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Design of an Allergy Immunotherapy Compounding Device

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***Abstract*—The preparation of allergy vaccines for immunotherapy requires precision, a personalized process and consistency. In many clinical settings this process is still performed manually, increasing the risk of human error and compromising the entire vaccine and, therefore, the patient's health is at risk. Additionally, a compounding device for allergy vaccines would facilitate the workload of physicians. Acquiring this kind of device is not easy, mainly because of the lack of information about it and that the technology developed for this medical area is aimed at the diagnosis of the specific allergy, but not to the treatment. As a first attempt to innovate and contribute to the area, this paper presents the initial design of an allergy immunotherapy compounding device that will allow physicians to automate the preparation process and eliminate human error.**

***Keywords*—Allergen, automation, compound, dilution, immunotherapy, vials.**

I. Introduction

The automation of different procedures such as the creation of allergy shots, or allergen immunotherapy, is something that nowadays is a need, but in a few years is going to be a must. The development of automation began around 100 years ago, or more, and it changed the industry. As an example of that, when car manufacturing began, they were handmade, and automation let the production increase while decreasing the time it took to produce them, as well as the human interaction the process needed. The automated machines were considered robots. They started to break out of the industry area to reach new ones, and the biomedical field was one of these. The first encounter that automation had with the biomedical field was when they created a machine to help with the chemical dispensing and measuring. Before this machine was created, all the procedures were handmade, and errors may occur, leading the researchers further away from the ideal methods. The movements needed for these procedures were repetitive, which benefited the use of automated devices or machines. The advantages of using automated devices were that they could work 24 hours if needed and would not get tired, letting the researchers and doctors focus on other aspects, such as, the process, the results, and the data obtained [1].

According to the World Health Organization, by 2050 at least one person out of two will suffer from an allergy disorder [2]. Due to the increasing allergy cases in human population specialists that can diagnose and treat the resultant allergies are needed. An allergist is a physician who has successfully completed both specialization and training in allergy and immunology and a training period in internal medicine or a sub specialization in dermatology, pneumatology, or otorhinolaryngology [3].

To help people's allergies, doctors have developed three ways to give the treatment to the patient. The sublingual immunotherapy (SLIT) method requires patients to place a pill or drops under the tongue, and the other two methods, subcutaneous immunotherapy (SCIT) and intralymphatic immunotherapy (IIT), are administered to the patient by vaccine, the difference between them, as their name indicates, is the place where they are administered [4]. One way to improve the time it takes to make a vaccine is to start designing a device or machine that can make the process easier and can help minimize manual labor for healthcare professionals. Currently, there are some machines that are used in the allergy field, but all are focused on the diagnosis of the causes of allergies, such as the OPTIGEN AP3600, this device is designed for easy and efficient in vitro allergy testing using a small amount of blood to measure the specific concentration of IgE in human serum [5]. However, this technology is not widely implemented in the Central America region, and most allergists still do it manually, using the Skin Prick Test (SPT). A similar situation occurs with the preparation of allergy immunotherapy, where the current method to do it is to use syringes and needles to mix and transfer the allergen extracts that will be used for the patient's treatment. This process requires strict aseptic conditions that the healthcare professionals may keep by keeping themselves and the work area clean to avoid contamination and keep the patient's safety [6].

To ease the workload of healthcare professionals in the region and improve how allergy treatments are prepared, this paper introduces the design of a new device intended to automate the compounding process for allergen immunotherapy. The goal is to create a system that is simple for medical staff to use, while ensuring consistency and safety. In this paper, we will describe its key mechanical and electronic components, how the automation of it will works, and the advantages it may offer over current manual methods.

II. Theoretical Framework

A. Allergy Immunotherapy

Allergies start in our immune system, which controls how our body defends itself [7]. They are caused by a dysregulation of it, and when that happens the immune reactions are inappropriate, and can be triggered by the exposure to common food, particles that can be floating in the air, drugs, insect stings, among other substances [8]; the cause of these reactions is denominated allergen, and for most of the population is innocuous. The ones that are susceptible to them, get a reaction where the immune system induces the production of Immunoglobulin E (IgE) [9]. IgE are antibodies that our immune system produces, and if you are allergic the immune system overreacts to one or more allergens causing the allergic reaction. It is important to emphasize that each type of IgE reacts to a specific type of allergen, consequently, a greater diversity of specific IgE antibodies means a greater diversity of allergies [10]. There are plenty of types of allergies such as food allergies, allergic rhinitis, allergic conjunctivitis, allergic asthma, drug allergies, among others. Most of them are treated using immunotherapy when the allergies are severe and frequent, the most common one of them all is allergic rhinitis with a percentage that goes from 10 up to 40% of the overall population [9].

