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Treball Final de Grau

Development of a process to clean the outside of the closed injectable ampoules

Desenvolupament d'un procés per netejar l'exterior de les ampolles d'injectables.

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Qui mou muntanyes va començà apartant pedretes.

Confucio

Doncs bé tal com va dir Confucio, si vols arribar molt amunt has de començar ben avall. Després d'aquests tres mesos de realització del meu treball de final de grau crec que he començat a moure aquestes *pedretes* per mica en mica anar construint el meu camí cap a l'èxit. El fet és que, tot i que sigui *el meu camí* no he estat sola en cap moment. Abans d'endinsar-nos en el sí del meu treball de final de grau m'agradaria donar les gràcies a totes aquelles persones que han format part d'aquesta experiència i que m'han ajudat a crear el camí.

Primerament, voldria agrair a la meva tutora d'empresa per la seva confiança dipositada en mi. Ella ha estat la primera persona que m'ha obert les portes al món laboral en l'aplicació pràctica de l'enginyeria química, que m'ha ensenyat com funcionen les coses més enllà de la vida de l'estudiant i que sobretot, ha confiat en mi per formar part del seu equip de treball. En aquest magnífic departament que he tingut donant-me suport en tot moment també m'agradaria fer-ne esment. Al trobar-me en un equip multidisciplinari he pogut aprendre com desenvolupar-me en una mateixa situació des de diferents punts de vista i criteris. M'enduc un bon grapat de coneixements diversos, de moltes experiències i sobretot d'un sentiment immens de formar part d'un gran equip d'experts i sobretot d'un gran equip de persones. Així mateix, totes aquelles persones de la companyia que han posat el seu granet de sorra per tal que aquest projecte fos una realitat també vull donar-los les gràcies.

Per altra banda, no puc oblidar totes les persones que des de la universitat m'han donat un cop de mà en la realització d'aquet treball de final de grau. Especialment al meu tutor el Dr. Juan Llorens Llacuna donar-li les gràcies per tutelar-me i guiar-me en el desenvolupament d'aquest projecte.

Tot i saber que aquest projecte tanca una etapa de la meva vida i que a més, simbolitza el principi d'una de nova que ara tot just comença, les expectatives i la motivació per continuar endavant amb nous reptes són enormes i és per això que m'agradaria donar les gràcies a totes aquelles persones que des de sempre han estat al meu costat recolzant-me i fent-me caminar apartant pedreta a pedreta. D'aquesta experiència en concloc que només coneixent el camí i recorrent tots els seus giravolts es podrà arribar allà on un/a es proposi.

REPORT

CONTENTS

1. SUMMARY

The project presented below was generated from a real need of a pharmaceutical plant to improve the production of one of their products. The proposed improvement project affects the manufacture of injectable ampoules, exactly the external washing of them once been filled and sterilized.

The external ampoule's washing is necessary because they will pass through an inspection stage where it will be detected if there are any impurities inside the ampoules. If ampoules are not externally clean the inspection line cannot distinguish whether the product have internal impurities or external, therefore, all of this ampoules will be rejected due to they will be unfitted for consumption. This external dirt mainly result during the sterilization stage due to rising temperatures and especially the pressure some of the ampoules do not withstand these conditions and endlessly they breakdown.

Until this moment, the company uses the autoclaves to carry out the ampoules external washing. In this project three different ideas for improving this process stage are proposed. The first two ideas, propose improving the ampoules external washing using elements and equipment the plant already have, meanwhile the third option proposes a totally innovative washing design.

The first option studied was the possible modification and improvement of the autoclave cycle to ensure, as already known, that there is no possible way an autoclave would carry out a good external washing. Its use is unique and exclusive to perform sterilizations.

The second option was proposed was to optimize the ampoules trays. They are used for transporting the ampoules between the different stages of the process. Trays are holoed stainless steel "boxes". Their holes allow draining any remaining water from sterilization, and until now, from the washing. Thus, their dimensions, material and even the pass area of water through it were studied, but this option presented limitations regarding its improvement as it was seen that all the were almost ideal for the process.

Finally, the last option was to design an ampoule's washing tunnel. Using the washing tunnel it was ensures a good external wash of the ampoules so they would pass through the inspection line without any problem.

This last option was the one presenting more improvements related to cost savings and especially time spent for company's workers hand-washing those ampoules detected for the inspection line one by one.

Keywords: improvement; injectable ampoules; washing tunnel; autoclaves; trays

2. RESUM

El projecte que es presenta a continuació es va generar a partir d'una necessitat real d'una planta farmacèutica degut a voler millorar la producció d'un dels seus productes. El projecte de millora afecta a la fabricació d'ampolletes d'injectables, exactament al rentat exterior d'aquestes un cop s'han emplenat i esterilitzat.

El rentat exterior de les ampolles és necessari degut a que les ampolles han de passar per una etapa d'inspecció que detectarà si hi ha impureses en el seu interior. Si les ampolles no estan netes externament la inspeccionadora no podrà distingir si les impureses són internes del producte o externes, per tant, les rebutjarà totes com a ampolles no aptes pel consum. Aquesta brutícia externa pot ser conseqüència, majoritàriament, que durant l'etapa d'autoclavatje degut a l'augment de les temperatures i sobretot a la sobrepressió, algunes d'elles no resisteixen aquestes condicions i acaben petant.

Fins ara l'empresa utilitzava les pròpies autoclaus per dur a terme el rentat exterior de les ampolles. En aquest projecte es proposen diferent idees de millora per el procés. Les dues primeres tenint en compte el elements i equips presents a la planta, mentre que en la tercera proposa un disseny totalment innovador.

La primera opció estudiada va ser la modificació i possible millora del cicle de l'autoclau per assegurar, com ja se sabia, que una autoclau de cap manera està preparada per dur a terme un rentat. El seu ús és únic i exclusiu per realitzar esterilitzacions.

La segona opció proposada va ser l'optimització dels carregadors d'ampolles utilitzats per el transport d'aquestes entre les diferents etapes del procés. Es tracten d'unes "caixes" d'acer inoxidables foradades per poder drenar l'aigua que pugui quedar durant l'esterilització, i fins ara, el rentat. D'aquesta manera es va estudiar les seves dimensions, material, inclús l'àrea de pas de l'aigua a través seu. Aquesta opció però va presentar certes limitacions en quant a la seva millora ja que es va veure que les dimensions, el material i l'àrea de pas eren casi les idònies per el procés.

Finalment, la última opció va ser dissenyar un túnel de rentat de les ampolles des de zero. D'aquesta manera es podia assegurar un bon rentat extern de les ampolles i per tant, que les ampolles passin l'etapa d'inspecció sense problemes.

Aquesta última opció va ser la que més millores va presentar en quan a estalvi de costos i sobretot de temps del treballadors dedicat a rentar manualment les ampolles detectades per la inspeccionadora amb brutícia externa.

Paraules clau: millora; ampolles d'injectables; túnel de rentat; autoclaus; carregadors

3. INTRODUCTION

In the nowadays market we can find a wide variety of pharmaceutical products. The same product can be sold by different brands, in different doses, and, above all, in different formats (capsules, syrups, sprays, injections...). The pharmaceutical industry is responsible for manufacturing this range of products.

One of the most complex products to be manufactured is the injected ones. It has to be considered the wide range of critical factors in its manufacturing. It is known that this kind of product will be directly inserted into patient's blood so; this is why the preparation of that product must be extremely careful. It must be kept in mind that patient's body will absorb the drug immediately so the preparation must ensure a completely perfection (pertinent doses, no impurities...)

3.1. INJECTABLES PROCESS OF MANUFACTURING

The manufacturing process for obtaining injectable products consists of six stages in which the final product, as it can be gotten from pharmacies, will be taking shape. These stages are:

1. MANUFACTURING

The product is manufactured from raw materials in some industrial reactors. The location of these reactors on the pharmaceutical plant enables using gravity to transport the product manufactured by pipelines to the next processing step.

2. FILLING

The product from the pipes is inserted into ampoules for injections in a careful and critical operation. A slight variation in the filling system could cause a major catastrophe in the final product. The filling stage, along with sterilization, is one of the most critical stage of the process as injectable ampoules must contain a precise amount of product, must have properly shaped head and last but not least , without any suspended particles inside or outside the ampoules; without impurities.

While the ampoules are filling the ones filled are introduced into trays. Once a tray is full, they are collocated into trolleys and transported to the next step, the sterilization.

3. STERILIZATION

Once the filling stage has been done, process proceeds with the external sterilization of the ampoules. For this stage autoclaves are used (explained in detail below). Into the autoclave sterilization, a stress test, and finally water shower are performed. The stress test causes breakdown of all those ampoules which are defective construction and thus avoid passing them to the next stage of inspection. Finally, into the autoclave it is performed a water shower for both purposes, lowering the temperature of the ampoules and making an external washing on them.

4. INSPETION

Following with the process, the ampules pass to the inspection stage. In this stage, they are selected based on specifications that must pass to meet the requirements of customers, in addition to the standards of sanity health.

5. LABELLED

After the inspection can be a labelling stage before the final packaging. This step is not always present in the manufacturing process of the ampoules for injection; it will depend on customer requirements.

6. PACKAGING

Finally, it is proceed to the packaging of ampoules. These can range from boxes that are distributed to pharmacies for its direct sale to public or can be packaged in large boxes for carry them to other plants in foreign countries.

Fig. 1. Process of manufacturing injectable ampoules

4. OBJECTIVES

The project developed below, emerges from the necessity of optimize the washing and drying of ampoules once the outside sterilization stage has taken place in the autoclaves. The detected problem lies on two pillars. On one hand, the fact of using autoclaves to clean the outside of the ampoules is not the appropriate mechanism as they are not designed to perform this function. On the other hand, and as a consequence from the first pillar, trays containing cleaned ampoules retain too much water to pass through the ampoules inspection stage. It involves a timeout drying by evaporation of the water for about 48 hours, approximately.

Improving this stage is important not only for reducing the waiting time for drying the ampoules, but also to reduce the numbers of ampoules re-inspected due to a first rejection for detected external dirt caused by the inefficient external wash the autoclave can provide. Some of the main customers the company have, evaluate in the same criticism the product quality and its presentation, either by themselves requirements or by health standard's requirements of the country.

As already mentioned, the sterilization with an external washing of the ampoules is one of the most critical stage in the process, so an improvement in this step would be an improvement in the whole process.

Coming up next, different responses to this problem will be presented and at the end of the document the conclusions will summarise all the options and identify the most suitable in response of the problem defined.

5. AUTOCLAVES STUDIO

Before begging with improvements for washing the ampoules it will be studied the current situation. On account of it will be explained first the autoclave functions, characteristics and its cycle operation, which is where the problem lies.

5.1. WHAT IS AN AUTOCLAVE? WHAT IS IT USED FOR?

An autoclave is a pressured chamber used to sterilize equipment and supplies by subjecting them to high pressure saturated steam at 121 °C for around 15–20 minutes depending on the size of the load and the contents. It was invented by Charles Chamberlandin 1879, although a precursor known as the *steam digester* was created by Denis Papin in 1679.

An autoclave is a device that uses steam to sterilize equipment and other objects. This means that they are able to neutralize potentially infectious agents by utilizing pressurized steam and superheated water.

Fig. 2. Plant autoclave

5.2. OPERATION OF AN AUTOCLAVE

5.2.1. Sterilization process

For moist heat sterilisation, two major types of process are typically used: saturated steam sterilization processes and air overpressure sterilization processes. Although saturated steam

processes are typically for sterilization of porous/hard good loads, while air overpressure is typically used for liquid product loads, the company uses a saturated steam process on the sterilization of the ampoules. This is because this kind of sterilizing process is commonly used when the liquid resides in a sealed rigid container.

