Robotics for Powder Sample Preparation

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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. 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, contributing to the optimization of pharmaceutical development. To this end, two workspaces were designed to and several modules were implemented, two for sample transportation, one for powder dosing , 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 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.
Keywords: Pharmaceutical Industry, Laboratory Automation, Robotics, Automated Sampling, Powder Dispensing, Small Container Handling

1. Introduction

Automation has been implemented in many areas of industry but due to the delicate nature of drug production, this sector is a late adopter. Due to the product created, the pharmaceutical industry has very specific and distinguished characteristics. Since its final product is meant to be used as medicine, its production is heavily regulated by norms referred to as Good Manufacturing Practices (GMPs) and Good Laboratory Practices (GLPs). These regulations make sure the quality standards imposed are fulfilled, in all the stages of drug development, from drug discovery, to preclinical and clinical research and finally market distribution. 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. This quality assurance is especially important in the case of Contract Development & Manufacturing Organizations (CDMOs), that manufacture products for different clients and have large amounts of projects and materials to manage.

The time-to-market of a drug is often over 10 years, giving an idea of the importance of process optimisation to minimize error and maximize throughput. Some of the opportunities for improvement in the industry are: slow and ineffective data flow, time-consuming stock management and material transport and slow manual preparation of samples, capsules and solutions. All of these issues could be solved with digitalization and automation, two concepts correlated with Industry 4.0. It is in this context that the fourth industrial revolution, intertwines with the pharmaceutical sector, a phenomenon called Pharma 4.0. The recent automation market brings a myriad of tools for the pharmaceutical industry. In 2005, the western European market of laboratory automation was estimated to be around $245 million, with roughly 20% representing robotics for drug development applications [7]. There is a current trend of automation growth in laboratories. Information tools and databases provided by the Laboratory Management Information System (LIMS) provide means for automating and integrating tasks [5] and are used to record and monitor performed analyses. increasing sample throughput and reducing turnaround times. Digitalization and simulation allow for better supply chain management and scheduling of activities [3], for example, by predicting product demand [1], reducing overall operation costs. As for automation, many systems have emerged from electronic notebooks and bar codes to fully automated laboratories.

The objective of this work is to 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.

2. Laboratory Automation Overview

Automation and robotics can promote productivity, facilitate process monitoring and reduce risks and human error. In the pharmaceutical industry specifically, safety and risk mitigation have great importance. Automation can shield the staff from harm by substituting it in dangerous tasks. Due to the regulatory entities, process transparency is also a concern and digitalization provides a way to make all data respective to any operation available for inspection. Another positive aspect of automation is that it removes human error and allows for incomparable repeatability. This is especially important in drug development, since small errors and variations can lead to significant negative effects on the final product. Robots also have higher availability and often speed and consequently higher throughput. This is further noticed when working with HPAPIs, which has no influence in a robotics environment. One last benefit is that it relieves staff of repetitive tasks and allows them to have a supervision role of many operations, while also letting them focus on tasks that require their cognitive skills.

During drug manufacturing, the product is frequently in powder form. Bulk solid dispensing automation emerges in the context of creating samples for testing and providing aid in many other tasks where powder is handled, such as capsule filling, creation of pills and dissolution analyses. Many analytical techniques are performed by instruments with built-in automation, but that is hardly adaptable to other processes, meaning there is always a need for the analyst to bridge the gap between laboratory equipment.

Related to this topic of incurable human intervention, most 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 sample small volumes of solids and liquids, from different sources and to many destination vessels. While automation of liquid dosing has been widely implemented, powder dispensing, still presents some unresolved challenges. Powder sample preparation is a lengthy, repetitive and labor-intensive process. Not only is it a very repetitive task but some speed and precision are required, making it a great candidate for automation. In 2009 a market survey indicated 24% of the respondents considered automation of powder dispensing to be a major issue in their company and 62% consider the automation useful to avoid time-consuming manual processing and increase productivity [2]. The survey also indicated that most powders used are considered problematic. The major concerns about automating solid dispensing are the waste of product, the minimum dispensed mass, the system robustness and the cross-contamination.

2.1. Powder Flowability Principles

Particle size and shape are the most important properties in bulk solid behavior [4]. Small non-spherical particles usually present worse flowability, due to adhesive interparticle forces [8, p. 23-31]. Density is related to particle size and has a great impact on powder behavior. It is used to compute many metrics to estimate flowability, although none are considered universally accurate. Electrostatic effects and humidity also have some importance. This nonexistence of a simple way to determine bulk solid flowability hinders theories of powder flow but does not inhibit the dynamic research of dispensing tools in the latest years [9].

2.2. Dispensing Methods and Market Solutions

Below is a list of the current powder dispensing methods, none of which has proven to be optimal for all powders and applications.