Allergen immunotherapy (AIT) is used as a therapy for established IgE-mediated hypersensitivity to common allergens. The first and classical protocol was introduced in 1911, and consisted of subcutaneous injections of increasing amounts of allergen, and a period of more than 3 years of maintenance injections to achieve allergen tolerance [11]. The incremental increases of the allergen doses help the patient to become less sensitive to it, therefore reducing the symptoms of the allergy [7]. AIT, although having some side effects, depending on each patient's response, is the only treatment that offers the possibility of long-term cure [12].

When a patient has a recurrent allergy profile, that couldn't be treated previously using regular medication like pills, and the patients cannot identify themselves the cause of the allergic reaction, the doctor refers the patient to a specialist, in this case, an allergist. The allergist is the one in charge of testing the patient's reaction to different allergies, and it can be done via Skin Prick Test or by in vitro allergen-specific IgE (sIgE).

Skin Prick Test (SPT) is used by allergists to determine which allergens affect the immune system of a patient by introducing the allergen into the surface of the skin as shown in Fig. 1, they make tiny cuts on the patient's skin and they wait around 30 minutes to check the diameter of the reaction comparing it to a reference spot; if the diameter is the same size or bigger than the reference spot, it means that the patients has an allergic reaction; if it is smaller, the allergist evaluates if give a treatment to that specific allergen [13].

In the other hand, sIgE only needs a blood sample of the patient to measure the specific concentration of IgE when exposed to a specific allergen or even if the patient is susceptible to develop an allergy, giving physicians the exact data obtained from blood serum. However, it has some disadvantages, such as the time it takes to get the results compared to the time of SPT, and also the cost of the test increases, compared to the other method [14].

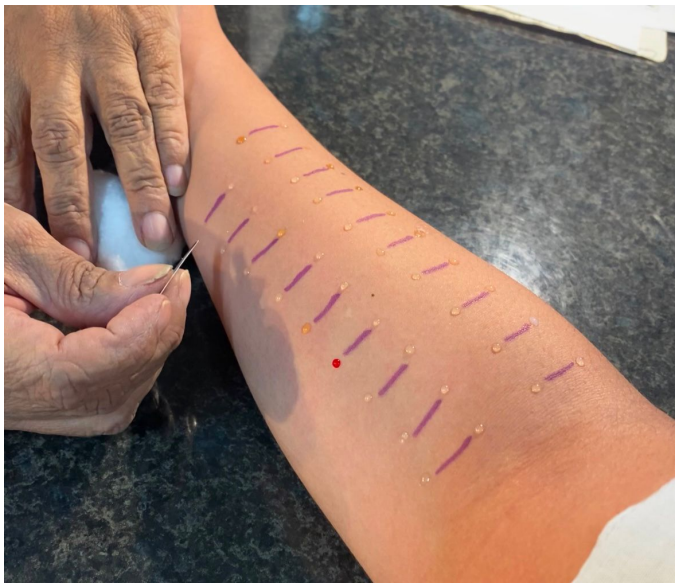

Fig. 1. Skin Prick Test

B. Allergy Vaccines Preparation

Normally, the preparations of allergy vaccines are done manually, and it takes a lot of work, as well as a time to calculate the doses of the allergen, or allergens in case the patient has more than one allergic reaction to specific allergens. The doses the patient receives gradually increase, so they can develop resistance and tolerance to allergens, and this process is called 'build-up'. This phase can extend from three to six months and it involves receiving injections with increasing amounts of allergens once or twice a week [7].

The level of dilution is an important factor in providing good treatment to patients. Wrong dosage of the allergen could worsen the condition of the patient instead of improving it, and it can put the patient's life at risk if they get anaphylactic reactions. To avoid that, allergists start giving a small dose or a really diluted amount of the allergen to the patient in the vaccines, this way the immune system would 'familiarize' with the allergen and will not start a severe allergic reaction. Physicians use (1) to calculate the correct extract dilution. They can solve the equation to obtain the desired information where:

V1: is the final volume physicians want to prepare.
C1: is the concentration of extract you want to prepare.
V2: is the volume of extract you would need for dilution.
C2: is the concentration of extract you would use [15].

$$V1 * C1 = V2 * C2 \tag{1}$$

After physicians did the calculation, the correct procedure is to keep the allergen extract and its dilutions correctly label,

and according to the American Academy of Allergy, Asthma & Immunology (AAAAI) they should also have color coding, adding a specific color to the bottle or numbering system as shown in Table I. For the numbering system, number one is the highest allergen concentration, the one that is not diluted, and the following number should be the 10-fold dilution, etc. The dilution ratio tells the proportion of concentration and diluter (i.e., 1:10 could mean 1 mL of concentrate and 9 mL of diluter) [16].