There are two possible load type ones selected the saturated steam overpressure as the sterilization process. On one hand is the pre-vacuum process and on the other the gravity displacement process.

The load type selected for the company to sterilize the product is the pre-vacuum process. It is the most commonly used saturated process. The pre-vacuum process is particularly suited for load items that can trap air. Vacuum pulsing processes are used frequently in the pharmaceutical industry to sterilize porous/hard goods loads that contain items from which air removal can be difficult. In this case the main reason to use is because this sterilization process is the best one to sterilize drugs in their final container.

This method removes air from the chamber using a mechanical vacuum pump or stem educator before the sterilization phase of the process begins. Many sterilizers have a purge cycle programmed as the first step in porous/hard goods cycles. Pulses can be made more efficient by pre-empting them with a gravity purge. Also, this may reduce wear and tear of the pump system.as well as remove condensate in the load. Alternating vacuum pulses and steam charges are used to condition the load prior to the exposure phase of the cycle. The numbers of pulses are load type dependent, typically 1-3 pulses are used for hard goods air removal; whereas, mixed or porous loads may require additional pulses.

Treatment of the load prior to the start of the sterilization exposure phase is important. If each vacuum pull is to 0.1 atmospheres, then each pulse will reduce the air in the sterilizer by 90%, or one log. Three vacuum pulses (there vacuum pulls with corresponding steam charges) create a 3-log reduction, effectively removing 99.9% of the air. Additional positive pulses (steam chargers with corresponding evacuations above atmospheric pressure to avoid air leaking into the chamber) may be added to condition the load. Through this approach, air removal efficiency can be increased, leading to shorter equilibration times. The precise number and type of pulses should be determined during the development of the cycle.

It may be beneficial to use already developed sterilization cycles to minimize the total number of different cycles used in a company in order to reduce the ongoing costs of qualification and requalification. Changing an autoclaves cycle implies re-determinate the physical parameters of the sterilization cycle to provide biological indicator acceptance and "a proven acceptable range" of critical parameters that will result in a product/material that is both sterile and functional after the sterilization process. This is the reason why in this project the autoclaves cycles have not been modified.

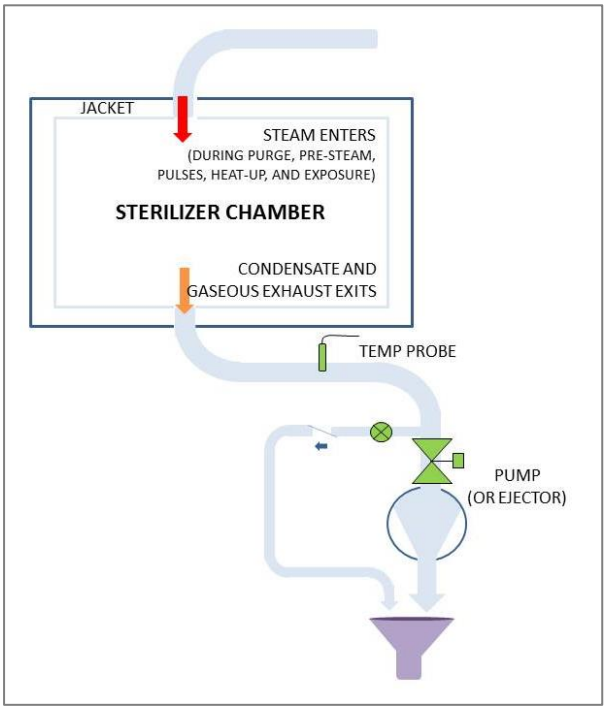


Fig. 3. Respresntation of an autoclve where used a pre-vacuum process

5.3. PLANT AUTOCLAVES

5.3.1. GMP compliance

Autoclaves used in a pharmaceutical plant must follow very strict health standards to prevent contamination of products. Rules to ensure compliance with these standards are called GMP (Great Manufacturing Practice).

It is commonly understood that a “GMP sterilizer” is a unit designed for moist heat sterilization, and built in accordance with current pharmaceutical industry sanitary design standards.

The characteristics must comply GMP sterilizers are:

- Typical applications include sterilization of products used in the testing or manufacturing of drug products, and terminal sterilization of liquids in sealed containers.
- Piping and chamber are designed to accommodate clean utilities such as pure or clean steam and process air. This includes stainless steel clamped and welded designs, proper slopes and deadlegs.
- Materials of construction are compatible and appropriate (e.g., non-particle generating) with products and processes ensuring no contamination (e.g., product or environmental). May be supported by certificates of inspection and traceability.
- Product contact utilities (e.g., water, steam, air) supplied to the sterilizers is suitable for its intended use and meets applicable Compendia expectations.
- Control and monitoring systems meets regional regulatory expectations for data security and integrity.
- Temperature monitoring and control devices (e.g. drain probes) are independent of one another.
- Performance meets requirements and specifications with Quality Unit oversight are expected.

The above rules must be strictly followed by all pharmaceutical plants without exception. They ensure the quality required by governments as well as health authorities.

5.3.2. Load distribution in the autoclave

Autoclaves filling lines are loaded by the gateway located in the injectable filling area; if sterilization is successful, the download is performed by the packaging area. If the cycle has not been correct, the autoclave security system only allows the gateway been oppened by the filling zone. This method prevent passing a bad steriloization cycle to the next process step and allow detecting the error earlie

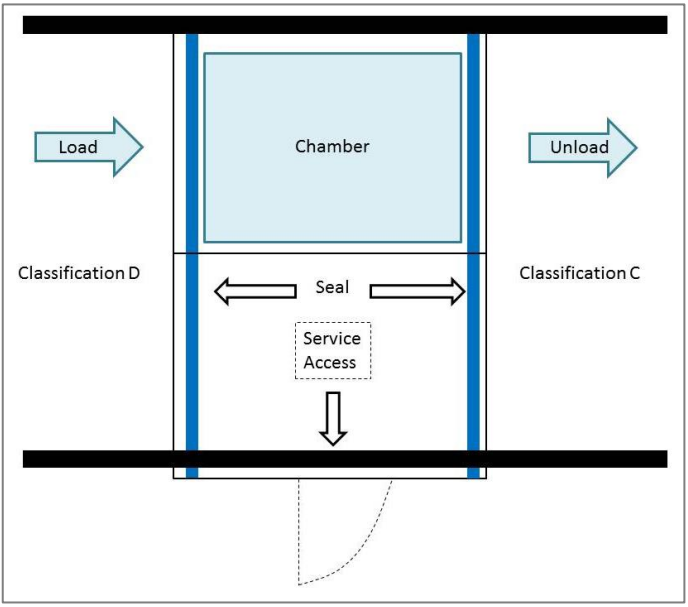


Fig. 4. Load and download of an autoclave

Autoclaves have a maximum capacity of three trolleys. A complete trolley consists of 88 trays arranged in 11 levels. Each level contains 8 trays and each tray contains a determinate number of ampoules. The number of ampoules would vary depending of the ampoules volume (1 ml, 2 ml, 5 ml or 10 ml). Although the number of ampoules varies depending on their volume, the maximum autoclave load would be the same. Contrary to the maximum load, the minimum load would entirely depend on the type of ampoules treated because of the minimum load would be defined according to the number of ampoules per tray.

The following table indicates the number of ampoules per tray according to their volume:

Format	Nº ampoules/Tray
1 ml	540
2 ml	535
5 ml	275
10 ml	190

Table. 1. Standard number of ampoules per tray

In this project the ampoules used would be of 5ml. The table above is used for most of the products manufactured in the plant, but there are ones due to their characteristics have other number of ampoules per tray. In the case of this project the format of ampoules is 5 ml but the number per trays is 270 due to the product inside the ampoules is so dirty and sticky so in case an ampoule crashes inside the autoclave the reduced number of ampoules allows them not to get glued.

Independently of the load of the autoclave, the first trolley must be placed always at the packaging nearest wall. The load of each trolley must be performed from the first floor, ascending to the top floor. The trays must be placed starting from the left bottom side of the trolleys and completing a floor with 8 trays.

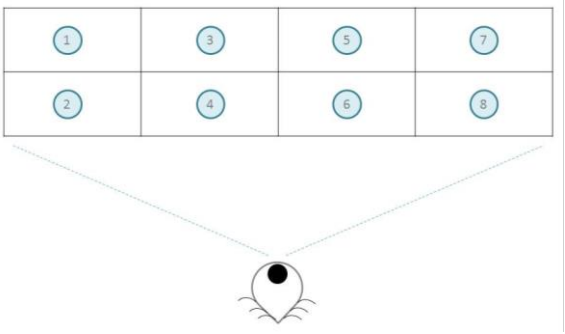


Fig. 5. Trays loading

According to all this information, the maximum load is three complete trolleys; if the last trolley is not full the load would not be distributed between the three trolleys, keeping the same order as the one indicated for loading one trolley.

While, the minimum load for a standard product sterilization cycle to start is 40 trays set in 5 levels (this is half completed load approximately). In the case treated on this project is 48 trays set in 6 levels for the same reason described on the upper paragraph.

6. TRAYS

Remembering the project objective was, on one hand, to reduce de among of water that places between the ampoules and on the other hand, to reduce the time spent waiting for the ampoules to be dried.

Once understood the operation of the autoclaves, and knowing that their cycles cannot be changed due to their work and costs associated, at first sight was thought of improving the trays used for contain the ampoules (changing the nowadays material, improving the pass area and even it was considered to change the holes shape).

In this section is described how getting deep in the study of the trays made the project change the way it was focused to be developed.

6.1. NOWADAYS TRAYS

Nowadays, trays used have a rectangular base shape with one of the two small walls mobile, as it shows Figure 6. This mobile wall is necessary to charge and discharge the trays with the ampoules on the different stages of the process.

Fig. 6. Nowadays trays showing the mobile wall

6.1.1. Dimensions

The dimensions of the nowadays chargers are:

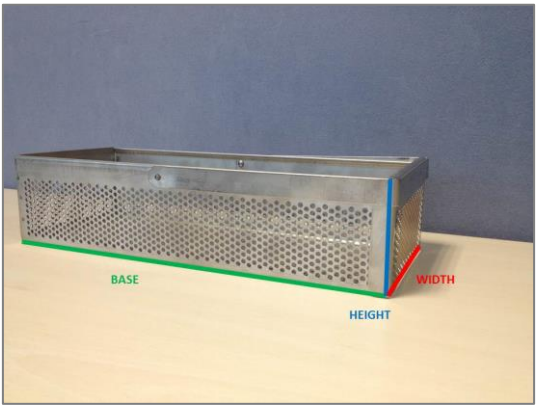


Fig. 7. Dimension of the trays

LENGHT	VALUE [mm]
BASE	390
WIDHT	150
HEIGHT	90

Table. 2. Dimensions on the nowadays trays

The dimensions of the trays are immobile due to the fact the autoclaves cycles are validated with these dimensions. Moreover, the minimum and maxim autoclave load depends on them and either with the quantity of ampoules inside, as explained before.

6.1.2. Material: AISI 304

The tray's material used nowadays is a stainless steel known as AISI 304. As said on the autoclave point all the materials used on the drugs manufacturing has to be under GMP acceptance.

Stainless steels are iron alloys with a minimum of 10.5% chromium. There is no only one reason for using this material, but it has lots of advantages. The main characteristic of stainless steel 304 is the high corrosion resistance compared to conventional steels. AISI 304 is applicable in a variety of weather conditions and in many corrosive media. Its characteristics are obtained by forming an invisible and adherent chromium oxide film.

The ordinary composition of this material is:

Composition element	%
Chrome	17,5 -20
Nickel	8 -11
Magnesium	2
Silicon	1
Carbon	< 0,08
Phosphorus	0,045
Sulphur	0,03

Table. 3. Stainless Steel composition

The properties obtained using stainless steels 304 are:

- Oxidation resistance in all environments except in polluted sea areas and highly polluted areas or contact with acids and similar.