- **Gravimetric-** Mechanically controlled flow from a storage container into a destination placed in a balance
- **Overhead hopper-** Dispensed mass is calculated based on the weight loss in the hopper.
- **Volumetric-** A specific volume is pulled into and pushed out of a probe and used to compute the mass dispensed based on density.
- **Electrically charged pin-** A voltage is applied to a pin, attracting powder, and is then shut off to dispense the powder.
- **Pneumatic-** Vacuum is created on a thin tube absorbing powder into it. Then, a positive pressure is applied, and the powder is pushed out of the tube into the destination.

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. All of them have satisfactory dosing precision but often only for free-flowing powders and only some of them include features to minimize cross-contamination. Another limitation is that most of the platforms are only capable of handling vials and not smaller containers such as crucibles or microplates. Additionally, only a few of them are not enclosed and can interact with external tools. A research showed that these automated solutions stall frequently, have trouble dispensing low volumes of solid and require a large minimum powder mass. Finally, all off-the-shelf present a big challenge in software integration with external equipment. They work independently when performing their tasks which inhibits automation between different instruments. For these reasons, pharmaceutical companies remain skeptical about the automation of powder sampling.

The desired implementation must be modular, so it is usable in other powder dispensing applications besides sampling and flexible to work with other laboratory instruments. The dispensing module must be effective with different powders and minimize cross-contamination. The transport module should be adjustable to a myriad of vessels.

3. Implemented Solutions

In this section, the studied manual sampling operation is explained and the two envisioned automated workspaces for sample preparation are presented. The modules implemented for each workspace and their components are described in terms of hardware. The software implemented is explored in terms of tasks and communication and the final experimental setup is presented.

3.1. Task Description

In the studied CDMO, the sampling process that has 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. This technique is used to evaluate the Glass Transition Temperature (T_g) and melting temperatures, for example. 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.

Currently, most of the sample preparation for DSC is made by hand. The analyst places the pan and lid in the balance and sets the weight as tare. He then takes the pan out of the balance and doses some powder into it. He then takes the pan back to the balance and checks for the powder mass. This step is repeated until a valid mass is reached. After that, the crucible is taken to a sealing press and permanently closed and sometimes the lid is pierced. The entire process takes around 5 minutes. For the manual process, the following components are necessary: a dispensing tool and source of powder, a balance and a way to register masses, pans, lids and a place for finished samples, a sealing press, tweezers and an optional needle.

3.2. Workspace A – Gripper Robot as Transport Module

Based on the robotic arm setups available in the market, a pick-and-place approach was used in the sample transport, making the system flexible to the addition of more tools. Given the round shape of the containers used, a 3-finger (self-centering gripper) would be more adequate. Regarding the dispensing, this would have to be done by another robot, since the end-effector must be compatible with a dispensing tool. As an initial workspace, the design represented in figure 1 was modelled.

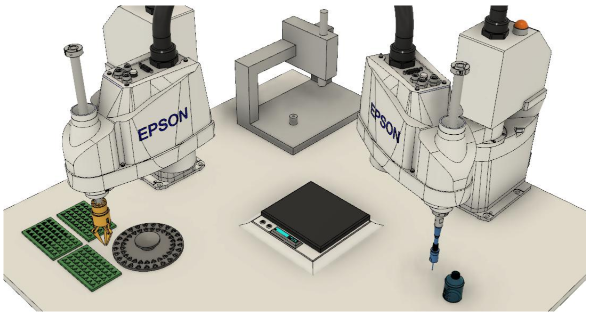

Figure 1: Modelled workspace A.

3.3. Workspace B – Carousel as Transport Module

Looking at the market turntable solutions, a different handling module was designed, a carousel that would hold the pans by their rim. The balance would be integrated in a section of the carousel. This solution reduces flexibility, but it removes the need for the transport robot. The workspace overview of this alternative is shown in 2.

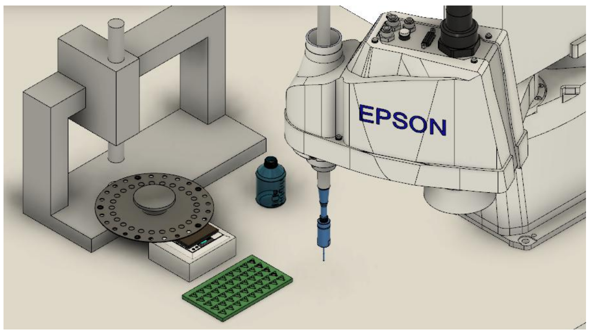

Figure 2: Modelled workspace B.

