

Figure B.6: Powder AC (Substance A + Substance C) inaccurately dispensed powder masses DoE mean plot.