- Good mechanical response: in welding, bending, shearing, laser cutting...

- Perfect finish and aesthetics.

- Great durability.

- It has not a great electric conductivity; it is not electrical nor is also not magnetic.

- It has a high resistance to corrosion compared to the usual steels.

- Easily mouldable into different shapes.

6.1.3. Holes

The stainless steels sheets for manufacturing the trays are holed with rounded holes with quincunx disposition. It is known as quincunx placing objects in different rows so that they are staggered, covering the holes from one row to another. The tray's holes in question are at an angle of 60 ° as shown on the figure 8.

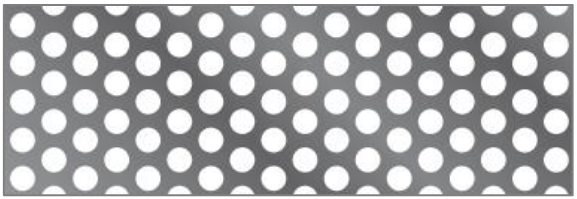


Fig. 8. Quincunx holes disposition (picture from company's stainless steel supplier)

6.1.4. Advantages and Disadvantages of nowadays trays

Advantages:

The actual trays are relatively cheap. The main reason for this is the use of AISI 304 as material for manufacturing the trays. Because of, their manufacturing is quite easily and, in addition this stainless steel is one of the most markets used, it contributes reducing the price too. Moreover, as long the number of trays ordered the lower prices it is achieved per tray.

Another important advantage, the main one, would be their strength, specially their resistance on the water corrosively. According to this resistance the trays last for more than ten years. Therefore, all the properties described before are good advantages on the nowadays trays.

It cannot be forgotten the compliance with the GMP rules.

Disadvantages:

Trays are too heavy for users to move them ergonomically due to their weight. As commented on the previous point, the maximum load of the autoclaves is 88 trays. Due to they are made of stainless steel and to their dimensions, the weight approximately per tray is 850 g, so a complete autoclave load supposes a total weight of 74,800g (74.8 kg) approximately.

Another disadvantage is the non-standardization of the "number" of holes and their dimensions (holes diameter and distances between their centres). Consequently, the weight of the chargers varies between one another and as a consequence the amount of water retained. It is known the more holes a sheep have, the less weight it would be.

6.2. CHALLENGING THE NOWADAYS TRAYS

Once described the characteristics of the nowadays trays the objective of this section is trying to find out some solutions for the disadvantages found on the study of the nowadays trays.

6.2.1. New materials

The first characteristic of the nowadays trays which has been challenged is the material. As said in the point above one of the problems of the actual trays is their weight. Their lack of ergonomics for the people involves on their transport and management is one of the company's priorities.

Presented below are two options for replacing the current stainless steel AISI 304.

A. AISI 200 series

The first proposed substitute for the AISI 304 is a stainless steel too, AISI 200 series.

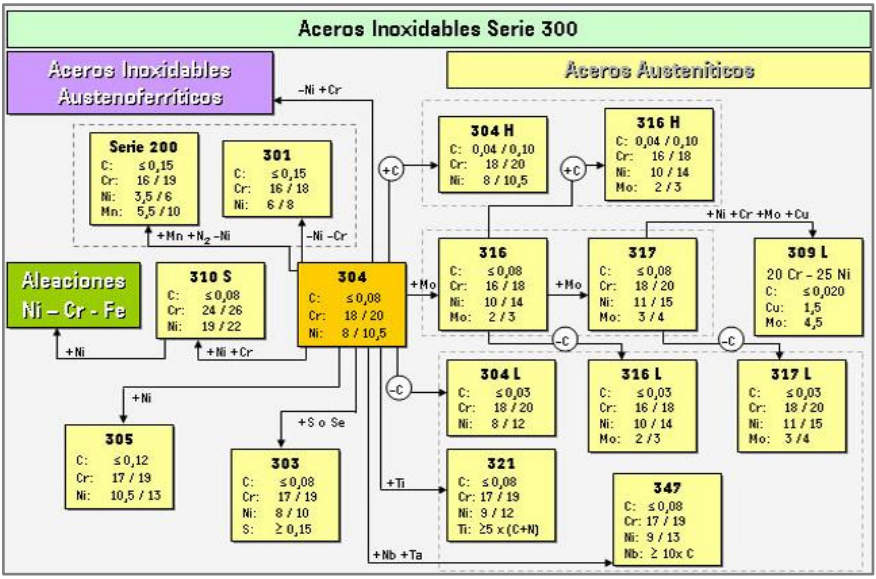


Fig. 9. Classification of steels according to AISI standards (*21/10/15 via Multimed*)

In the above figure it can be highlighted the 200 series (austenitic stainless steels) as an alternative to classic stainless steel AISI 304. These are steels with a nickel content of 1% to 4%.

Stainless steel is used for its oxidation resistance, hardness, hygiene and beautiful finish. The 200 Series, non-used so far, remain the same properties as the AISI 304 but with a cheaper price.

The technical basis for these new stainless steels (AISI 200) is the combination of nickel (Ni), the chromium (Cr) and magnesium (Mg). In addition, these alloys are corrected with copper (Cu) and nitrogen (N) to obtain materials with the best properties. The result is a more than 30% below current costs stainless steel.

Alloy 304 is an austenitic stainless steel used for general purposes with centred cubic structure faces. It is essentially non-magnetic in the annealed condition and can only be hardened by cold. Low carbon content regarding to alloy 302 gives better corrosion resistance in welded structures and all these characteristics are contemplated on series AISI 200.

Although all the factors indicates that the series AISI 200 would be one of the best substitute for the actual material it cannot be used. The reason is because they are not approved for the GMP rules. The quality assurance of the pharmaceutical industry is heavily restrictive with the materials used because they have to assure no impurities inside their drugs.

Discarding series AISI 200 as one of the options for replacing AISI 304 it has been studied another type of material. There are lots of options on the market but it must focus on ones that can simulate the stainless steel properties as far as possible. Searching has been found the anodized aluminium as one of the possible substitutes.

B. ANODIZED ALUMINIUM

Many metals are structurally weakened by the oxidation process, but not aluminium. Aluminium can actually be made stronger and more durable through a process called 'anodizing'.

It is called anodized to the electrochemical process of passivation (a forced oxidation) used to increase the thickness of the natural rusty layer on the metallic surfaces. This layer is created by electrochemical process. The process itself involves placing a sheet of aluminium into a chemical acid bath (generally acetic acid). The sheet of aluminium becomes the positive anode of a chemical battery and the acid bath becomes the negative. When the current passes, oxygen is freed and addressed to the node where aluminium resides creating an oxide layer whose thickness depends on the time the current has been passed. For closing the porous the anodized aluminium layer has it is submerged in warm water. This is the last step for the process to finalize; the shelf life of the layer is proportional to its thickness which is between 5 µm and 20 µm.

Unlike iron or carbon steel where oxidation creates a layer of corrosion or rusts the anodizing process actually enhances the properties of aluminium. The hard oxidized layer becomes a part of the aluminium, creating numerous beneficial properties. Since the layer has been integrated it cannot be scraped or peeled.

The layer depends basically on the electrolyte, the current used, the water's warm and the duration of the process.

The benefits of the anodized aluminium are:

- Durability: since anodized aluminium extrusion products have a protective layer, they are more resistant to wear grim normal handing and usage.
- Finishing: the process creates a more aesthetically pleasing finish, with either a clear or colourized appearance.
- Corrosion resistance: the thick outer coating produced, along with proper sealing, increases the corrosion resistivity of the surface as it prevents further oxidization.
- Strength: the anodized aluminium surface is harder than pure aluminium, only grated by diamonds due to its hard crystalline structure. Anodized aluminium can be nearly as hard as diamond under the right anodizing process.
- Not abrasion: Heat is distributed evenly across anodized aluminium, and the process of anodizing provides a naturally protective finish.
- Lasting colour: the colour finish added to anodized aluminium is more enduring due to the surface obtaining more adhesive and porous qualities during the anodizing process. The resulting anodic film coating allows for effective dyeing processes to be applied.

Although it can be thought that anodized aluminium would be the best candidate to substitute the stainless steel used until now, the GMP rules do not allow use this material on a pharmaceutical company again. Besides the prototype's budget were ordered and the costs per tray were too much expensive so the company refuses changing the stainless steel used for the anodized aluminium.

6.2.2. Study of the pass area and its improvement

Once studied the material and dimensions of the trays and conclude that they are unchangeable, it was proceeded to study the pass area of water through the holes to see if there is any chance of improved it.

The pass area would be one of the essential parameter to understand why the water remains into the trays and consequently, be difficulty to dry the ampoules inside.

In addition to the information above, having so much weight it is not only because the material used, but also to the tan per cent of sheet's area holed.

The object of this part of the project was study the pass area available through the trays sheets. For being the holes on a quincunx disposition, the tan per cent of pass area would be calculated using the following formula:

$$\frac{D^2 \; x \; 90{,}69}{T^2} \qquad \textit{eq. 1}$$

Where D is the diameter of the hole, and T is the "pass", the space between the centres of two staggered holes as shown in figure 10.

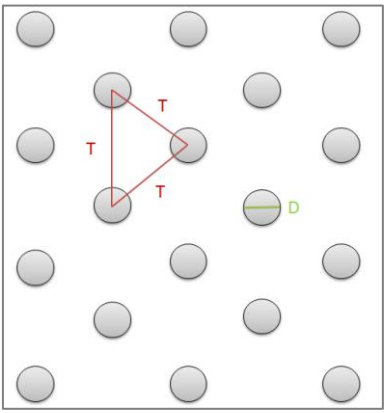
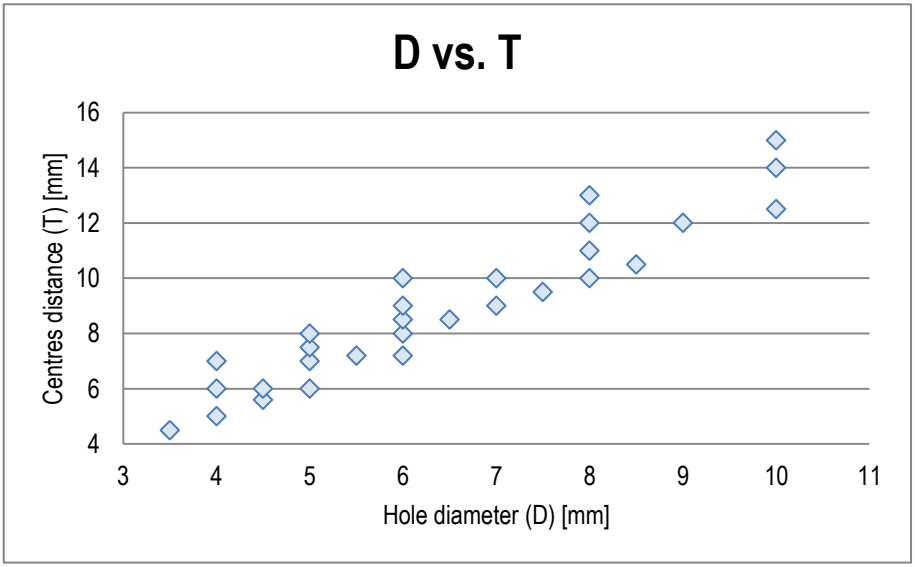


Fig. 10. Parameters of the quincunx holes

For trays used on the company it is found holes diameter that varies between 3-4 mm and a space between them centres is about 5-6 mm.

It was studied the relationship between the diameter and the pass trying to find the relation between them that creates the maximum pass area. For this purpose it was searched information from different suppliers and other sources of information. The information searched was related with the different pair diameter-pass area given from the suppliers. It was collected all the information found in a summary table with all the dates. The graphic below shows these dates in a more grateful way for interpreting the results found.