3.4. Hardware components

The two workspace have the same master, dispensing module and weighing module but different transport modules. The hardware components used in each module are presented in this section.

3.4.1 Gripper robot

The robots used are from Epson, model T3 401S SCARA. It has three revolute joints and one prismatic joint giving it 4 degrees of freedom: position in x, y and z and rotation in z. As imporant specifications, the load capacity is $1kg$ and the repeatability is $0.02mm$ (horizontal and vertical).

Due to its availability and simplicity to implement, an Arduino UNO was used to control the stepper motor drivers. Due to the low forces and speeds but high precision required for the desired tasks, a small stepper motor was adequate. A 28BYJ-48 stepper motor with a ULN2003 driver board were used. As notable specifications, the step angle is $11.25°/64$ and its gear ratio is $64 : 1$ giving it a minimum shaft rotation angle of $0.176°$.

Given the small dimensions of the crucibles, market grippers were not adequate, so a prototype of a gripper was created and is shown in figure 3. A planetary gear design was used, requiring only one rotating motion (provided by the stepper motor) to move three fingers in a curved trajectory to the center, facilitating the centering and grabbing of the parts. The stepper motor used coupled with a gear ratio of 2 means every step of the motor is about $0.043mm$ of finger travel distance (around 1.3% of the radius of the parts to grab). The gripper parts were manufactured and assembled and then attached to the robot's shaft.

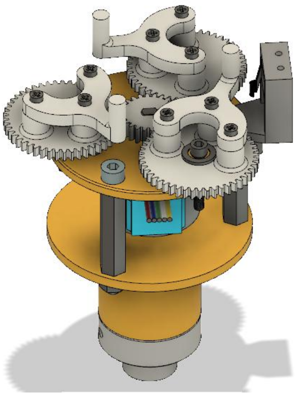

Figure 3: Modelled and manufactured 3-finger gripper.

To avoid the need for the gripper to pick up the parts from a flat surface, some trays were made by additive manufacturing (illustrated in figure 4. They have specifically designed slots to be compatible with the gripper's fingers.

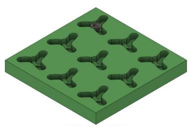

Figure 4: Crucible tray.

3.4.2 Carousel

The DSCr compatible disk was manufactured to transport the pans in holes with a specific diameter that hold the pans by their rims. The movement of this disk is provided by a stepper motor controlled by an Arduino. The described components are shown in figure 5.

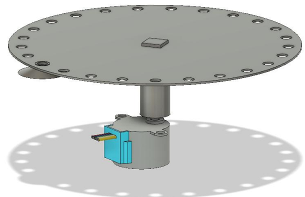

Figure 5: Modelled and manufactured carousel and conical part used to push the pans up.

The objective of having the pans protruding out of the disk's bottom, is to be able to weigh them. With a specifically designed part, every individual pan is pushed up as it goes over the balance, allowing their mass to be measured.

3.4.3 Powder Gun and Vacuum Generator

Because of its immediate availability in the lab, the dispensing method used was pneumatic, a powder gun illustrated in figure 6. This tool is connected to a Venturi vacuum generator that 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 manual foot switch was disassembled and replaced by a relay. The pressure of the compressed air and vacuum fed to the powder gun can be manually regulated. The powder gun is composed of two parts with thin hollow tubes at their tips, with very close diameters. 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. The dispensing range is from $1mg$ to $10g$ but must be adjusted manually. An adapter was designed and manufactured by additive manufacturing in order to fix the powder gun to the robot, and is shown in figure 6.

Figure 6: Powder gun attached and its adapter.

Two smaller components were added to this module, an anti-static ring that minimizes static electricity with and a paint brush to remove excess powder from the tip of the powder gun.

3.4.4 Raspberry Pi and MX5 Balance

In terms of communication in the workspace, there would be a master that dictates the tasks to run during the sampling. To create the link between all the slaves, one option was to use a component from the transport module and the other is to have an external device. Since flexibility was always a concern, a separate device was opted to be master, a Raspberry Pi.

The weighing of the powder mass used in a DSC sample must be very accurate. For this reasoning, the MX5 microbalance from Mettler Toledo was used as the weighing module, since it was the smallest balance available with the required precision.

3.5. Software Architecture

In this section, the algorithm for each module is explained. Transport module B can directly influence the weighing and dispensing modules' operations, while transport module A is easy to troubleshoot separately. To improve experiment validity when testing the complete system, the master-slaves architecture implemented in the laboratory was the one designed for workspace A.

The components 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. Using a cascade setup, the master-slaves setup is illustrated in figure 7.

