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Development of product range for testosterone treatments.

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CONTENTS

SUMMARY

Testosterone is a sexual hormone that can be synthesized in different pharmaceutical product presentation for medical purposes. In the present project, a pair of treatments have been selected for which to develop a range of products. The first one being testosterone replacement therapy, in the specific case for male hypogonadism, that affects the pituitary system and makes it not segregate enough testosterone; and the second one transgender hormonal therapy. Several presentations for medical testosterone have been contemplated, but just two have been selected.

In the first case, gels have been selected as the presentation of testosterone for hypogonadism's hormone replacement therapy. The conceptualization of the product has been defined, as well as the establishment of its quality factors, the most important ones being the gels rheological properties, like viscosity, and its sensorial factors, like how smooth it feels on the skin. For this, a selection of ingredients has been made, having in mind their different properties and the microstructure necessities.

Another point in this project has been designing a process for manufacturing and picking the required equipment. In the processing of the gel, agitated vessels have been selected for dissolutions, several heat exchangers are to heat or cool the compounds to conditionate them, crushers are used to reduce the API's particle size, and a pressure homogenizer is in charge of preparing the emulsion. In the end, it has been decided that testosterone gels would be packed in sachets, so a last equipment for the filling is required.

On the other hand, the selected product presentation for transgender hormonal therapy has been tablets, which are not used nowadays. The same procedure has been made as with the gel. In this case, the most important quality factors are the chemical ones, and the particle size is important when manufacturing. The selected ingredients for the tablet match the products properties and have been selected to optimize the API's penetration in the system.

The design process for the solid product consists of crushers and granulators that regulate the particle size, as well as blenders that mix the different ingredients. The final steps consist of tableting the product by compression and coating it, to comply with the desired sizes and sensorial factors.

Keywords: Testosterone, hypogonadism, transgender hormonal therapy, testosterone treatment, testosterone gel, testosterone tablet, testosterone undecanoate, process design, API.

RESUM

La testosterona és una hormona sexual que pot ser sintetitzada en diferents presentacions de productes farmacèutics amb fins mèdics. En aquest projecte, un parell de tractaments han estat seleccionats per als quals es desenvoluparà una gama de productes. El primer és la teràpia substitutiva de testosterona, en el cas específic de l'hipogonadisme masculí, que afecta a la glàndula pituïtària i fa que no segregui suficient quantitat de testosterona; el segon es la teràpia hormonal per homes transgènere. Diverses presentacions per la testosterona s'han contemplat, i finalment s'han escollit dues.

En el primer cas, s'ha seleccionat un gel per tractar l'hipogonadisme en homes adults. S'ha fet una conceptualització del producte i s'han definit els factors de qualitat del producte. Els més importants són els que es refereixen a la reologia del semi-sòlid, com la viscositat, i als factors sensorials, com per exemple la sensació al tacte. Per això, s'ha fet una selecció d'ingredients tenint en compte les diferents propietats i la microestructura necessària.

Un altre punt ha estat dissenyar un procés de manufactura i escollir els equips requerits. En el processament d'un gel, s'utilitzen diversos tancs agitats, així com també intercanviadors de calor per condicionar els productes per les diferents operacions unitàries, molins per reduir la mida de partícula de l'API, i un homogeneïtzador a pressió que prepara la emulsió. Al final, s'ha decidit que la testosterona en gel es distribuiria en sobres, pel que es necessita un equip per omplir-los.

Per l'altra banda, la presentació del producte per la teràpia hormonal per transgèneres ha estat la pastilla, tot i que avui en dia no s'utilitza. S'ha seguit el mateix procediment que amb l gel. En aquest cas, els factors de qualitat més important eren els químics, i la mida de partícula també es important a l'hora de dissenyar el procés. Els ingredients seleccionats per les pastilles concorden amb les propietats que es volen obtenir i s'han seleccionat per optimitzar la penetració de l'API en el sistema.

El procés de disseny pel producte sòlid consisteix en molins i granuladors que regulen la mida de partícula dels ingredients, i també mescladors que barregen els diferents compostos.

L'últim pas consisteix en comprimir el producte en forma de pastilla y fer-li un recobriment, per complir amb les mides y factors sensorials desitjats.

Paraules clau: Testosterona, hipogonadisme, teràpia hormonal transgènere, tractament amb testosterona, testosterona en gel, testosterona en pastilla, undecanoat de testosterona, disseny de procés, API.