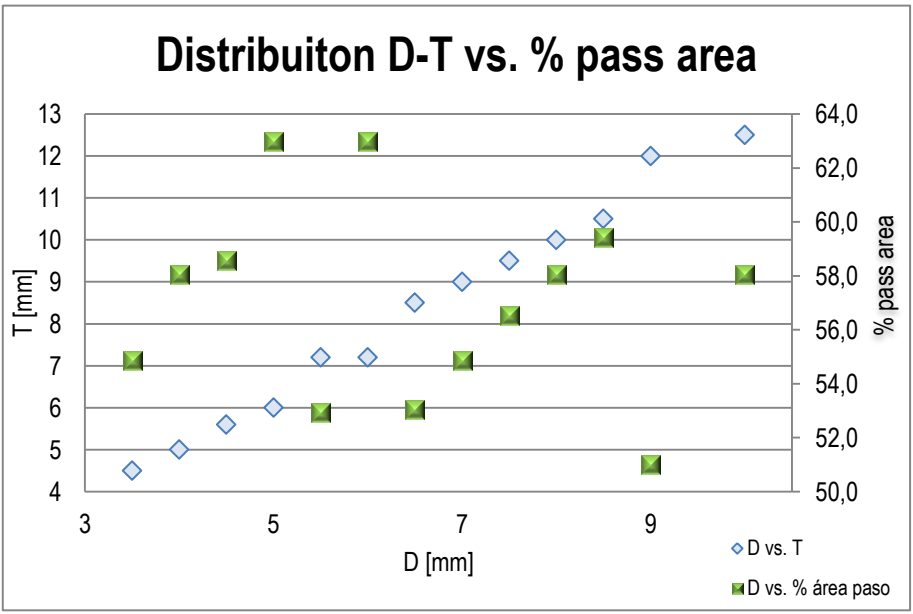
Graphic. 1. Relation between the holes diameter and their centres distance

As shown, the relation between D-T is lineal, so it can be rapidly concluded that the best pair of numbers for increasing the pass area, would be the ones with the largest values.

Due to the diameter of the ampoules the studied range would be between 3-10 mm. The lower boundary is just to assure that the pass area have an interesting tan per cent. Contrarious, the larger one exist because the smaller diameter of the bottles is 11 mm so it has to be guaranteed the non-passed of these bottles through the holes.

Another fact visible on the graphic is the frequencies of the diameters are repeated. According to the information of the suppliers, the ones more repeated are the more usual diameter. Which pair of the ones repeated, whose holes diameter is the same but they differ on the centres distance value, would have a different tan per cent pass area.

Studying holes parameters and their effect on the water retention, it cannot only be considered holes diameter versus centres distance; it may be studied how this pairs of values effect on the tan per cent of area available for the water to be filtered. In order to find out the best pair D-T vs. % pass area, the graphic below shows the result of selection of that areas with a tan per cent pass area major than a 50%.



Graphic. 2. Pass area versus best D-T pairs

Just observing the graphic above the best pair holes diameter-centres distance that allows a major pass area are the ones with 5-6 holes diameters and 6-7.2 centres distance, respectively. The pass area reached is 63%.

At the beginning of this point it was said that the actual trays have holes diameter that varies between 3-4 mm and a centres distance between 5-6 mm. It can be concluded that tray's holes used nowadays are not too far from the ideal model holes. In conclusion, the size of the holes cannot be so far improved. The only useful think the study of the holes concludes is that the standardization of the holes can be made based on the information above presented.

According to the standardization of the trays and the results of the studies done it was decided to change gradually the nowadays trays for ones with a quincunx distribution holes with a 5 mm diameter and a 6 mm distances between their centres, according to the distribution shown below.

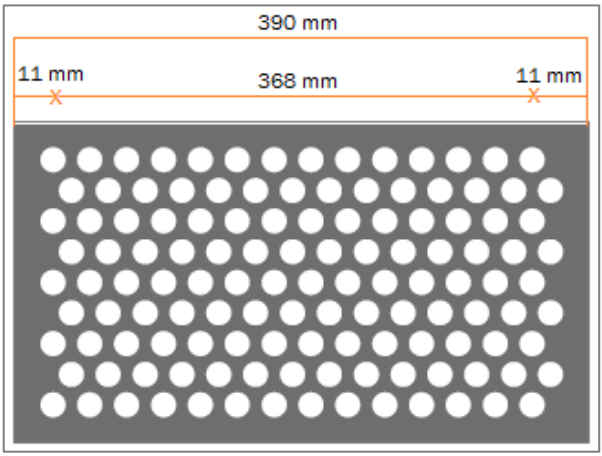


Fig. 11. Example of the new holed sheets distribution

Initially, this project was focused on the re-design of the trays. This re-design had the main point on re-defining the holes size. Although at the beginning of this point it was commented to modify the holes shape, while the study of the trays advanced, it was decided not to continue investigating a new type of hole. The main reason for taking this decision was the fact it was not possible to reduce the water on the trays just changing the shape or dimensions of the holes. The only way to reduce the amount of water would be placing the ampoules one by one instead of putting them all together in the trays. This way would avoid ampoules create water's surface tension to make more difficult for ampoules to get dry in a short period of time.

7. SURFACE TENSION

As commented, ampoules generate water's surface tension due to their disposition in the trays. Also, the surface tension exists between the ampoules and the holes too. Although it has not the same importance as the one create for two ampoules in contact.

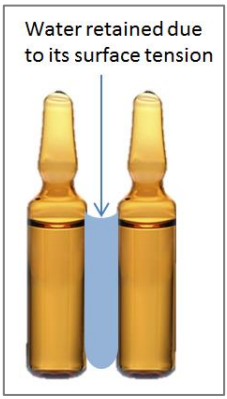
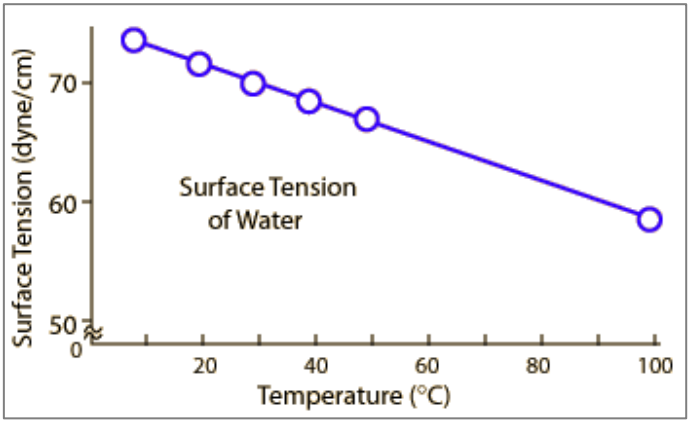


Fig. 12. Water surface tension between ampoules

The cohesive forces between liquid molecules are responsible for the phenomenon known as surface tension. The molecules at the surface of a glass of water do not have other water molecules on all sides of them and consequently they cohere more strongly to those directly associated with them (in this case, next to and below them, but not above).

Surface tension could be defined as the property of the surface of a liquid that allows it to resist an external force, due to the cohesive nature of the water molecules.

A very important point for this project is that the surface tension of water decreases significantly with temperature as shown in the graphic below. It is related due to the more temperature the water achieve the most water vapour would be created.



Graphic. 3. Graphic water surface tension (27/11/15 via Hyperphisics*http://hyperphysics.phy-astr.gsu.edu/hbase/surten.html*)

7.1. COHESION AND ADHESION

Molecules liquid state experience strong intermolecular attractive forces. When those forces are between like molecules, they are referred to as cohesive forces. For example, the molecules of a water droplet are held together by cohesive forces, and the especially strong cohesive forces at the surface constitute surface tension.

When the attractive forces are between unlike molecules, they are said to be adhesive forces. The adhesive forces between water molecules and the walls of a glass tube are stronger than the cohesive forces lead to an upward turning meniscus at the walls of the vessel and contribute to capillary action.

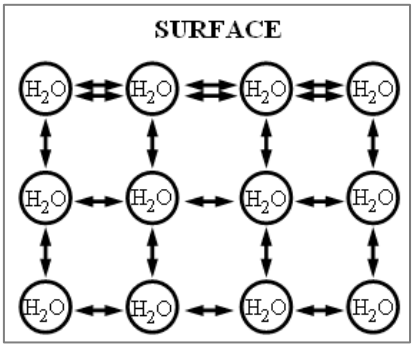


Fig. 13. Surface tension - molecules at the surface form stronger bonds

(*7/12/15 via USGS: science for a changing world*)

The cohesive forces between molecules in a liquid are shared with all neighbouring molecules. Those on the surface have no neighbouring molecules above and, thus, exhibit stronger attractive forces upon their nearest neighbours on and below the surface.

Due to the surface tension, small objects will "float" on the surface of a fluid, as long as the object cannot break through and separate the top layer of water molecules. When an object is on the surface of the fluid, the surface under tension will behave like an elastic membrane. Because of this effect, the possible micro-impurities that may be on the surface of the water when it dries remain attached to the outer wall of the ampoules.

7.2. MENISCUS

A meniscus is a curve in the surface of a molecular liquid substance when it is within a column of another material.

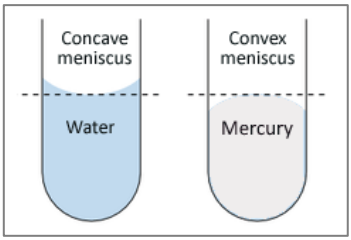


Fig. 14. Varieties of meniscus

(*7/12/15 via USGS: science for a changing world*)

The meniscus appearance has to do with the nature of the water molecules and glass molecules themselves. Water is made up of polar molecules, which have positively and negatively charged ends. Since opposites attract, the positive sides attract the negative sides, and all of the molecules stick to one another. This is why water droplets can form. Glass molecules also happen to be polar. Water molecules are attracted to the molecules in the wall of the glass beaker. And since water molecules like to stick together, when the molecules touching the glass cling to it, other water molecules cling to the molecules touching the glass, forming the meniscus. They will travel up the glass as far as water's cohesive forces will allow them, until gravity prevents them from going further.

8. TUNNELS

Due to not being successful improving the autoclave cycles, owing to these equipment are not designed to develop the functions of washing and drying the outside of the ampoules, and neither the trays characteristics the project changes its focus 180 degrees.

Remembering, the main point of this project consist on obtaining the most properly cleaned and dried ampoules to pass the inspection step reducing the re-inspection and the time spent waiting for the ampoules be dried. Consequently, on this part of the project has been designed a wash and dry tunnel, similar as the ones used on cars, after the sterilization on the autoclave.

8.1. CYCLE'S DEFINITION

As said on the introduction, the manufacturing of injectable is based on six steps. It is easy to imagine that one of these steps would be the slowest one due to this a continuous process. Owning to known information, it will be considered that in this case this step is the filling of the product inside the ampoules. To ensure that this hypothesis is correct it would be calculated the rate of ampoules per minute that an autoclave cycle can provide with a maximum load.

The filling lines go on 400 ampoules per minute (400 amp/min). This would be the supposed objective to achieve for the tunnel constructed below in case the autoclave rate would be higher than this value.

It could be thought that the autoclave would be the slowest step in the project, and in terms of time it is, but ones the autoclaves has been done it can provide the next step with 71,280 ampoules, approximately, at one blow.

First of all, for proving the hypothesis above presented it would be calculated the numbers of ampoules come out of a maximum load of an autoclave for this purpose it will take into account the information described in the autoclaves point. On the above point, it is said that the maximum load into the autoclave is 3 trolleys, in which trolley contents 88 trays (11 levels with 8 trays per level). Resolving a simple equation it can rapidly be concluded that the maximum load of an autoclave is 264 trays. On the same point above, is mentioned the quantity of ampoules that can be in each tray. It is said that for ampoules of 5 ml the capacity of a tray is about 275

but in the case of this project as a result of treating a dirty and sticky product the number of ampoules is reduced to 270 per tray (is the equivalent to a one less line of ampoules). For this reason, the total number of ampoules for a maximum autoclave load is 71,280 ampoules.