TABLE I
COLOR CODING AND LABELS

No.	Color code	Serial 10-fold dilution	Dilution ratio
#1	RED	Concentrate	1:1
#2	YELLOW	10-fold dilution	1:10
#3	BLUE	100-fold dilution	1:100
#4	GREEN	1000-fold dilution	1:1000
#5	SILVER	10000-fold dilution	1:10000

III. COMPOUNDING DEVICE DESIGN

Now that we know all the work it takes to create a personalized vaccine for allergen immunotherapy it is important to determine the technologies we are going to use to achieve the first design of the compounding device. For the first tests of our ideas, we use the online tool Tinkercad, which allows designers and students to create prototypes, circuit design, and 3D simulations, avoiding ruining hardware while testing.

The compounding device is designed to do two operations, dilution and compounding. When the device is turned on, the user can choose which operation they need, and according to the selection the device reminds the user that they need to place the supplies needed to complete its task. As a micro controller we use an Arduino UNO in the simulation of Tinkercad, a buzzer, a LCD I2C display, and a matrix keypad. For the movements needed to pick the allergen and the diluter we are going to use stepper motors to push the pipettes, placed on rails, so they can move to the location of the allergen substance and back to the compounding vial, but that part is going to be discussed in future research.

A. Dilution Mode

When the device is started, after the welcome message, it asks you to choose a mode to work, dilution corresponds to D key on the keypad. Before starting the dilution, the device asks or reminds the user of the need to place vials in the tray shown in Fig. 2. Slot A is where the diluter must be placed, and slot B will be explained in more detail later. The vials for each dilution rate must be placed starting from concentrate (1:1 ratio) allergen in slot number 1, 10-fol dilution in slot number 2, and continuing like that until 10000- fold dilution. This mode is meant to dilute the concentrate of the different allergens, in this stage of the design of the compounding device, we are only diluting in a serial 10-fold dilution ratio, this means it is going to follow the workflow shown in Fig. 3 where 1 part concentrate is going to be diluted by 9 parts of diluter obtaining a 1:10 rate. With the result of the last dilution, we are going to make the next one, we are going to take 1 part of the 1:10 dilution, and 9 parts of diluter, this way we obtain a 1:100 dilution rate.

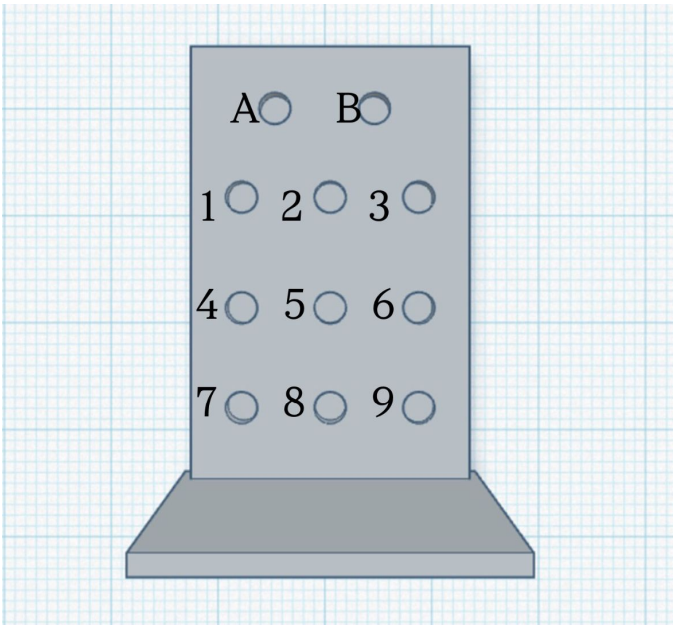

Fig. 2. Aerial view of slots tray designed in Tinkercad

The device continues diluting the last dilution obtained until we reach the 1:10000 dilution rate. When all the dilutions are finished it activates a buzzer that acts as a sound indicator that the process is finished. Finally it shows a message to go back to the main page where they choose the mode they need.