INTRODUCTION

Testosterone is the primary sex hormone in males. It is secreted in males and females (in much less quantity, about eight times less) by the testicles and the ovaries respectively.[1] In the case of humans, testosterone is in charge of the male reproductive system development, like testes and prostate. It is also responsible for the increased muscle and bone mass that males tend to have in front of females, and for the growth of body hair. A diminish of the normal level of testosterone in men can lead to health problems. [2,3]

Testosterone (C19H28O2), with its IUPAC name being 17βHydroxyandrost-4-en-3-one, is a biological organic compound consisting of a core of four rings containing 17 carbon atoms, with a double bound between C4 and C5, a ketone group (R2C=O) at position C3, and a hydroxyl group (R-OH) at position C17.[4] It forms different esters when changing the group hydroxyl for a fatty acid ester, deriving in testosterone propionate or testosterone isobutyrate for example, which are depicted in Figure 1. Testosterone can be found in the organism in a free form, or in a bioavailable form. Free testosterone is the portion that circulates not bounded to the sex hormone binding globulin protein (SHBG).[13] This protein is produced in the liver and bonds with both male and female sexual hormones to control the amount of them sent to the body tissues. Levels of SHBG can show how much testosterone the system is using. [25]

Apart from its natural activities, testosterone is also used in medicine for the treatment of diseases and deficiencies, such as hypogonadism in men or breast cancer in women.[5]

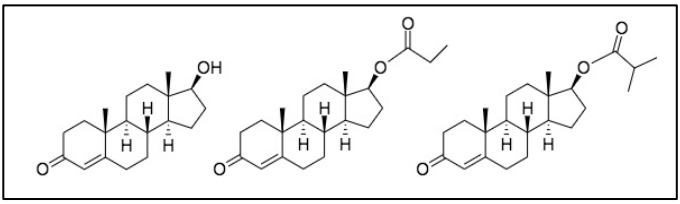


Figure 1. From left to right: chemical structure of testosterone, testosterone propionate and testosterone isobutyrate.

1.1 BIOSYNTHESIS OF TESTOSTERONE

Testosterone is derived from cholesterol ($C_{27}H_{46}O$). An enzyme oxidizes the side chain of cholesterol and catalyzes the reaction to form pregnenolone. Then two carbon atoms are eliminated by another enzyme located in the endoplasmic reticulum of the cells, forming dehydroepiandrosterone. Next a hydroxyl group is oxidized deriving into androstenedione. Finally, the ketone group is reduced, obtaining testosterone. This process (Figure 2) takes place in the male testicles (>95%) and the adrenal glands.[6] In women testosterone is produced in the ovaries instead.[7]

Testosterone in men is produced by the rate of 6.5 mg/day, while in women it is as low as 190 µg/day.[8] The hypothalamus is in charge of the regulation, as it controls the pituitary glands. The factors affecting the levels of testosterone in the system are the ones that affect the state of this organ, which can be the following: age, exercising/sedentarism, nutrients deficiency, sleeping schedule, etc. [9,10,11,12]

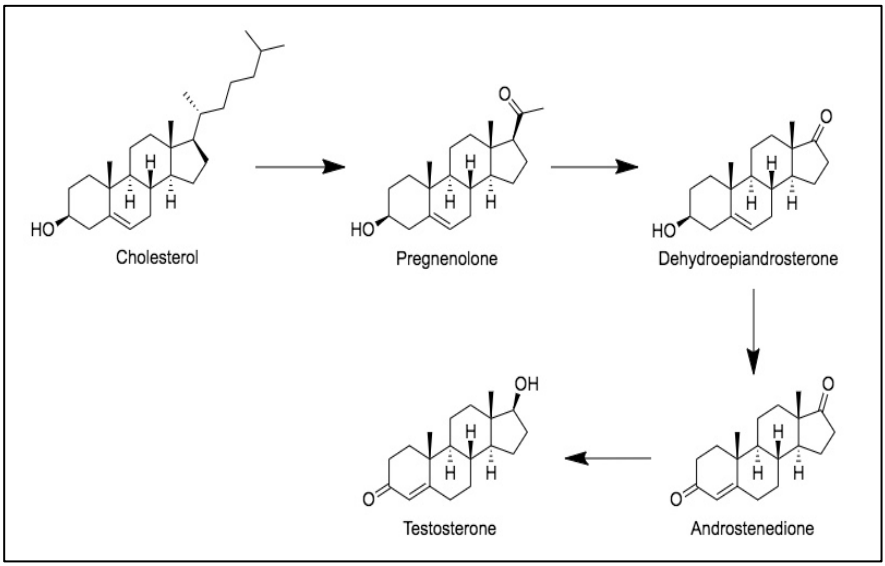


Figure 2. Formation process of testosterone

The level of testosterone for newborns is between 2.6 and 13.9 nmol/L in males and 0.7-2.2 nmol/L in females. It drops to almost 0 in the childhood stages, increasing again when reaching puberty. At this stage, testosterone levels in males can reach 33.7 nmol/L, while in females its maximum is 1.8 nmol/L. When entering adulthood, the amount of the hormone still increases, reaching its peak at the ages of 20-39. Then it starts to decrease, for males down to a minimum of 12.2 nmol/L and for females until 0.2 nmol/L. The complete data can be found in *Appendix 2* in Table A. [13]

Regular consumption of alcohol, anemia, obesity, Down-syndrome, renal diseases, HIV, arthritis or type 2 diabetes have shown to reduce total levels of testosterone in humans, while adrenal, testicular and ovarian tumors, eating disorders or abnormal menstruation have shown to increase them. With free testosterone, severe acne in females and pollutants put up its levels whereas epilepsy, weight gain or hypogonadism bring it down.[13]