Knowing that an autoclave cycle duration is 1 hour and 12 minutes, it can be calculated the number of ampoules per minute treated on a maximum load. Transforming the hours to minutes and adding the 12 minutes more, the time spent on the autoclave step is about 72 minutes. If divided the number of ampoules from the maximum load on the autoclave (71,280 ampoules) between the autoclave cycle time (72 minutes) it shown that the autoclave rate is 990 ampoules per minute (990 amp/min).

As said hypothetically, the tunnel should clean and dry the ampoule at a rate of 400 ampoules per minute at least due to it is the slowest rate on the manufacturing of the injectable. Considering that one tray's load is approximately about 270 ampoules, to reach the minimum required speed the tunnel should wash and dry two chargers simultaneously or increase its velocity to achieve the objective. Another factor takes into account when determining the number of trays treated is the time spends for the washing and for the drying. This information will be useful later when the tunnel must be dimensioned.

For determine the time the tunnel should spent treating the ampoules (washing and drying them) it only needs to be resolved a simple multiplication. If it is considered that two trays would be treated simultaneously, 540 ampoules would be treated at once (270 ampoules per tray); and if the tunnel rate is 400 amp/min, the time for treating the two trays would be 1.35 minutes. This value would be used as reference of time when determining the washing and drying parameters.

8.1.1. Determination of the washing and drying requirements

The first things may be in consideration are the different variables that would effect on the final aspect of the ampoules. The variables considered for the construction of the tunnel washing and drying sections would be: temperature, pressure, velocity of the trays and the time of a cycle

- Temperature: the temperature can vary between 20 and 65 Celsius. Increasing the water's temperature to achieve better results on the cleaning it must be arranged in a rank. This range exists due to not lose sterility properties and not effect on the

product's conditions of stability. Air's temperature would be the ambient (about 20 Celsius).

- Pressure: it can vary between water and air. The maximum pressure of the water's installation when manufacturing is 2.0 bars while the air pressure is 6.4 bars.
- Velocity of the trays: the velocity of the trays must beat least 400 amp/min in order to assume a complete maximum autoclave load. Later in this point, the calculation for expressing the tray's velocity with units of length and time would be made.
- Time of a cycle: the time would be limited both with tray's velocity and the washing and drying requirements of the ampoules.

It must be considered that the water used for the cleaning is deionized water, so it has their own properties different from the ones in the convectional water's circuit.

These variables will be modified and combined in order to test the outside cleaning and drying method using ampoules which are externally contaminated with the product.

The quantity of 324 ampoules as a sample will be studied under different combinations of the variables already mentioned. It will be checked visually whether the contamination is cleaned and the ampoule is dried too through an installed spraying system. The best combination will be applied through an entire tray. To confirm if the variables will ensure a good cleaning and drying achievements the ampoules will pass through an inspection line.

It is shown next a picture of the initial state of the ampoules.

Fig. 15. Initial state of the ampoules before started the cleaning and drying test

This picture above shows the worst case, ampoules have been soiled with the product and it has been dried. It is not usual that ampoules arrived with the dried product on their outside, but in the cases it happens this dried product is more difficult to clean that the one steel wet. To cover the worst case, in this project are used ampoules with soiled dried on their outside.

To start up with the determination of the parameters for the washing and drying of the ampoules, it was decided to determinate the washing parameters for the different variables first. Once these parameters were obtained it was proceeded with the determination of the drying ones.

8.1.1.1. Washing requirements

For the washing requirements it must be worked in the laboratory with water's temperature, pressure and the time needed for obtaining goods results. The water used for the cleaning will be deionized water to avoid soiling the ampoules ones the water will be evaporated.

As mentioned above, the water temperature should be in a given range not to interfere with the product. Therefore, the temperature was set at 20 degrees as it is the lowest temperature that can be applied on ampoules once leaving the autoclave. Moreover, this temperature is approximately the water's circuit temperature so the requirements for regulating it would be quite low. In addition, using this temperature can ensure not to interfere with the product characteristics or stability. Another point to be considered is that using a temperature lower but near the one the ampoules leave the autoclave helps freezing the ampoules and consequently the product inside.

Once the water temperature was set, the pressure which the water must clean the ampoules was studied. The pressure selected must assure the cleaning of the ampoules without breaking down anyone. Three pressure values were set, always lower than the maximum system pressure of 2.0 bars. The three values selected were 1.0 bar; 1.5 bar; 2.0 bar. These values were selected not to overpressure ampoules causing breakage of them for stroke among themselves or with the trays walls.

Further, another parameter studied was the repetition of the three selected pressure values. Each of the selected pressures could be repeated once, twice or three times to check its effectiveness. It allows seeing the impact of the repetitions on the final wash.

It must be taken into account the time spent for the washing. As can be rapidly concluded it will increase as the repetitions do. The time used as reference will be the 40% of the time above calculated for a theoretical total time needed to treat two trays (540 ampoules). It was chosen the 40% of the time and not the half because is considered the existents of blanks inside the tunnel (sections were no treatment is taking place). With this hypothesis in mind, the 40% of 1.35 minutes is 0.54 minutes, transforming in seconds is a value of 32.4 seconds. For making the practical part easier 30 seconds would be the time reference instead of 32.4 seconds.

Each pair of pressure-repetition number will be applied on an ampoule's group for 30 seconds.

Pictures below are a sample of the final state of 324 ampoules under different water pressures and different repetition, each applied for 30 seconds. Each pair of pressure and repetition number has 36 ampoules to be tested.

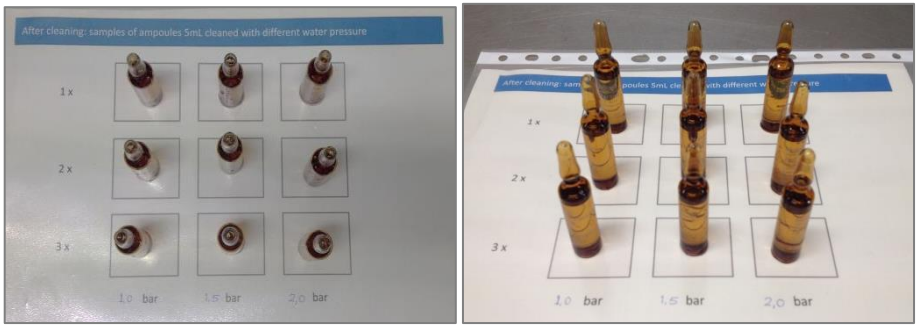


Fig. 16. Example of ampoules cleaned with different water pressure and repetitions

Ampoules were atmospherically dried leaving them two days until water were naturally removed. Drying this way ensure the uniformity of the drying through all the ampoules cleaned.

As it can be seen with naked eyes, the cleanest ampoule is that with a stronger pressure (2.0 bar) and three repetitions but there is a narrow difference with the group treated with 2.0 bar and two repetitions. Apart from the first impression, it must wait for the inspection stage to conclude which pair of pressure and repetitions are the ones which it can be obtained the best cleaning results.

All the 324 ampoules were passed through the inspection line to determinate the best pair pressure-repetition number. As aforementioned above, each pair pressure-repetitions number

has a total of 36 ampoules. Considering 36 ampoules for each pair of values as the 100%, the table below shows the tan per cent of acceptance obtained by the different pairs.

Nowadays, the acceptance of ampoules is about 73% of the total ampoules inspected. This number increases if it is considered also those ampoules accepted in a second round of inspection. Not all the ampoules rejected at the first inspection would be re-inspected; the only ampoules that would be re-inspected are the ones rejected for external dirt. The amount of ampoules were re-inspected due to outside dirt was approximately 11%.

One of the consequences for this project to be applied is the reduction of the ampoules re-inspected so it would have an indirect impact on the time company workers spent hand-washing the ampoules, one by one, rejected on the first inspection round due to external dirt.

The tan per cent goal in this project considered as a good result would be more than an 83% of ampoules accepted on the first round. Increasing only the 10% ampoules accepted at one round implies a reduction, not only of the company workers time, but also a reduction of the money wasted on using machines unnecessarily.

Pressures	Repetition number	% of acceptance
1.0 bar	1 repetition	8.33
	2 repetitions	19.44
	3 repetitions	30.56
1.5 bar	1 repetition	38.89
	2 repetitions	25.78
	3 repetitions	61.11
2.0 bar	1 repetition	75
	2 repetitions	86.11
	3 repetitions	94.44

Table. 4. Tan per cent of acceptance with the different washing pairs of pressure-repetitions number

Confirming the expectations deduced with naked eyes, the best options for washing the ampoules are 2.0 bars of pressure with two or three repetitions. Both options exceeded the minimum level proposed of acceptance (83%) this is why the reason for choosing between one and the other was strictly for convention of the needs and requirements of the company. Commenting the results obtained with the company experts was decided to use only to repetitions and not three. It was several reasons for choosing this option. First, repeating the washing twice reduces the water needs. Another point was the fact that the tunnel will be constructed in continuous working, it means that the washing's repetitions will be done with different "showers" and not with the same. Because of the washings will be done one after the other the length of the tunnel would be modified and increased as the repetitions increase too. It supposes another increase in the budget for manufacturing the tunnel (material, difficulty…). Finally, but not less important, the tunnel would be located at the autoclave's output and the space is limited. The more reduced the tunnel's length the better operating with the space had.

Summarising, the water parameters would be 20 Celsius for the temperature, 2.0 bars for the pressure with two repetitions and a time spend for the washing of 30 seconds. Related with the time it must point out that during the experiment 30 seconds were clearly enough to allow good cleaning results.

8.1.1.2. Drying requirements

For determining the drying parameters was used the same methodology as in washing. Three different compressed air pressures were chosen to apply over the ampoules. These pressures were 2.5 bar; 3.0 bar; 3.5 bar. Similarly to the washing pressures, drying pressures were selected below the maximum pressure of 6.4 bars.

For selecting the best air pressure it was taken into account the repetition of application too. As in the case of the washing, each pressure could be repeated once, twice or three times.

The air used is the same that the plant uses to sort the zones plant classification so it can be supplied for the same plant installation.

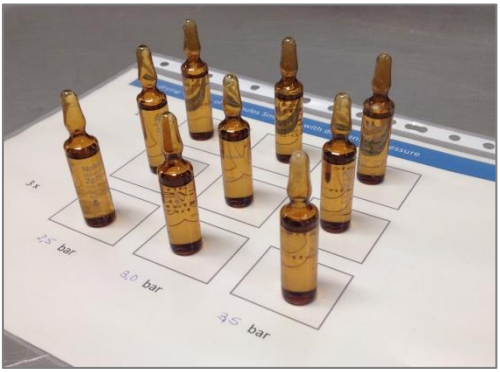


Fig. 17. Example of ampoules dried with different air pressure and repetition number

Ampoules taken as sample for drying were different from the ones used for the study of washing pressure. It was taken another group of 324 ampoules for study the drying parameters. In this case all the ampoules used on the drying tests were previously cleaned with the washing parameters above determined.

As in the washing, it was determined that the time for the drying must be 40% of theoretical time. Consequently, each pair of pressure-repetitions number values was applied for 30 seconds.

As it was trying to be analysed the drying parameters, ampoules had to be wet. For this reason, the group of 324 ampoules were divided in subgroups of 36. Did it this way allowed washing the ampoules just the moment before of applying them the compressed air.

The better pressure for the compressed air would be the intermediate one (3.0 bar). Using the maximum compressed air pressure for drying the ampoules causes on them too much vibration and made them collide with each other and with the tray's walls. In the case of the lower pressure many repetitions were required so, the time spent for the drying increases.