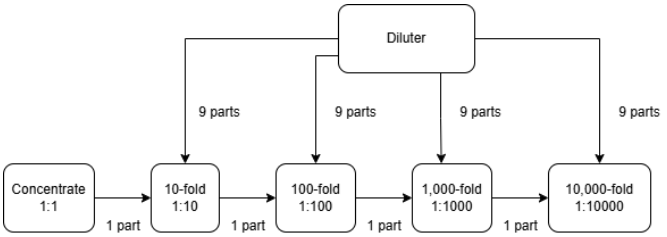

Fig. 3. Dilution process workflow

B. Combination Mode

This mode, as dilution mode, can be selected in the main menu screen, displayed on the LCD, and it also shows the message to place the vials and supplies on the slots tray. For this mode the arrangement changes a little bit, the location for diluter is going to be the same as in the Dilution mode, in slot B the user must place the empty vial for the compounding. In Slots 1 to 9 the user must place in the order they desire the allergens they are going to add to the personalized vaccine. They must use the diluted rate they desire, taking in count they have done the dilution before, or they are going to use the concentrate allergen.

Once they have placed allergens, diluents, and empty vials on the tray, they must select the combinations of allergens and the quantity they need for a specific patient. The micro controller oversees saving the data collected for compounding, the first step is to choose the number of the slot where the user puts the allergen they want to use, and then the quantity in ml from 1 to 9. If there is more than one allergen needed for the compounding the device automatically asks for the need combination to save it in a matrix with 2 columns corresponding to allergen and its quantity.

In Table II we can see an example of how the micro controller saves the data; in this case the user only chose 5 allergens. The micro controller reads the information of the matrix line by line and sends the pipette on the rail to get the amount of allergen desired to put in the empty vial until it finishes all the lines. Then, just like the other mode, a buzzer activates as a sound indicator, to let the user know that the compounding process is finished.

TABLE II
ALLERGENS AND THEIR QUANTITIES

ID	Allergen	Quantity (ml)
0	Pollen	3
1	Dust mites	1
2	Pet dander	1
3	Cockroaches	2
4	Mold	1

The device is intended to be used with vials that can contain a maximum of 12 ml, so if users introduced a combination that exceeds its volume capacity, they are warned, and the process does not continue. In the other hand, when the user does not exceed the capacity of the vial, the remaining volume is filled with diluent.

IV. RESULTS

A. Block Diagram

In Fig. 4 we show the block diagram we are using for the device. Three of the electronic components of the device are supplied by the micro controller such as the LCD, the keypad, and the buzzer. We added the future sensors we will use for the device to know where it must stop. We will also use an external voltage supply, because we will use stepper motors to move to the desired spot in the tray, according to what the user needs. We will use 3 stepper motors to move in X, Y, Z axis through rails, and the micro controller does not supply enough current. The pipette is also going to be supplied externally.

B. Workflow

Even though the project is in its initial phase of development, the prototype showed us the possibility of integrating the keypad so the user can choose the processes, quantities, and allergens, obtaining serial feedback to control both processes. The system we created could manage the data entry, validate the capacity of the vial, and simulate the dilution protocol with real time feedback. The workflow resultant for this first stage of the project is shown in Fig. 5 starting from welcoming the user, moving to choosing the operation mode, and their internal processes, to finally indicate via sound that the process is finished