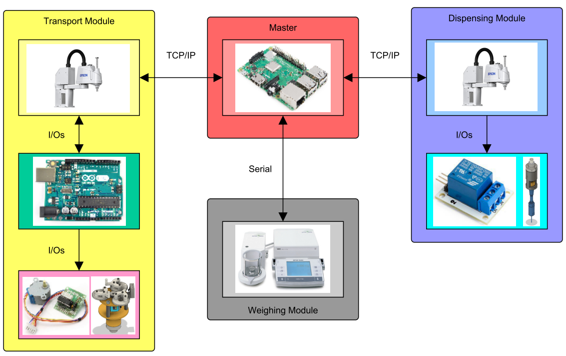

Figure 7: Master-Salves cascade setup.

This methodology makes it easier to separate each module for testing. To note are the colors used for each component, used in the below presented flowcharts for an easier understanding of the involved components in each step.

3.5.1 Weighing Module

The MX5 balance operates in MT SICS programming language. The master sends commands in the form of strings and the balance responds with other strings. The commands used are the orders to zero the balance, tare the balance and return the mass measured.

3.5.2 Master

The master's program was coded in Python 3 language and is designed to coordinate the top-level slaves present in the workspace. First, the master establishes communications with the slaves, zeroes the balance and homes the two robots. It then initiates the sampling sequence, illustrated in figure 8.

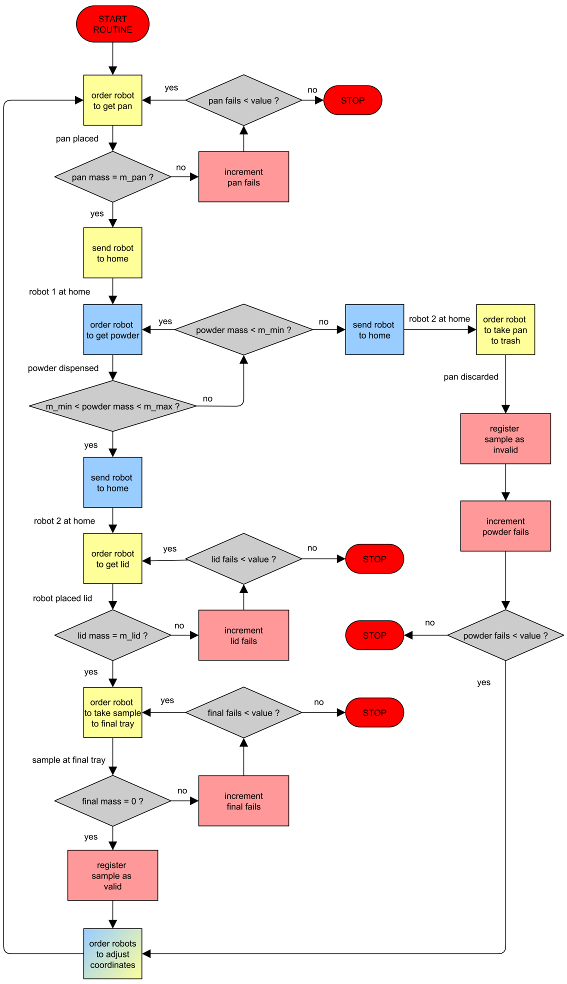

Figure 8: Master flowchart.

The balance is used as a sensor to determine if the transport module was successful in placing the parts. After the dispensing module runs, the amount of powder dispensed is either too small and another dispensing run is made, it is in the valid range and the dispensing is successful or it is too large and the sample must be discarded. In the two later cases, the transport module is ordered to take the sample from the balance to a designated location. The *'increment ... fails'* give the system a specific amount of times to attempt a task before a human needs to intervene (labelled as *'STOP'*). The command sent from the master to the robots to adjust coordinates is used so the transport modules grabs parts from a new tray slot (getting a new set of pan and lid) and so the dispensing module absorbs powder from a slightly different location.

3.5.3 Dispensing Module

This module's loop routine starts with the master's order to dispense powder until the right amount of mass is reached. The robot takes powder from the source and moves to the balance. It then lowers the powder gun to the pan and activates the relay, dispensing powder into the pan. It ends with the robot travelling to its home position and receiving the order to adjust its coordinates for a new run.

3.5.4 Transport Module A

This module stays in a loop and depending on the task ordered by the master, it goes to different positions in the workplace. All routines are shown in figure 9. The robot can also be ordered to adjust coordinates for the next pan and lid and go home, to give space to the dispensing robot.