The final decisions for the drying parameters were a selection of a 3.0 bars pressure for the compressed air applied 30 seconds and with only one repetition. Obviously, with more drying repetitions also it could be acquired good results but was not required to make a greater number of drying repetitions due to it would be a waste of time and money.

The following table provides a global overview of the parameters the tunnel should have for washing and drying the ampoules.

Treatment	Pressure	Repetitions	Duration
Washing	2.0 bars	2	60 seconds (30 seconds per wash)
Drying	3.0 bars	1	30 seconds

Table. 5. Final washing and drying parameters

8.2. TUNNEL STRUCTURE

To determine the size and structure of the tunnel we must consider the following factors: tray's dimensions and needs of washing and drying.

8.2.1. Dimension

The method used for defying the dimensions of the tunnel will consist on begging from the inside out. Whereby the first parts being determined will be the pipelines used for the washing and drying.

8.2.1.1. Width

At the beginning of this section was made a hypothesis saying that to reach a rate of 400 ampoules per minute the tunnel should treat two trays simultaneously. Doing this consideration was observed that the total cycle time of the tunnel was 1.35 minute. This hypothesis has so far been successful in the laboratory so, it was decided that for the tunnel's structure and dimensioning will also be considered that two trays would be treated at the same time.

Making a quick reminder of the tray's dimensions, they have 390 mm long; 150 mm of width and 90 mm of height. As concluded on the paragraph above, it must be treated two trays at once to make the washing and drying on the tunnel, so the minimum width that the pipelines must have to allow the trays pass under them and cover the tray's width during the washing or drying is 300 mm. To ensure the trays pass inside the tunnel without problem the pipelines would be 80 mm wider than the total of two trays width. It also ensures the trays not to touch each other and avoid them to create surface tension between the walls of the two trays so the water cannot be retained there. The distances from the pipelines to the tunnel's walls would be 20 mm (10 mm per side) so the total tunnel's width would be 400 mm plus the 20 mm (10 mm per side) of the sheets thickness.

Contacting different suppliers and seeking other sources of information it was decided to use a square ring shape pipelines. It allows placing the water/air entrance and the exit on the same side of the tunnel. This square ring shape allows the pipelines expel water and air through outlets on their top. Following the supplier's recommendations, it was considered that pipelines will have a diameter of 5 mm and an outlets diameter of 1.5 mm, and each outlet will be located 2 mm from the next one. The pipelines will start and finish with 2 mm distance between the first/last outlet and corner of the pipe.

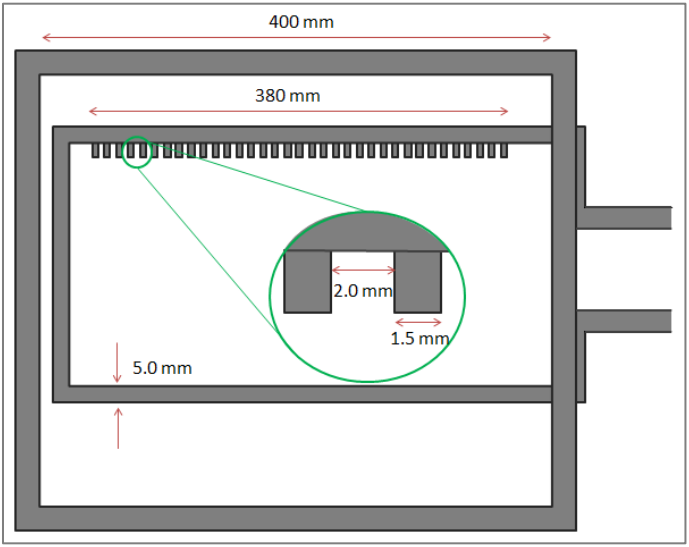


Fig. 18. Square ring shape pipelines

Considering the information given can be calculated the number of outlets each pipeline must have. For resolving this question, would be considered each outlet and the 2 mm in front of it as a group. So groups of 3.5 mm will be taken (1.5 mm from the outlet's diameter and 2 mm from the space between outlets in front of each). It should also be remembered that between the last outlet and the pipeline corner will have a space of 2 mm. By subtracting this 2 mm from the back's outlet of the total pipeline's length (380 mm), this would be 378 mm to place the outlets. If one divides this value (378 mm) between 3.5 mm for each group outlet-space before we get a total of 108 holes with the corresponding separation between them.

The pipelines will be made on measurement for the tunnel as thus to achieve the most accurately when designing them.

The pipelines will be made of stainless steel 304 thanks to its characteristics, which have already been explained above, this material is determined for use in the pharmaceutical industry for all elements that are indirectly in contact with the product. One of its main characteristics is the resistance to the corrosion and its strength. The pipelines must have both characteristics due to stand the test of flow water and air pressured.

8.2.1.2. Length

To determine the tunnel's length it must be remembered the time spent washing and drying the ampoules as well as repetitions of these treatments. This would determine the speed of the tunnel must have to treat the ampoules in maximum time of 1.35 seconds.

For the water section two rounds of pipelines would be required as concluded on the point *8.1.1.1*., which is said that the tunnel must clean the ampoules twice. According to the same information, the drying section only needs one pipeline to be done.

Analysing the information collected in the laboratory and with the expert's help, it was determined that the two water pipes could be closer together than the minimum distance corresponding to a tray's length. It represents the second wash cycle would begin while the first cycle it is not finished yet. It was decided to separate these cycles a distance of 273 mm. this distance corresponds to 70% of the length of a tray. It ensures reducing the washing zone but also the cleaning of the ampoules. This distance is set to prevent the over ampoule's vibration during the cleaning by water pressure causing breakage of the same for stroke.

The drying's pipeline will be exactly located at 400 mm from the last washing pipeline. This distance is not random, it correspond to a little bit more than the length of a tray. Leaving this space procured the trays to slightly decrease the water excess before doing the drying and also avoid the over vibration of the ampoules.

According to this information it can be calculated the speed needed for the tunnel to transport the ampoules achieving a total cycle time of 1.35 minutes. To determinate the tunnel's velocity it would be taken as reference the information of the washing. As said the distance between the washing pipelines would be 273 mm corresponding to the 70% of the tray's length. If considering the 70% of the total time spent doing the washing (30 seconds) it can be concluded that this time would be 21 seconds. These 21 seconds would correspond at the time the trays are moving 273 mm to the second washing round. Knowing the time and the distance

the velocity can be calculated. The velocity of the tunnel would be 13 mm per second (13 mm/s).

Once the tunnel's velocity is known it can be calculated all the parameters missing. Firstly, it can be calculated the time between the second washing pipeline and the air one. If their distance is 400 mm, the time spent is 30.77 seconds. Secondly, the final distance of the tunnel is missing too. If the drying treatment would last 30 seconds the minimum distance for treating a complete tray's length would be 390 mm.

According to the information given, the tunnel length would be 1.063 mm (273 mm between the washing pipelines; 400 mm between the washing pipeline and the dying one; 390 mm for doing the drying). This is the distance to ensure the cycle treatment of the ampoule, but to make the tunnels more ergonomic it would be added 500 mm before the first washing pipeline and 110 mm more on the tunnel's exit. This distances added wouldn't be taken into account during the cycle time of 1.35 mm. they are just the minimum space to load and download the trays into and out to the tunnel.

On the scheme below it is summarized the tunnel's length distribution.

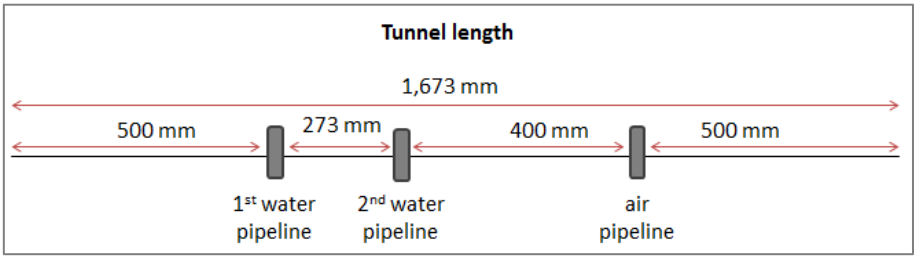


Fig. 19. Distribution of the tunnel length.

8.2.1.3. Height

To know the height of the tunnel it should be considered all the levels would be found inside the tunnel. Starting from the top the first tunnel's requirement found are the pipes for treating ampoules. They have a diameter of 5 mm corresponding to its height. In case pipes must be changed or repaired the manufacturer's recommendations, was to place them at a distance of 50 mm from the upper sheet of the tunnel. Continuing downing, the next element found is the trays. These have a height of 90 mm and for the effectiveness of the treatment trays must be placed at a distance of 20 mm from the pipelines. After that, it must be found the transporting

belt, which would be made of holed stainless steel. It has to take in to consideration that the belt used must be holed to drain the water used during the wash. The transporting belt would occupy a space of 200 mm. This distance includes the thickness of the belt itself and the rotation angle needed to complete the rotation circuit. The transporting belt would not be separated of the trays so there is no distance between these two elements. Below the transporting belt would be located the drainage system. It will consist on a stainless steel platform that will collect the wash water to a pipeline where it will be conducted to be treated and then reused. This drainage system would be located 40 mm lower the transporting belt. The drainage system would have an inverted truncated pyramidal cone shape, so the height of it will increase as it approaches the centre. The height of the drainage system including the pipeline would be 200 mm on the depth part.

The final height of the tunnel would be 605 mm. The tunnel would be elevated 1,500 mm from the floor to be more practical to load and download the trays for the users. So the total height of the tunnel would be 2,105 mm (or 2.1 m).

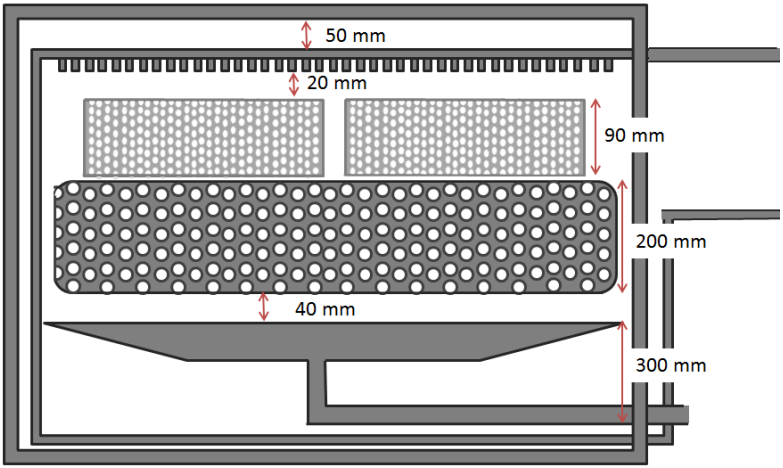


Fig. 20. Distribution of the tunnel height

8.2.2. Materials

To cover all the elements inside the tunnel it would have a rectangular base prism shaped. The materials of manufacturing the tunnel will be the same as the pipelines, stainless steel (AISI 304). The stainless steel sheets used, according to the supplier specifications, would have a

thickness of 20 mm. They must be fairly thick to allow the perforations for the inlet and outlet of the pipelines.

8.3. TUNNEL COSTS

The last step for ending the tunnel was to calculate raw materials costs. It would not be into account on this project the costs related to the manufacturing of the tunnel due to the company prefers reserving this information from the public's eyes.

To calculate the water's flow fall on the ampoules it should be considered the following information. Firstly, it must be known the water's and air's pressure (P) contained inside the pipelines. This would be the same that the one exited through the outlets. Few paragraph above, it was explained, by laboratory experiments, which pressures were needed for washing and drying the ampoules. Remembering it was decided to use 2.0 bars for the washing and 3.0 bars the drying. Another parameter must be known is the diameter of said outlets (d). This would be 1.5 mm for both washing and drying. The final component to calculate the water's and air's flow is the time spent for each treatment (30 seconds for the washing and for the drying).