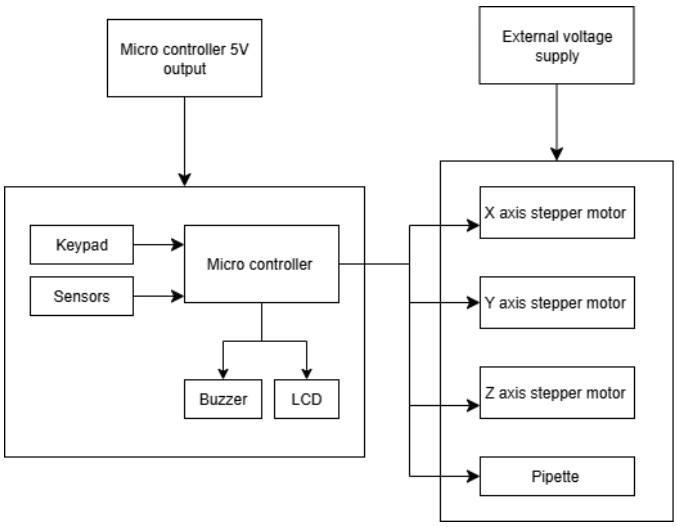

Fig. 4. Block diagram

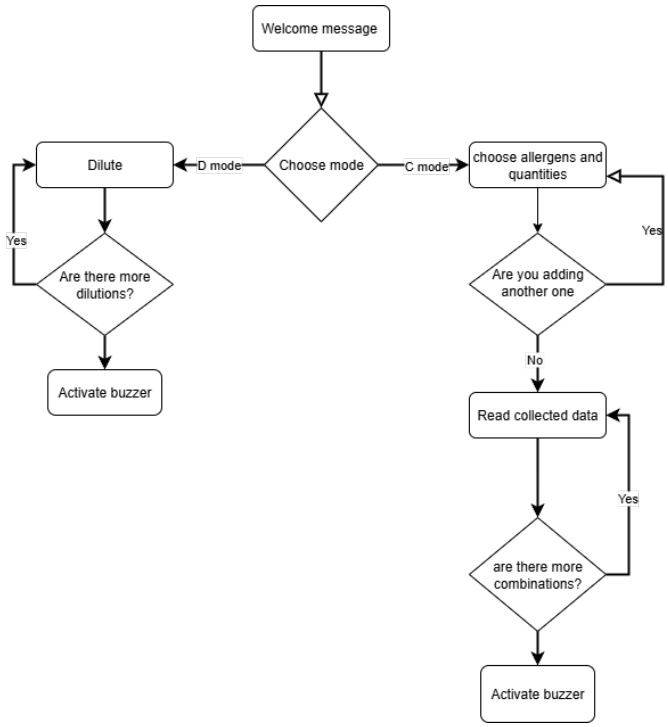

Fig. 5. Compounding device first workflow

C. Case design

Currently, it only shows the external case of the device and the vial's tray with its slots. In Fig. 6 we can see that the housing has several open spaces. The bigger one on the side is for the tray, so it can be removed to place the allergens, vials and diluent before the process, and to take them back

to storage after the process is finished, considering many of them cannot be without of refrigeration for long time. The other three spaces are for the keypad, located under the LCD display. The last space is intended to be a window seal with an acrylic piece to make sure the aseptic measures are not being vulnerable by external agents. It will be sealed at the top and will only be open by technical service providers in case of maintenance.

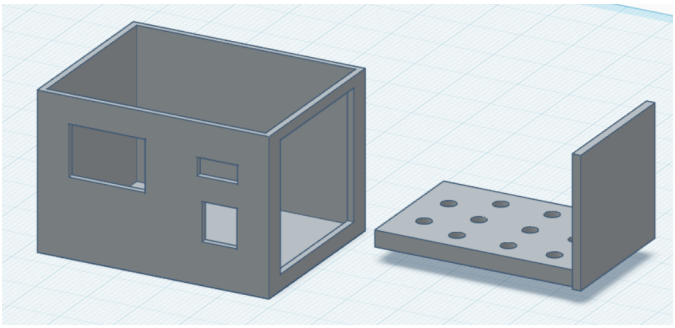

Fig. 6. Compounding device first workflow

D. Limitations

The project does not calculate the dose of the patient; the physician is supposed to calculate it before the process, so they can choose the allergens and their quantities. The rates of dilution are set be in a serial 10-fold dilution, which means that the physician can choose between 5 options of dilution. And the selection of the quantity only accepts integers. All of theses aspects are going to be revisited and developed for future research.

V. Conclusion

This article presents the preliminary design of an automated device for the preparation of allergen immunotherapy, in response to a present need in the biomedical field, since this process is currently carried out manually, which implies a high risk of human error, variability in vaccine formulation and a significant workload for the health personnel involved, especially in areas with little access to automated technologies, as is the case to a large extent in Central America.

The proposed design has two main functions: the serial dilution of concentrated allergens, which is essential for the tolerance induction process and the customized combination of these, allowing the user to select both specific allergens and volumes. Through a simulation in Tinkercad, the technical functionality of the system was corroborated, which includes the integration of a keyboard for data entry, vial capacity validation and real-time feedback of the dilution process. In addition, an initial design of the housing was developed that incorporates the principles of sterility and ease of use.

Validation and additional tests will be needed in real medical environments to assess precision, safety, and usability. However, the current results represent a great step towards the development of an automated system for allergen immunotherapy.

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