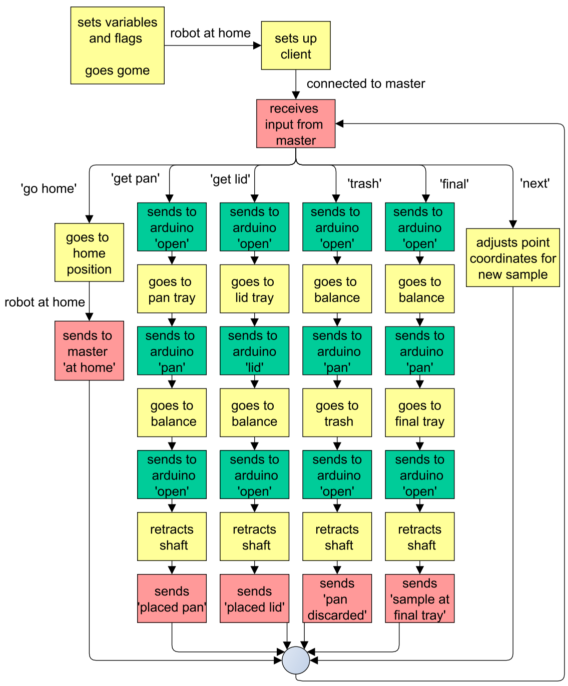

Figure 9: Transport module A robot flowchart.

To grab the parts, it sends outputs to the Arduino to command the gripper to open or close. The Arduino UNO runs a simple script that consists on setting step values and then staying in an infinite loop, that depending on the input from the transport robot, orders the gripper to move its fingers to different positions.

3.5.5 Transport Module B

The manufactured disk has 25 holes (where the pans will be located) around its 360°, resulting in a specific number of steps between two neighboring positions: $steps_{next}$. The Arduino listens for an input position from the master and moves $steps_{next}$ times the number of positions between the input position and the current one.

3.6. Final Implementation

For the reasons stated in the beginning of this section and due to the results presented in the experiments, workspace A was the one implemented in the laboratory for full system experiments. This setup is presented in figure 10.

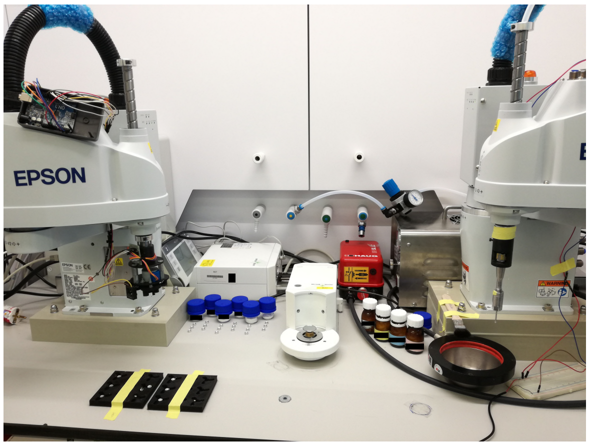

Figure 10: Setup implemented in the laboratory and used for the full system experiments.

4. Experiments and Results

In this section, the experiments carried out and the results obtained are presented. First, the two transport modules are evaluated. The gripper, regarding the reliability when handling the pans and lids. The carousel, in terms of how accurate it allows the weighing to be. Then, the dispensing module is extensively tested, regarding powder source surface condition, dispensing air blast parameters (time, pressure and distance to target) and powder gun tip's path when absorbing powder inside the flask. Finally, a full system test took place, to roughly quantify throughput and overall functionality and the resulting samples analyzed in the DSCr.

4.1. Gripper Handling

The first gripper experiment consisted in closing and opening the gripper and registering the finger's locations of both positions in a millimetric paper. Correction fluid was applied to the tip of each finger and the markers were posteriorly enhanced. These marked dots describe two triangles, whose center point coordinates were computed. Six observations were performed, and one of them is shown in figure 11. The center of triangle ABC will be referenced as O and the center of abc as o.

Since the gripper is self-centering, the center point coordinates (O_x, O_y) and (o_x, o_y) should be the same. Across all observations, the distance $\overline{Oo}$ was always smaller than $0.4mm$, proving the self-

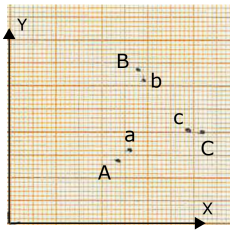

Figure 11: Triangle *A,B,C* corresponds to *open* position and *a,b,c* to *closed* position.

centering ability of the gripper. To check if the spacing between closed fingers is constant, some distances between points were computed: $\overline{oa}$, $\overline{ob}$, $\overline{oc}$, $\overline{ab}$, $\overline{ac}$ and $\overline{bc}$. The maximum difference between distances across all observations was $1.4mm$, 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 could be influenced by human error and the marking methodology used, so more exact positioning methods should be tested with.