1.2 BIOLOGICAL EFFECTS

Testosterone boosts the synthesis of proteins and subsequently the growth of tissues with acceptors for this type of hormones. It has two types of effects: anabolic and androgenic. The anabolic effects consist of the growth of bone and muscle mass, and general strength. For the androgenic effects, there is the maturation of the sex organs (penis and scrotum), having a deeper voice, dense facial hair, and basically many of what is referred as male sex characteristics.[14]

On early stages of life before puberty, testosterone is accountable for the developing of organs, including the brain, higher stature, odors, acne, facial, pubic and armpit hair, etc. When humans reach puberty, testosterone levels are higher than normal, and cause the maturity of sexual organs in men and women, male fertility, the increase of sexual drive, prominent facial structure, broader body structure, and extension of body hair to most of its area. In adults, testosterone is necessary for the production of sperm. All of the effects tend to decline as the adult ages, because the secretion of the hormone declines.

1.3 IMPORTANCE OF TESTOSTERONE

Testosterone is an important hormone in the human body for both men and women. In males it is responsible for the development of the reproductive and sexual organs, as well as the masculine traits like body hair, strength, deep voice… In females it has a minor role, but also takes part in the development of the reproductive system. Due to different diseases or as an adverse effect of some medical treatments, some people may present low levels of testosterone. The deficit is caused by hypogonadism, which can appear naturally or after medical treatments such as chemotherapy or radiotherapy, that can affect the glandules' functioning.

Thus, the importance of the development of products with testosterone as the active ingredient, to treat persons with hypotestosteronemia so they can carry on with their lives as comfortably as possible. In addition, more and more these days, the use of testosterone has been used for the treatment of transgender males, born females who feel identified with the opposite sex.

OBJECTIVES

The main objectives of this work, which are reflected in the different sections of the memoir, are the following:

First of all, to do a bibliographic study of testosterone to be able to select the desired products. Then, with the information recapped, select the treatments for which to develop the range of products and its presentations, taking into account the performance and facilities they offer respect others. Once the presentation of the products has to been decided, develop its conceptualization, the establishment of its quality factors, and the selection of its ingredients, which is an important part. For this section, the necessary ingredients have to be selected taking into account their function and medical safety, as they must be consumed by humans. Lastly, to elaborate a basic design of a manufacturing plant for the selected range of products, selecting the equipment necessary for their manufacture.

The work above is done with bibliographical data, different articles, books or sites, and applying the skills and abilities acquired during the Chemical Engineering degree, mostly from the course of *Product Development*.

3. SELECTION OF TESTOSTERONE TREATMENTS

Male hypogonadism, breast cancer or male sex reassigning therapy (gender dysphoria) are nowadays usually treated with the help of testosterone.[5,15] It was first used in 1939, and its use has increased since then.[16] From 2008 to 2018, it had been prescribed around 50 million times in the United States.[17] In 2011, 4% of men in their 60s were taking testosterone. In 2013, more than 2 million Americans were being treated with testosterone. [26]

The most common problems for which it is prescribed are deficiency due to malfunction of the production system, low levels due to aging and hormonal therapy.[18] Deficiency of testosterone is known as hypotestosteronemia and results in low levels of the hormone in the organism. It is caused by hypogonadism, when testicles do not function well. As men age, their natural levels of testosterone decrease, thus they can be treated with supplemental testosterone, though the benefits have not been confirmed. Lastly, transgender men who want to have a male appearance might take medical testosterone to develop male traits due to its virilizing effects.

The dosage of testosterone varies in front of gender, age, type of testosterone and form of administration. As some examples, when injected, testosterone dosages might be between 100-200g/mL of testosterone cypionate, 200mg/mL of testosterone enanthate and 250mg/mL of testosterone undecanoate. Meanwhile, when taken in the form of implants, the dosages range from 12.5 to 75mg.

3.1 TREATMENTS FOR WHICH TO DEVELOP A RANGE OF PRODUCTS

The selected treatments for which testosterone products are going to be studied are the ones mentioned before. Here below, they are more widely explained.

3.1.1 Testosterone replacement therapy

Testosterone replacement therapy (TRT) aims to replace the natural hormone medically through the administration of testosterone. The cause of the non-production can be the person having a disease or the side effects of its treatment.[19] For example, some cancer treatments like radiation or chemotherapy can reduce the level of testosterone, or obesity, diabetes and HIV.[21] In male, the main cause of testosterone deficiency is hypogonadism. In females, TRT in low dosage along other hormones treatments are used to prevent some effects of menopause, like fatigue, bones diseases like osteoporosis, or absence of sexual libido.[20] Moreover, testosterone can be used to treat severe depression and misbehavior conducts.