Before calculating the water's and air's flow, it would be necessary to calculate the velocity of both fluids (v_W for the water's velocity and v_A for the air's velocity).

- Water's velocity:

The expression used for the water's velocity calculations is:

$$v_W = [\frac{2\ xP}{\rho}]^{1/2}\ [m/s] \qquad \textit{eq. 2}$$

$$v_W = [\frac{2\ x\ 2.0\ bar\ x \frac{100{,}000\ Pa}{1\ bar}\ x\ \frac{1\ \frac{kg}{ms^2}}{1\ Pa}}{1{,}000\ \frac{kg}{m^3}}]^{1/2}\ [m/s] \qquad \textit{eq. 3}$$

$$v_W = [\frac{2\ x\ 2.0\ x\ 100{,}000\ \frac{kg}{ms^2}}{1{,}000\ \frac{kg}{m^3}}]^{1/2}\ [m/s] \qquad \textit{eq. 4}$$

$$v_W = [400\ \frac{m^2}{s^2}]^{1/2}\ [m/s] \qquad \textit{eq. 5}$$

$$v_W = 20\ [m/s] \qquad \textit{eq. 6}$$

- Air's velocity:

The expression used for the air's velocity calculations is the same as the used for the calculating the velocity for any other gas:

$$v_A = [\frac{\gamma \; x \; R \; x \; T}{M}]^{1/2} \; [m/s] \qquad \textit{eq. 7}$$

Where γ is the adiabatic dilatation coefficient [for is 1.4]; *R* is the gases universal constant [8.314 kg·m²/mol·K·s²]; *T* is the temperature of the air [K]; and *M* is the gas molar mass [for air 0.0289 kg/mol].

$$v_A = [\frac{1.4 \; x \; 8.314 \; \frac{kg \; m^2}{mol \; K \; s^2} \; x \; (20 + 273)K}{0.0289 \; \frac{kg}{mol}}]^{1/2} \; [m/s] \qquad \textit{eq. 8}$$

$$v_A = [\frac{1.4 \; x \; 8.314 \; \frac{kg \; m^2}{mol \; K \; s^2} \; x \; (20 + 273)K}{0.0289 \; \frac{kg}{mol}}]^{1/2} \; [m/s] \qquad \textit{eq. 9}$$

$$v_A = 343.52 \; [m/s] \qquad \textit{eq. 10}$$

Once known the velocity of the fluids it can be calculated their flow.

The water's flow ($\dot{q_W}$) and the air's flow ($\dot{q_A}$) would be calculated with the following expression:

$$\dot{q_W} \; or \; \dot{q}_A = v \; x \; S \; [m^3/s] \qquad \textit{eq. 11}$$

Where *S* is the fluid pass section through the outlets [m²].

- Water's flow calculation ($\dot{q_W}$):

$$\dot{q_W} \; = v_W \; x \; S \; [m^3/s] \qquad \textit{eq. 12}$$

$$\dot{q_W} \; = v_W x \; \pi \; x \; [\frac{d}{2}]^{\,2} \; [m^3/s] \qquad \textit{eq. 13}$$

$$\dot{q_W} \; = 20 \; \frac{m}{s} \; x \; \pi \; x \; [\frac{1.5 \; mm \; x \; \frac{1 \; m}{1{,}000 \; mm}}{2}]^{\,2} \; [m^3/s] \qquad \textit{eq. 14}$$

$$q_W^{\cdot} = 3.53\ x\ 10^{-5}\left[\frac{m^3}{s}\right] = 127.23\ [\frac{l}{h}] \qquad \textit{eq. 15}$$

- Air's flow calculation ($q_A^{\cdot}$):

$$q_A^{\cdot} = v_A\ x\ S\ [m^3/s] \qquad \textit{eq. 16}$$

$$q_A^{\cdot} = v_A x\ \pi\ x\ [\frac{d}{2}]^{\,2}\ [m^3/s] \qquad \textit{eq. 17}$$

$$q_W^{\cdot} = 343.52\ \frac{m}{s}\ x\ \pi\ x\ [\frac{1.5\ mm\ x\ \frac{1\ m}{1{,}000\ mm}}{2}]^{\,2}\ [m^3/s] \qquad \textit{eq. 18}$$

$$q_A^{\cdot} = 6.07\ x\ 10^{-4}\left[\frac{m^3}{s}\right] = 2{,}184.34\ [\frac{l}{h}] \qquad \textit{eq. 19}$$

Once known the water's flow and the air's flow needed it can be calculated their costs. It must be considered the quantity of raw material used; the time spent using them as well as its overpressure. In the case of water the cost of the same is 0.18 €/m³, while the cost of treated air is 0.13 €/m³. Pressing both fluids costs 0.12 €/kWh.

- Water's cost:

$$W_{costs} = q_W^{\cdot}\left[\frac{m^3}{s}\right] x\ t\ [s]\ x\ 0.18\ \left[\frac{€}{m^3}\right] + P\ [Pa] x\ q_W^{\cdot}\left[\frac{m^3}{s}\right]\ x\ t\ [s]\ x\ 0.12\ [\frac{€}{kWh}]$$

eq. 20

$$W_{costs} = 3.53\ x\ 10^{-5}\left[\frac{m^3}{s}\right]\ x\ 30\ [s]\ x\ 0.18\ \left[\frac{€}{m^3}\right] +$$
$$+\ 200{,}000[Pa]\ x\ \frac{1\ kg/ms}{1\ Pa} x\ 3.53\ x\ 10^{-5}\left[\frac{m^3}{s}\right] x\ \frac{1\ J}{1\ kgm^2/s^2} x\ \frac{1\ kWh}{3600{,}000\ J} x\ 0.12\ [\frac{€}{kWh}]$$

eq. 21

$$W_{costs} = 1.9\ x\ 10^{-4}\ [€] +\ 2.35\ x\ 10^{-7}[€] \qquad \textit{eq. 22}$$

$$W_{costs} = 1.9\ x\ 10^{-4}[€] = 0.02\ cnt. \qquad \textit{eq. 23}$$

- Air's cost:

$$A_{costs} = \dot{q}_A \left[\frac{m^3}{s}\right] x\ t\ [s]\ x\ 0.13\ \left[\frac{€}{m^3}\right] + P\ [Pa] x\ \dot{q}_A \left[\frac{m^3}{s}\right]\ x\ t\ [s]\ x\ 0.12\ [\frac{€}{kWh}]$$

eq. 24

$$W_{costs} = 6.07\ x\ 10^{-4} \left[\frac{m^3}{s}\right]\ x\ 30\ [s]\ x\ 0.13\ \left[\frac{€}{m^3}\right] +$$

$$+ 300{,}000[Pa]\ x\ \frac{1\ kg/ms}{1\ Pa} x\ 6.07\ x\ 10^{-4} \left[\frac{m^3}{s}\right] x\ \frac{1\ J}{1\ kgm^2/s^2} x\ \frac{1\ kWh}{3600{,}000\ J} x\ 0.12\ [\frac{€}{kWh}]$$

eq. 25

$$W_{costs} = 2.37\ x\ 10^{-3}\ [€] + 3.06\ x\ 10^{-6}\ [€] \qquad \textit{eq. 26}$$

$$W_{costs} = 2.38\ x\ 10^{-3} [€] = 0.24\ cnt. \qquad \textit{eq. 27}$$

As can be deducted, the functional costs of the tunnel for the cleaning the outside of the ampoules are so low. The biggest inversion would be only the construction of the tunnel. Moreover, the installation of the tunnel represents an iceberg's top from a chain of saving. All the costs associated due to the ampoule's external dirt would be almost disappeared, so the plant could reduce the total costs for manufacturing the injectable ampoules.

9. SURFACTANTS (SURFACE ACTIVE AGENT)

Although washing and drying of the ampoules through the tunnel designed achieves the customers and sanity requirements and specifications, it is proposed for a next step of this project, to improve it through the study of the use of surfactants in addition to the external washing of the ampoules.

Surfactants can help cleaning the outside of the ampoules due to their characteristics. They are compounds that lower the surface tension (or interfacial tension) between two liquids or between a liquid and a solid, when used in very low concentrations. Surfactants may act as detergents, wetting agents, emulsifiers, foaming agents, and dispersants.

Surfactants are usually organic compounds that are amphiphilic, meaning they contain both hydrophobic groups (their *tails*) or water-insoluble (or oil-soluble) component and hydrophilic groups (their *heads*) or water-soluble component . Surfactants will be placed such that the hydrophilic group remain in contact with water while the hydrophobic group remain in contact with the solid or oil this means that surfactants will diffuse in water and adsorb at interfaces between oil and water or solid and water.

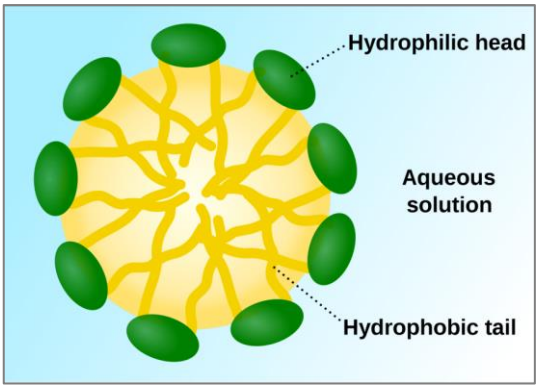


Fig. 21. Surfactants forming micelles O/W

(*13/12/15 via Wikipedia*)

9.1. SURFATANTS IN PHARMACY

To determine the appropriate type of surfactant for cleaning the ampoule's outside it was contacted an external company for information to be given about the options when choosing one or another type of surfactant. Their recommendation was a wetting agent surfactant.

A wetting agent is a surfactant that, when dissolved in water, lowers the advancing contact angle, aids in displacing an air phase or solid at the surface of the material, and replaces it with a liquid phase creating a surfactant layer at the ampoules surface. The application of this agent in the pharmaceutical plant would be displacing the solid residues from water remained after the first ampoules wash. In this way, all solid particles that could be found in water (although this is deionized water) would be drawn after the second wash so it allows the ampoules after drying being totally cleaned on the outside.

The contacted company recommended one of their products, which in this project will be known as X product. The main reason for the external company for recommending this product was because it is a low foam wetting solution based on water. The X product, builds up a stable and homogenous thin water solution film on hard surfaces at very low foam, offering a high wetting at very low dosage. This layer, based on colourless and transparent nanoemulsions, is easy to remove meaning that it could be withdrawal with deionized water.

Although the wetting solution was not studied in depth in this project, the company offers the option to adapt their commercial wetting solution to the requirements of the ampoules washing. It is possible due to the product X gives a high flexibility in the formulation criteria, stability and efficiency in a wide range of working conditions.

The time for the wetting solution to be applied would be after the first wash but before the second. This distribution allows the first wash withdraw the outermost dirt and larger particles too. Then the action of the surfactant must help to finish cleaning the outside of the ampoules.

10. CONCLUSIONS

The first conclusion that can be reached after performing the above project presented is that the current model of exterior washing and drying of the ampoules thereof can be improved. To improve the process already seen it has been demonstrated that it is not enough to using only the equipment present now on the pharmaceutical plant.