The second tests performed were to evaluate the reliability of the gripper in pick-and-placing the crucibles. The objective was to check if the gripper robot could place the pan exactly in a target drawn in millimetric paper, place a lid on top of the pan, and finally pick up the crucible set and return it to a tray. The pan was dropped by the gripper from $2mm$ above the target and the distance to it evaluated. This was the most important output since it can influence the dispensing module's accuracy. For all of the 20 observations, no part was damaged or dropped and all complete sets (pan and lid) were picked up and correctly placed in their slot. Using this methodology, the distance to the target was not quantifiable, since the pan was always placed in it. To simulate an anomaly in the balance's weighing platform, the same experience was performed but now dropping the pan from a height of $5mm$. The worst result obtained was a distance to target smaller than $2mm$, an error small enough to not compromise the sampling operation.

In an end-to-end system test, the gripper's performance, if poor, could negatively impact the dispensing operation. After these tests, it was concluded to be reliable enough to be implemented for the full system experiments.

4.2. Carousel Transport Weighing

To evaluate the workspace B transportation method by checking if the weighing of a protruding crucible was accurate, 4 pans were placed on different positions in the carousel and the stepper was ordered to move them to the position over the balance. Three similar scenarios were used: one with the 4 pans placed in neighboring positions, another with 5 empty positions between two pans and one with the lids on top of the pans. For all scenarios, after just one full rotation (clockwise or counter-clockwise), some measurements would start to be erroneous, since the mass values would diverge from the pans' true masses, or in worse cases, the balance would not stabilize to be able to output a value. In the third scenario, the inclination of the pans (from being pushed up by the piece on the weighing platform, shown in figure 12) would sometimes result in the lids sliding out of place.

Figure 12: 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.

It was concluded that, to use this transport module effectively, the carousel and the balance piece would have to be manufactured differently and it would have to return to its original position to avoid rotations. In its current state, this transport module was inferior to transport module A.

4.3. Dispensing Module

To test the dispensing module some powders composed of substances labelled from A to C, were acquired. Substance A has the largest particle size, highest density and is considered cohesive. Substance C has a very small particle size, low density and is considered free-flowing. Substance B has medium particle size and density.

4.3.1 Powder Surface Condition

The first thing to establish was which conditions were important to keep in the powder source. The conditions tested were: powder compaction (bulk or tapped density), powder available (small or large volume), surface angle (straight or inclined) and presence of a hole in the surface (due to successive absorptions from the same exact place in the flask). Using substance C, the absorption was tested qualitatively, by checking not the absolute mass but which case of absorption occurred: no powder was absorbed, the powder created a slug in the powder gun, the powder adhered to the outside of the tip or some powder was properly absorbed.

The conclusions were that the volume of powder and the slope had little importance, as long as there was a minimum powder height to absorb (approximately $1mm$). The compaction did not stop the absorption but made the occurrence of slugs more frequent, so keeping the powder in bulk form would minimize errors. The hole created by successive runs lead to no powder being absorbed after a few dispensing runs. This meant it was a requirement to keep changing the absorption location slightly.

4.3.2 Dispensing Design of Experiment

The objective was to quantify the amount of variability in mass dispensed depending on the changes in parameters defined by the user. The interval of time for compressed air must be enough to expel the powder but not enough to spread the powder already dispensed. The air pressure fed into the system directly influences the flow rate of air. Too much pressure and the powder spreads before reaching the pan, too little pressure and the more cohesive powders will not be expelled from the tip. 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 powder in the pan (especially for high pressure and long air time cases). Given the possibility for large variations due to a certain combination of these 3 factors, a 2-level full factorial design was chosen, to provide information about which factors are more relevant, what are the effects of their interactions [6] and in what ranges of values they should be at. It also shows how sensitive the system is to relatively small parameter changes.

This design results in 8 combinations of parameters set as high $(+1)$ or low (-1). The recorded outputs are the mass dispensed and how much of it missed the pan. Center point runs with standard parameter values (0) were performed, every 8 observations. After some testing with the aid of an expert, the ranges for the parameters were chosen: pressure from $0.15bar$ to $0.25bar$, air time from $0.3s$ to $0.7s$. and distance from $6mm$ to $8mm$. To remove powder source influence, a new flat surface was created before each run. Factors such as temperature, humidity and air flow were kept constant, as was the volume inside the powder gun's tip. One last factor that must be mentioned it the condition of the filter that is placed inside the powder gun. In this tool's manual usage, the filter is changed regularly, because with every absorption, some powder gets lodged in it. 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.

The resulting data was graphically represented in DoE scatter, mean and standard deviation plots. Scatter plots allow for a quick identification of outliers, useful to detect samples with invalid mass, a slug occurrence indicator. Mean plots are useful to check which factors have the most significant impacts and to easily compare the mass of powder dispensed outside of the pan. Standard deviation plots are used to evaluate variation in powder dispensed, which is desired to be minimized.