Even though this method had been contraindicated by medics in the past for patients with prostate cancer, recent studies have found that there is no risk in this practice, therefore helping those who have to combine both treatments: prostate cancer treatment and testosterone deficiency.[22] Other studies have been published about the use of testosterone to prevent/revert type 2 diabetes in overweight men, who tend to show low levels of testosterone concentration.[23]

In the specific case of male hypogonadism, the production of testosterone is affected by the malfunctioning of the hypothalamic-pituitary-gonadal axis. The problem could be genetic, an illness like organ diseases and their treatments or an infection.[43]

3.1.2 Transgender hormonal therapy

Also known as masculinizing hormone therapy or THT, this treatment is used in female-to-male gender switching. The objective is for the person to acquire more masculine features so that he can be in comfort with his physical appearance, as it is applied to transgender men. This is accomplished maintaining the testosterone levels in the range as non-transgender male. When being treated for THT, the patient takes testosterone which suppresses the menstruation cycles and reduces the production of the female sexual hormone in the ovaries: estrogen. [44]

As testosterone's biological half-life is around the hour, it has to be regularly supplied. This type of therapy must be lifelong, so lots of studies are centered around its effects and the correct dosage. The secondary undesired effects are long to list but rare. The most common ones are cardiovascular complications, the appearance of acne and changes in the metabolic system.[24]

4 CONCEPTUALIZATION OF PRODUCTS TO BE DEVELOPED

Testosterone can only be obtained with medical prescription in drug stores. These hormones can be bioidentical when they match the natural chemical structure, or synthetic when their structure is altered. This last type of testosterone tends to cause more side effects when used medically. The forms in which it is distributed are gels and creams, injections, patches, pellet implants, capsules and tablets and suppositories, with the last one being the less common.[26] The following Table 1 resumes testosterone administration forms and its active ingredient (API) [28].

Table 1. Presentation forms of testosterone for medical use

Route	API	Form
Oral Buccal	Testosterone undecanoate	Capsule
	Testosterone and esters	Tablet
Transdermal	Testosterone	Patch, gel, cream
Intranasal Inhalational	Testosterone	Spray
Injection	Testosterone and esters	Oil solution
Implant	Testosterone	Pellet
Rectal	Testosterone	Suppository
Vaginal	Testosterone	Creams, suppositories, rings

4.1 CAPSULE AND TABLET

Capsules are a medical product presentation where the medicament is taken orally, and the API is liberated in the digestive system. It consists of a biodegradable shell enclosing the ingredients. When swallowed, it is broken in the digestive system, releasing its contents. This are absorbed into the circulatory system and metabolized in the liver. Moving on, tablets are compressed in the form of powder, which is released in the digestive system and absorbed in the bloodstream. They are also administered orally and come in all types of forms, normally being round or oval. Apart from the API, they tend to contain additives to enhance its

qualities.[29] The main difference between these two product presentations is that capsules have an outer shell, thus being able to contain liquid ingredients. Tablets have the advantage of being inexpensive, long-lasting, come in higher doses than capsules, and can be cut in halves. On the other hand, capsules act quicker and do not contain that much of additives, making them more effecting and less sensitive to possible allergic reactions.[29]

Tablets and capsules are not the most used administration form of testosterone, though they are sometimes used to treat delayed puberty in men or breast cancer with metastasis in women. [26] Tablets' active ingredient is testosterone, or methyltestosterone, fluoxymesterone, metandienone, tibolone, etc. and are manufactured by brands such as Testoral or Striant. Meanwhile, capsules' API is testosterone undecanoate, distributed by Andriol or Jatenzo.[28] This last brand was approved by the FDA (Food and Drug Administration) in 2019.[40]

Figures of the chemical structure for the mentioned testosterone esters in this section and the following can be found in *Appendix 1: Chemical structures*.

4.2 PATCH

Testosterone can be absorbed through the skin continuously with patches. These are stickers that contain medical ingredients that are gradually taken via transdermal absorption. The ingredients then travel around in the circulatory system. For testosterone, there exist two types of patches: scrotal and non-scrotal, commercialized by Testoderm and Androderm or Intrinsa respectively.[28] The patches need to be changed every day around the same hour, and applied in different spots.[26] The disadvantage they present is that the dosage delivered is not precise, so they are made to contain more testosterone than the necessary. Patches can also produce irritation. [31]

4.3 GEL AND CREAM

Gels and creams are another dermal way to administer testosterone. They are directly spread on the skin, usually in the torso. The differences between gels and creams are that the first ones have a transparent appearance due to being mostly water based and are more easily absorbed, while creams contain oil, making them thicker, and take longer to absorb. [30] Testosterone gel is one of the most common methods used these days. The APIs applied in gel

form are testosterone or androstanolone. It can be dangerous if not taken care, as it can be transferred to others by touch, leading to problems. [26] If women come in contact with testosterone gel, they may develop androgen sex physical features, like growth of facial hair. Examples of brands that sell testogels are Androgel and Testim. [28]

4.4 SPRAY

Sprays can be administered via nasal or inhaled. They are a liquid mixt of ingredients, with a propellent that allows it to be sprayed in micro drops. A study proved that a single dose of inhaled testosterone in postmenopausal women was safe and lifted the androgen hormone levels, however those went back to the initial pretreatment levels in a short time.[37] In the case of testosterone as the API, Natesto produces them. [28]