The best way to ensure a good washing and drying of the ampoules, as has been shown, is by building a washing and drying tunnel. The main characteristics this tunnel would achieve in difference from the nowadays method for cleaning the ampoules would be the followings. First of all, the external wash would consist on pressurized water's shower performed by outlets on a pipeline just design for this function, instead of re-using the autoclave for a "washing program". The immediate consequence of a good washing is the reduction of the re-inspection times the ampoules have to pass through the inspection lines owning to external dirt. It also would have a direct impact on the time spent on the inspectors as they would not spent their journal time hand-washing the ampoules one by one. Secondly, the fact of having a drying treatment inside the tunnel would affect directly on the cycle time for the ampoule's manufacturing. Before this project exists, the ampoules were dried with the ambient air by passing the hours just waiting them to be dried. The drying pipeline would reduce this waiting so the inspectors could treat the ampoules once the cleaning treatment would be finishing without any waiting time. Another important point for using a drying system is because the compressed air would help to reject the water from the ampoules surface and avoid it to be dried leaving solid dirt stacked on the ampoule's surface.

Even though the plant has 8 autoclaves so it would represent the construction of 8 washing and drying tunnel, the company has been so interested on this project so they are making financial consideration to make this project a reality.

11. REFERENCES AND NOTES

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APPENDIX

APPENDIX 1: OTHERS STERILIZATION PROCESSES

Saturated steam process

There are two main types of saturated seam sterilization processes; prevacumm and gravity displacement.

- Prevacumm process

It's been already explained on the project above presented.

- Gravity displacement process

The typical gravity displacement process is based in the principle that cold air within the chamber is heavier than the steam entering and will sink to the bottom of the chamber. As the steam enters the chamber, air is pushed out of the drain at the bottom of the chamber and exits (with the condensate) through the steam trap. The success of the process in removing air depends on the correct operation of the trap and the proper distribution of steam. Steam is injected into the sterilizer chamber through a baffle or spreader bar (such as a perforated pipe). If stream is added too rapidly or nor distributed properly, air pockets may be trapped near the top of the load. Of steam is added too slowly, the air can be heated, diffuse unto the steam, and become more difficult to remove.

Gravity displacement sterilizes are less efficient in air removal then other designs and are not recommended for items with air removal challenges. Figure 21 depicts a gravity displacement sterilizer. The red arrows represent steam entry through the steam inlet, displacing the air downward through the air/steam trap (drain), as shown by the blue arrows.

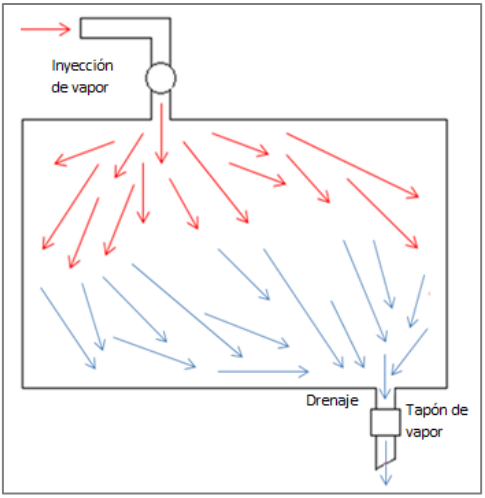


Fig. 21. Air removal

Air overpressure

In nearly all liquid containers, there is gas (air, nitrogen or other inert gas) in the headspace above the liquid. As the liquid is heated, the headspace gas expands pressure within the container increases.

For most liquid load applications, such as prefilled syringes, some glass bottles for vials, plastic bags and semirigid containers, the chamber pressure needs to be increased to minimize the differential pressure (between the internal container pressure and the chamber), maintaining the container shape and closure integrity, and in the case of syringes, stopper position. The air overpressure needed to compensate for internal container pressure may vary significantly, depending on the item type.

There are two common air overpressure process types.

- Steam-air mixture (SAM) process

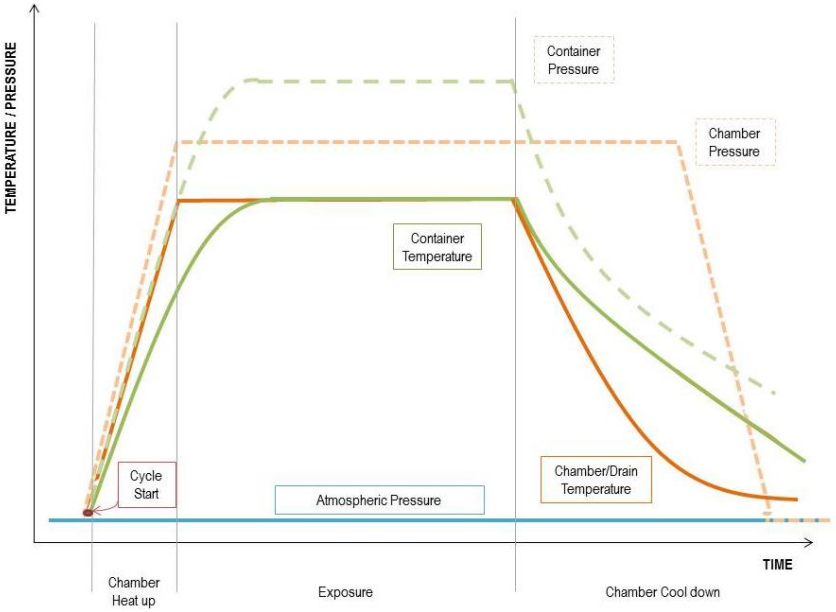
When air is added to steam to create a total pressure above the saturation pressure of the steam the (at specified temperature), it is called a steam-air mixture process. The presence of air, although necessary, reduces the heat rate when compared to saturated steam. The steam-air mixture process must continuously circulate the steam and air to:

· Prevent stratification and formation of cold spots within the load

· Reduce depletion of steam in the steam-air mixture next to the cold container

Fans are typically used to circulate the steam-air mixture.

The steam-air mixture process can use various methods to cool the product after the exposure phase. The most common method is to cool the recirculating air by adding chilled water to the sterilizer jacket or to coils within the sterilizer. Some steam-air sterilizers reduce the product temperature by spraying cooling water over the product.



Graphic. 4. Steam-Air Mixture Process Cycle Exchange

- Superheated water process

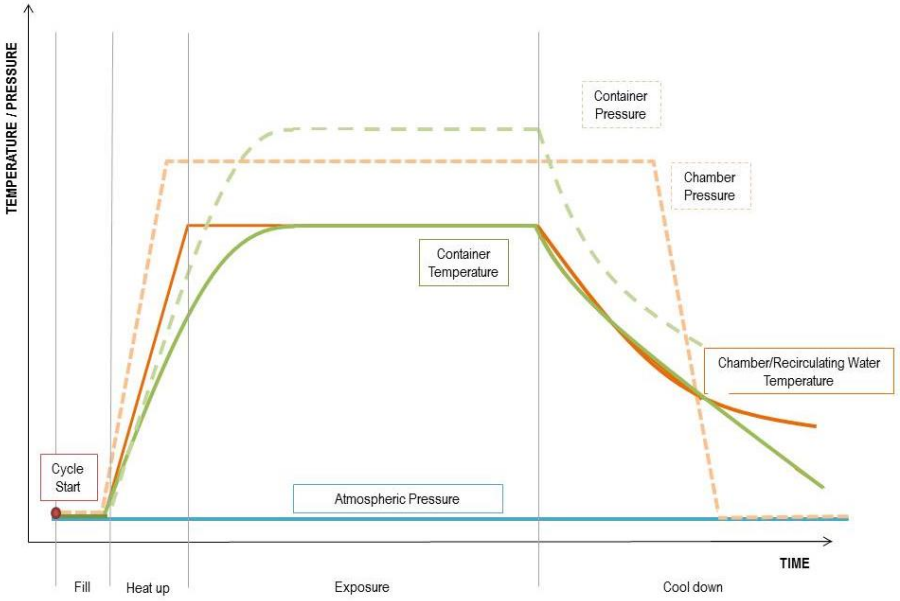
Sterilization of liquid-filled containers with recirculating superheated water is an efficient way to sterilize some products. There are many types of recirculating superheated water processes, the most common of which uses a pump to continuously recirculate water from the bottom of the sterilizer (below the load zone) to spray nozzles above the load zone. A slight modification to this process is the use of a water distribution plan to create a water cascade in lieu of spray nozzles.

The recirculating water can be heated and cooled, either directly by the injection of steam and cooling water or indirectly via heat exchanger(s). When using the indirect heating and cooling method (via a sanitary heat exchanger), almost any type of steam or water can be used

on the non-sanitary side of the heat exchanger. Use of an indirect cooling method is preferred, because the cooling water that directly contacts the sealed containers has been sterilized along with the product.

One of the primary advantages of the recirculating water process over other steam sterilization methods is that the heat-up and cool-down rates re easier to control and, if set up properly, are not influenced by variations in product load and utility supply. An example of the superheated water process is depicted in figure XX.

The primary quality attribute of the water used for a superheated water process is the microbial content of the water. The water may be sterilized in the chamber with the load, sterilized in a separate vessel, maintained at elevated temperatures, or chemically treated to maintain the desired low microbial content. Internal container pressures and temperature dynamics are a function of the container type, fill volume, head space volume, and chamber temperature.



Graphic. 5. Superheated water process cycle

APPENDIX 2: DESIGN APPROACHES FOR AN AUTOCLAVE

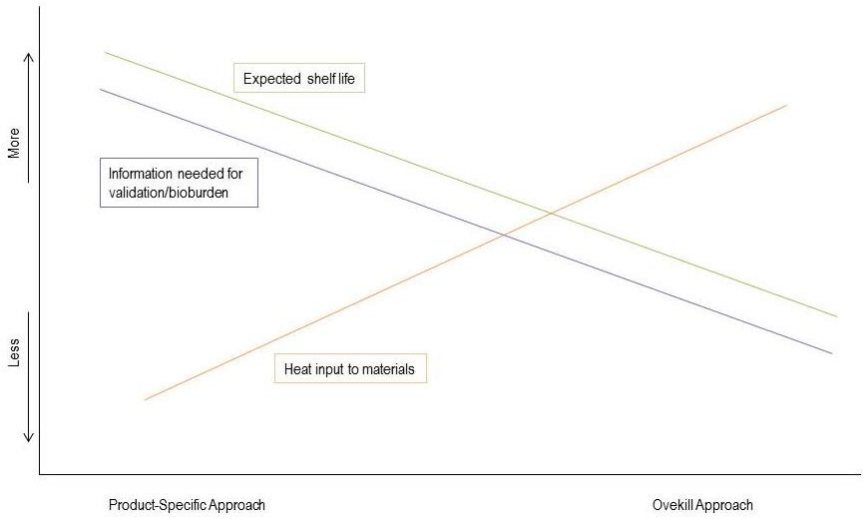
Two principal sterilization cycle design approaches that may be used for the development of sterilization processes are the overkill design approach and the product-specific design approach. Both of these approaches are able to provide the same level of sterility assurance to the product or materials being sterilized.

In the design of sterilization cycles, the choice between the two design approaches is largely based on the thermal stability of the product or materials being sterilized.

The overkill design approach requires less initial and ongoing information on the bioburden of the material being sterilized than the product-specific design approach, as depicted in XX. It requires a greater heat input, and consequently has a greater potential to degrade the items being sterilized.

The product-specific design approach requires a greater amount of initial and continuing information on the items being sterilized, the indicator organisms and the bioburden levels then the overkill design approach. The accumulation of this information provides a confidence in the values determined in the development to use a lower thermal input than required for the overkill design approach.

Using a lower thermal input also has the added benefit of providing greater stability of the materials being sterilized, potentially increasing their life. For this reason, the product-specific design approach is more appropriate for the terminal sterilization of heat-labile formulation in their final containers



Graphic. 6. Comparison of sterilization approaches

Product-specific design approach

An overkill design approach can not ordinarily be used when sterilizing heat-labile products or items. This situation is often the case in the terminal sterilization of drug products. A cycle must be developed which will adequately destroy the microbial load but will not result in unacceptable product degradation. The cycle is dependent on studies to determine the number and heat resistance of microorganisms in the product. Once the heat resistance and population of the bioburden organisms are characterized, a cycle can be design