4.3.3 Absorption Routine

To start, the module was tested using substance B. Figure 13 shows the masses dispensed using a single run approach, and the large variations in mass are clear, even for the same parameter values.

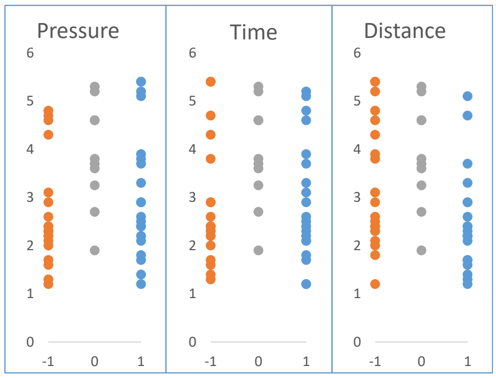

Figure 13: Substance B powder masses (mg) scatter.

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. The powder gun's tip was shortened to absorb less powder, and the master would order the dispensing module to run repeatedly until the target mass was reached.

To avoid the creation of the hole in the powder surface after some runs, a path inside the flask was implemented. The first pattern tested was a simple square motion in the XY plane at a constant Z value, which would decrease after every run. Using center point parameter values, this approach was tested 10 times and all samples had more than $3mg$ of powder. One observed result was the pushing of some powder away from the path, making it impossible to grab on the next runs, so to increase the reach of the tip, the path was changed to a circle. Its diameter would decrease before Z was changed, to absorb powder pushed to the center of the flask. The decrease in Z was also changed to be dependent on the mass previously dispensed. These changes were tested with substance C using the same full fractional design and the resulting masses from the 46 observations are shown in figure 14. The masses recorded outside of the pan were so small that for all 8 combinations and center-point run combined, the measurement was always smaller than $0.2mg$.

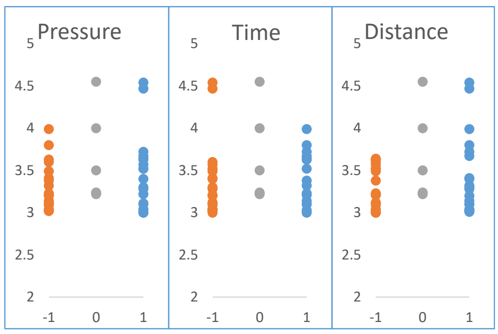

Figure 14: Substance C powder masses (mg) scatter.

This proves that with the multiple dispensing runs approach, the system would create samples with small mass variation even for different parameter values. However, the filter was changed before every center point run because the powder gun would lose suction power. This was possibly a result of sliding the tip across the powder during its path after it was already full. To minimize this effect, a new pattern was defined for the tip. Instead of describing a circle at a certain Z value, the tip would create 9 small holes (one in the center and 8 around it) for every Z value. One hole would be made for each run, and only after 9 runs would the shaft go lower, so it would be more powder efficient, albeit possibly slower to reach the $3mg$.

This method was first used with a mixture of substances A and B (powder AB). A similar full fractional design with some alterations was used. Pressure parameter unchanged. Three air blast instead of one, to help avoiding powder accumulation. Distance range changed to $7mm$ to $9mm$. Each combination was observed 3 times and the 28 sample masses are presented in figure 15. All samples had valid powder mass the shaft only descended in 2 observations, showing how effective this path is. The filter also did not need to be changed.

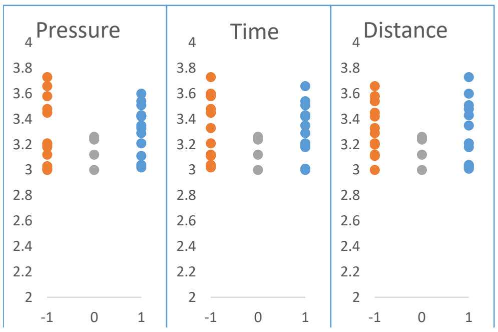

Figure 15: Powder AB powder masses (mg) scatter.

The powder that missed the pan averaged about $0.08mg$ per observation. From the DoE mean plot corresponding to the mass that missed the pan, it was concluded that while pressure did not have a big impact, a short air blast time and a shorter distance to the pan improved dispensing accuracy.

The same exact experiment was performed for powder AC (a mixture of substances A and C). 5 of the 28 samples had less than $3mg$ of powder, due to uncompleted dispensing runs caused by slug occurrences, one of which was removed during an air blast and is shown in figure 16.

This frequent slug occurrence could be result of substance A being cohesive and substance C having a very small particle size, which increases its accumulation in the filter, making the pressure in the tip insufficient to push the powder out.