4.5 INJECTION

Injections are liquid solutions administered through intradermal, intramuscular or directly into blood with the help of medical shots. As the active ingredient is directly introduced in the muscle (generally the gluteus), it does not have to be absorbed, therefore acting steadily and fast. It also allows a high dosage of the active ingredient. After all, it is the best way to administer testosterone for therapy. [31] Injections are divided in several types, depending on what the API is:

- Testosterone enanthate. Brand: Delatestryl and Xyosted. Coming in doses of 100-200mg, they should be administered every 5 days. [32]
- Testosterone cypionate. Brand: Depo-Testosterone, since 1979, one of the oldest. It acts for a long time. Doses of 100-200mg weekly. [26,32]
- Testosterone propionate. It acts rapidly, showing peaks of testosterone levels just a few hours after its injection. Frequent administration, every 2-3 days. Just for special cases.[31]
- Testosterone undecanoate. Brand: Aveed, Nebido and Neandron. Administered every 2-3 months.[33]

- Testosterone suspension. Could be one of the strongest injectable steroids, as it does not have esters. Not recommended, it has to be administered 3 times a week in doses of 25-50mg.[32]
- Mixture of testosterone esters. Brand: Sustanon. Contains 4 testosterone esters: propionate 30mg, phenylpropionate 60mg, isocaproate 60mg and decanoate 100mg.[34]
- Others like testosterone isobutyrate and phenylacetate.

4.6 IMPLANT PELLET

Implant pellets are small and in the form of a cylinder (3mmx9mm).[35] They are inserted under the skin of the hip or the gluteus in a minimal surgical intervention.[36] Testosterone pellets, branded Testopel, deliver continuously crystalline testosterone. They contain 75mg and last for 3-6 months.[27,35] Other brands offer reduced dosages. Once the doctor finds the correct dosage, they are reliable and do not need weekly administrations, which makes them appealing for patients. They present an inconvenient: in the early stages they release too much testosterone and, in the latter, not enough.[31]

Figure 3 visually represents the amount of hormones that different product presentations release in front of time.

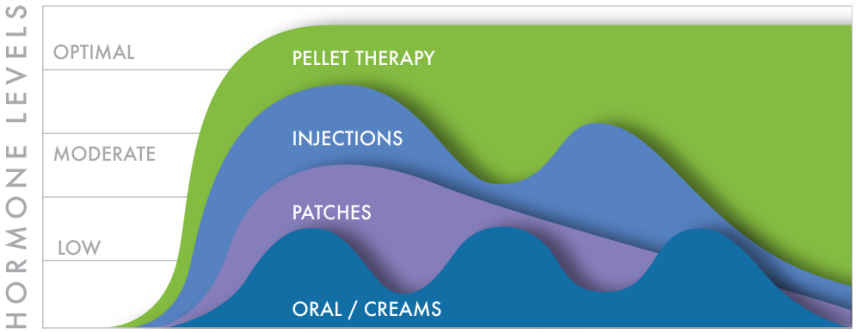


Figure 3. Released hormone levels in front of time for different product representations.[58]

4.7 PRESENTATIONS APPROPIATE FOR THE CHOSEN TREATMENTS

Knowing all of the available presentations for treatments with testosterone, the next step is to choose the proper one for each of the treatments selected before. When choosing tablets or capsules, it does not matter, because the main difference between the forms of presentation is the time they take to act. As hormone therapy is a long-term treatment and does not need immediate effects, the results of oral ingestion of tablets or capsules should be similar. Patches have been determined to be imprecise with the absorbed dosages and to cause irritation, so they will not be selected in this case. Gels and injections are the most common administration forms, hence why they are selected in this assignment. Implants are a good choice for long-term treatments, but it is difficult to find the correct dosage, so it needs a long time to adjust it to the needs of the patient. Sprays are still being studied and investigated, there is less information compared to other presentations, but they have indicated to not have that much effectivity. An article from 2015 comparing the safety of the different dosage forms concluded, with monitorization of more than half million patients being treated with testosterone, that those who took injections had a greater risk to suffer from cardiovascular complications, being hospitalized or dying compared to those who were using gels or patches.[41]

So, taking into account different variables like popularity, commodity, effectiveness and safety, it has been decided that the most adequate forms would be tablets and gels. They are both well studied and there is more information about their properties, they are the safest (causing less side effects), and the dosage is controlled. The two of them are of daily intake.

Table 2 has been elaborated summarizing the treatments and the presentation forms of testosterone selected for both of them.

Table 2. Selected treatments and administration forms of testosterone

Treatment	Administration form
TRT: Hypogonadism in males	Gel
THT	Tablet

5 DEVELOPMENT OF PRODUCTS SELECTED

In this section, the conceptualization of each of the products previously selected and the establishment of their quality factors has been made. These are the first two steps in the procedure for the synthesis and development of a product according to a 2002 article from Christianto Wibowo and Ka M. Ng.[42] The third step is the selection of the ingredients, which is found in a subsection for each product.

For the product conceptualization, the consumer needs and wants, safety and legal issues have to be taken into account. For the quality factors, the ones that affect the product have been selected out of a full list of existent quality factors. As for the ingredients chosen, different bibliography has been read and own criteria has been applied.