The objective was to minimize the variation in final powder mass and the mass outside the pan.

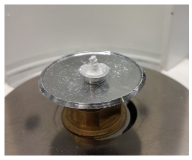
Figure 16: Powder slug that was pushed out of the gun during an air blast. It can compromise lid placement.

This was done by taking the lowest values from the dispensed masses standard deviation plot and masses outside the pan mean plot. Using a simple metric that gives both objectives the same weight, the best combination overall was (-1,-1,1), meaning short air blast time ($0.3sec$), shorter distance to the pan ($8mm$) and higher pressure ($0.25bar$). Despite this result, by analyzing all the DoE plots, one can conclude that the variability caused by the powder and the dispensing routine is more significant than the one resulting from input changes. This demonstrates that the dispensing repeatability, using the absorption method arrived at, is almost insensitive to alterations in these 3 parameters.

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 work without human intervention. As mentioned previously, transport module A was the one chosen for this test. 3 pans and 3 lids were placed in the trays at the start and the powder flask placed in its determined position. The objective was to create 3 samples of each of the 4 powders used:

- Powder 1: subst. A 5% + subst. B 95%
- Powder 2: subst. A 15% + subst. B 85%
- Powder 3: subst. A 10% + subst. C 90%
- Powder 4: subst. A 15% + subst. C 85%

After trying to create samples from powders 3 and 4, it was clear that the slug occurrence was still very frequent. With the aid of a flow sensor, the pressures were increased to create a $0.1l/min$ flow rate in the powder gun when the filter was already used (since this is its most common state), which was enough to push most slugs out and still avoid excessive splashing. Another attempt at the full system test was made, using powders 1, 2, 3, 4, AB and AC, meaning a total of 18 samples with no filter change or slug removal by human intervention.

This experiment resulted in 18 valid samples and less than $1.4mg$ of total powder wasted in the balance. However, a noticed flaw was the powder that was dispensed onto the rim of the pan, which could influence lid placement and posterior pressing. Regarding speed, the system ran for 3 hours, averaging 10 minutes per sample, slower than an average analyst, but since it has triple the availability, it results in a higher throughput of 144 samples per day. This would be increased with higher robots' movement speed and a sensor to detect the powder surface, since depending on the product volume in each flask, the dispensing robot had to perform some runs until any powder was reached.

4.5. DSC analysis of prepared samples

The obtained samples created from powders 1 to 4 were analyzed in the DSCr, to evaluate their validity, as well as one manually prepared sample of each of those powders. For all powders, the resulting graphs from automatically prepared samples were very similar, and the manually created sample's result was difficult to distinguish from the other 3.

Knowing the T_g's of each of the substances and their proportions in each powder, the powders' T_g's were estimated. Using the DSCr's software, the T_g's of the samples analyzed were computed. Across all 12 evaluated samples, the largest difference between estimated and DSCr obtained T_g's was $5°C$, with most differences being less than $2°C$.

The melting peak temperatures computed from the graphs were also compared to the theoretical values and were also very similar, with the melting of each individual substance identifiable in the graphs. This further indicates that the DSC samples created by the implemented solution are reliable enough to make decisions about the substances and proportions in the produced powders.

5. Conclusions

The primary goal of this project was to implement a versatile powder dispensing and sampling platform, objective achieved with a modular solution. Despite the general success of the modules, there is room for improvement. The dispensing module presented great results in filling crucibles and showed possibilities to be used with other containers, constituting important steps towards a reliable solid dosage tool. It could be improved with a slug detector and removal tool and a proximity sensor to identify the powder surface would lead to better robustness. A filter cleaning procedure and an online pressure control to regulate air flow rate, could minimize powder particle spreading. The gripper robot had exceptional performance and transporting crucibles and its concept could be used with heavier vessels in other applications. As improvements, higher quality manufacturing would make it more durable and allow the fingers to be longer. A dust proof assembly could help reduce cross-contamination. Induction sensors should be used for better handling of the parts. The carousel, although less flexible, proved this transport method and weighing possible. With proper manufacturing, this module had potential to be the best transport method to the specific DSC crucibles. The master and the cascade methodology proved successful in coordinating the modules during the full system experiment, but connection to more sensors would improve overall automation.

In the end-to-end test, the system was able to create 18 valid samples with good repeatability and the mass measurements were registered and outputted (for monitoring) by the master. The system functioned for 3 hours unsupervised and it evidenced a higher throughput that an analyst, even at lower robot speeds, due to its availability. Its robotic nature means it can work with dangerous powders, reducing human exposure to them.

Concluding, the work developed achieved a fully automated system for sample handling and accurate powder dispensing. With more external tools, such as a sealing press, the complete automatic DSC sample preparation is possible.

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