5.1 GEL: CONCEPTUALIZATION AND QUALITY FACTORS

In the treatment for hypogonadism in males, gels are commonly used because of their simple application. They just need to be spread on the skin in a body region, usually the shoulders and the upper back, and let them sit to be absorbed. Gels are viscous liquids, thus needing to be contained in some kind of package. Plastic bottles and squeezable tubes are common packaging for creams and pastes, but in this case the selected delivery system are small plastic sachets, with dosages of 5 grams each. The sachets would be commercialized in packs of 30 contained in a cartoon box. This way, if the gel needs to be applied daily, the consumer has enough in the box for a month. If taken twice a day, then the box has to be replenished every two weeks.

Quality factors will be divided into different groups: sensorial, physicochemical and rheological. The sensorial factors that need to be considered are the visual aspect of the product, which will be transparent, without color; the smell, which needs to be pleasant or inexistent, so the patient does not feel rejection to it; in this case, as gel is not ingested, it does not matter the taste of it; and the sensation on the skin, that has to be smooth and feel fresh, not sticky, nor irritating. As for the physiochemical factors, it needs to be stable and have a long

shelf life, of at least 2 years, keeping in mind the time it takes to be distributed to the pharmacies, sold to the patients, and applied (a single box can last for a month from its opening). The gel also has to melt at body temperature for an easier spreading and faster absorption. The rate at which the active ingredient is released is the rate at which the gel is absorbed in the skin. Lastly, the rheological factors for viscous liquids are of great significance. Gels need to be easy spread, so viscosity is an important parameter when designing it, and they have to flow when squeezed out of the sachet. Moreover, they ought to give a uniform coating, so the release of the API is uniform in all parts of the zone where the gel is applied.

In terms of viscosity, we are looking for a pseudoplastic, where the viscosity decreases with increasing shear rate. That means, that when the product is applied and spread with strength, it becomes more liquid, less viscous. So, n<1 in the viscosity equation (1). Typical shear rates in s^{-1} when applying gels and creams are: 10^{-3}-10^{-1} for the suspension of the active ingredient in the product, 10^{1}-10^{3} when squeezing it out of the sachet and 10^{2}-10^{4} for the topical application, when spreading and rubbing.

$$\mu_w = \frac{\tau_o}{\dot{\gamma}} + K\dot{\gamma}^{n-1} \qquad (1)$$

$$\mu = \mu_w + (\mu_o - \mu_w)\left\{1 - exp\left[-\left(\frac{t}{t_r}\right)^a\right]\right\} \qquad (2)$$

As for the Complex modulus, we expect a viscous behavior, the material cannot return to its original state after applying a force. So, G' = 0, G'' = $\omega\mu$ and N_{De} = 0 in equations (3) and (4).

$$G^* = G' + iG'' \qquad (3)$$

$$N_{De} = \frac{G'}{G''} \qquad (4)$$

From formula (3), G* = i$\omega\mu$ is deduced

5.1.1 Selection of ingredients

For the development of this section, the patents and articles consulted can be found in *References and Notes 45-46-47.*

The first step is to determine the API and its concentration. Normal testosterone concentrations in existing gels range between 0.5-2% in weight. The selected concentration is 1%, which makes it 50 mg of testosterone per dosage, as the sachets contain 5 g of the formulated product.

Common dosages for treating hypogonadism in puberty are: 50-400mg every 2-4 weeks for testosterone cypionate or enanthate and 750mg once a month for testosterone undecanoate. When treating delayed puberty in men, it is common to take 50-200mg of testosterone once or twice a month for half a year. In the case of breast cancer in women, 200-400mg of testosterone enanthate once or twice a week is prescribed.[27]

In the case of hypogonadism in male adults, the common dosage consists of 50-100 mg of daily testosterone. Therefore, with the selected dosage form and its concentration, the patient would apply 1-2 sachets a day.

The next step is to determine the different excipients that give the gel its physical, chemical and rheological properties. The product needs a thickener, also known as gellant, to reach the desired viscosity; a moisturizer that helps the absorption of water; an emulsifier so the immiscible compounds can be mixed; a dispersant to keep the API uniformly distributed in the liquid phase; a buffer to control the pH; and a stabilizer that prevents the degradation of the product. Other agents could be useful. Its preferable to use short chain alcohols to reduce irritation, long chain alcohols can be used in small concentrations but, if possible, should be avoided.

Bibliography shows that the most common thickener used for testosterone gels is carbomer. Also known as carbopol, it is a white solid hydrophilic polymer consisting of acrylic acid monomers ($C_3H_4O_2$). When mixed with water, it expands due to its carboxyl groups and it increases the liquid's viscosity, making it perfect for gel formulations. The polymer is used in low concentrations because it can absorb water up to 100 times its weight. Carbomer is safe for human application, it is not carcinogenic, nor toxic or allergic. Acrylic acid melts at 49ºC. When liquid, it is colorless, so the gel made of carbomer can be transparent.[48] Carbomer also works as a dispersant, because it keeps the testosterone suspended in the gel, and as an adhesive

agent, making it easier for the gel to attach to the skin. Another property it has, is that it can act as a stabilizer of the emulsification.[49] For topical applications, the recommended concentration is between 0.5 and 3%.[49] According to this data, the product should have between 25-150 mg of carbomer per dosage. Taking 1.5% as the concentration, each sachet should have 75 mg of carbomer.

Another important compound is the moisturizer, because it helps in the penetration of the product through the skin into the organism. Based on the patents, isopropyl myristate, propylene glycol and diethylene glycol monoethyl ether are used for this purpose. The combination of the three could give good results, but it would be expensive. To make it more affordable, propylene glycol could be used in 14%, combined with isopropyl myristate in 1%, so that the total concentration of moisturizer would be 15%. Propylene glycol is non-irritating and has low volatility, so it will remain in the solution when applied, it will not evaporate (boiling temperature 188.2ºC). It is miscible with water, alcohols and ethers among others. It has a viscosity of 42 mPa·s.[50] Isopropyl myristate has also low volatility and a viscosity of 5-6 mPa·s.[51] Propylene glycol has higher viscosity, therefore it is used in higher concentrations respect isopropyl myristate. The patent “Formulaciones de testosterona” deduces that dosages with 1% testosterone show better absorption with propylene glycol at 15% than 20%. Therefore, the selected concentration in this case is 14%.

Ethanol can also work as a moisturizer, but it has another important property: it is used as an emulsifier. It is necessary to mix immiscible compounds. Ethanol (C_2H_6O) is a colorless liquid compound of high volatility miscible in water and many compounds, making it a great emulsifier. When mixed with water in a 96% proportion, it creates an azeotrope. Its viscosity is 1.07 mPa·s. In the case of testosterone gel formulations, ethanol is the most concentrated product. A solution of 96% in ethanol is used in the bibliography, so the same will be used here. The patent that does not use propylene glycol as a moisturizer uses around 74% of ethanol, because it uses ethanol as both an emulsifier and a moisturizer. In the other patent, that already uses 15% of propylene glycol and 5% of isopropyl myristate, the concentration of ethanol decreases to 44%. In conclusion, both patents use emulsifiers and moisturizers in a combined composition around 70%. In the present case, the moisturizers sum 15% of the concentration, so a good value for the concentration of ethanol would be 55%, making it a total of 70% too. Having a low concentration of alcohol makes the product really viscous, while having too much makes the

product too liquid. According to the patents, 55% of ethanol would give good results in the final viscosity.

An important parameter to have in mind is pH. The gel is applied on the skin, so it has to have a similar pH for avoiding irritation or dryness. The skins pH is slightly acid, ranging from 4.5 to 5.9.[52] A buffer is used in formulation to regulate the pH. The current mixture of products for the development of the gel is acid, since it has a high concentration of ethanol. To make it more alkali, triethanolamine (TEA) is used in one of the patents. It has a neutral 6-7 pH. Mixed with the other ingredients, it can change the pH to a more suitable value for the skin. The compound ($C_6H_{15}NO_3$) is a viscous colorless liquid with low volatility and miscible in water and other solvents. Low concentrations are enough for buffers, since we need the gel to be weakly acid. Accordingly, a value of 0.5% of concentration would be adequate. Other patents use NaOH 0.1M as a neutralizer, in concentrations of 4-7%.

Tables B and C are extracted from a patent [46] and show results of viscosity and pH obtained with different concentrations of the ingredients. They can be found in *Appendix 2: Tables*. Table C shows that pH does not very much from one formulation to another, meaning that the concentrations analyzed did not have big impact in the gel's pH. Taking this results in consideration, a pH around 5.6-5.9 would be obtained for the gel's formulation.

Although carbomer acts as a stabilizer too, a chelating agent is used to help stabilize the formulation and avoid the degradation of the gel or the precipitation of the API. They also soften water, attaching to calcium or magnesium. EDTA is a known chelating agent, but nowadays phytic acid is becoming popular, especially in cosmetics. In one of the patents, disodium edetate is used, but here it is proposed phytic acid to innovate, as it has antioxidant and hydrating properties that can help.

Lastly, the solvent used to dissolve all the compounds above is water, as the majority of them are miscible in it.

The estimated value of the viscosity for this formulation would be similar to the results shown in table C, as the variations in the compounds and their concentrations is minimal. So it would be between 20-30 Pa·s.

Table 3 has been elaborated to neatly summarize the selected compounds and their respective concentrations.

Table 3. Formulated gel compounds and concentrations

1 sachet: 5 g dosage (5000 mg)			
Compound	Function	Concentration (%)	Weight/dosage (mg)
Testosterone	API	1.0	50
Carbomer	Thickener, dispersant, stabilizer	1.5	75
Propylene glycol	Moisturizer, penetrator	14.0	700
Isopropyl myristate	Moisturizer	1.0	50
Ethanol 96%	Emulsifier, moisturizer	55.0	2750
TEA	Buffer	0.5	25
Phytic acid	Stabilizer, softener	1.0	50
Distilled water	Solvent	26.0	1300

Table 4 shows testosterone solubility in ethanol/water solutions.[53] In our case, we have 55% ethanol and 26% water, which is the same as a 68/32 ethanol-water mixture. According to the table data, testosterone solubility would be between 0.035 and 0.061 g testosterone / g ethanol. We have 50 mg (0.05 g) of testosterone and 2750 mg (2.75 g) of ethanol 96%, which makes a 0.018 g/g rate. Then we conclude that the amount of testosterone is soluble in the formulation elaborated.

Table 4. Testosterone solubility in ethanol-water solutions

95% ethanol (v/v)	Testosterone solubility (g/g)
56/44	0.027
63/37	0.035
74/26	0.061
84/16	0.146

Table 5 shows the values for viscosity on a testosterone gel with carbomer depending on the ethanol content.[53] There is a significant difference from 50% of ethanol to 65%, viscosity decreases almost 20 times. That means, that the optimal rates for which to achieve higher viscosity should be above 55%, which is the present situation.

Table 5. Viscosity depending on ethanol content

95% ethanol (%)	Viscosity (Pa·s)
50	15.00
55	6.50
60	2.38
65	0.80

Hence, the conclusion is that the values of concentration for the selected compounds seem to be optimal and practical for the desired rheological properties of the product.

5.2 TABLET: CONCEPTUALIZATION AND QUALITY FACTORS

For this case, tablets are used to treat male transgender therapy. Pills are affordable, effective and most people is used to taking them. They are taken orally, and once swallowed and in the digestive system, they melt and release its active ingredient. Tablets are solid particles of different ingredients compressed into the shape of, commonly, round or oval. Typical diameters can range between 6-11 mm with 2-4 mm of height. In this case, the selected shape will be a 8mm x 3mm round, having a superficial area of 176 mm^2 or 1.76 cm^2 and a volume of 151 mm^3 or 0.15 cm^3. For their preservation, they need to be wrapped. In this case, they will be individually wrapped in aluminum foil, forming a blister of 30 tablets. By packing them individually they can last longer, because they are not exposed to external factors like air or microorganisms until they need to be taken. The blisters would come in cartoon boxes containing 3 of them. That makes a total of 90 tablets/box, so in the case of a single daily dose the patient has enough for 3 months; and in the case of a three doses/day there is enough for a month.

The quality factors to be considered with tablets are extent. They are solid, so there are no rheological factors. The most important sensorial factor is the taste, because they are buccally taken. Although a good taste is difficult to obtain, try to reduce the bitterness by applying a coating to hide it. The color does not matter but could be white as it is visually more appealing; tablets do not smell, and if they do it is very superfluous and does not affect the product quality. They should have a pleasant size to swallow, not too big. For the physical quality factors, testosterone tablets need to be hard (so they do not break during manufacturing processes) but not too tough (so the consumer can break it into two for personal purposes). The coating used to hide the bitter flavor also helps to its stability in front of external environment. The compositions in each tablet are to be uniform and the same. The functional quality factors are its ability to disintegrate in the desired time (not too soon, either too late) so that the API is released where and when it should for its optimum absorbance. Tablets need to be resistant to long periods of shelf life. In this case, the individual packaging helps to preserve them.

5.2.1 Selection of ingredients

For the development of this section, the patents and articles consulted can be found in *References and Notes 54-55-56.*

The first step is to determine the API and its concentration. For THT treatment, the active ingredient would be testosterone undecanoate. It is usually presented in capsules, but in this case, tablets are proposed. Common dosages in female-to-male hormone therapy treatments for testosterone undecanoate range from 40 to 80 mg 2-4 times a day. 40 mg 3 times a day will be taken as a reference, so the tablet's API content should be 40 mg. The tablet will weight 500 mg. Accordingly, the selected concentration for the API is 8%. Testosterone undecanoate presents the inconvenient of being insoluble in water

The next thing is to select the excipients. Table D in Appendix 2 lists the typical excipients used in tablets, capsules and powders, helping in the selection of the different ingredients. According to it, a tablet needs a diluent to create the desired size and form, and binder that holds the different solid particles together to form granules. There are some ingredients that can act as both filler and binder. Another excipient would be the disintegrant, that gives the tablet the facility to brake, in case just half a dose is needed, or the person has problems swallowing pills. Anti-adherents and glidants reduce friction between the particles and the environment, so they can be easily transported during manufacturing. A lubricant will also help avoiding the sticking of the capsule in the different machines of the production process. Lastly, pigment and flavoring can be added to modify the color and flavor of the tablet.

Ka Y. Fung and Ka M. Ng comment on some heuristics for the excipients' selection. Generally speaking, all the ingredients are to be physiologically inert and chemically stable on their own and combined.

Starting with the binder, examples such as sucrose, starch and cellulose are given. Microcrystalline cellulose is a glucose polymer that forms a 3-dimensional crystalline structure that is insoluble in water. A surfactant or a plasticizer can be combined with a binder to improve the cohesive properties. Bibliography recommends using propylene glycol, which is soluble in water. The binder is added during granulation. In the case of many solvent needed, the binder should be added in the form of solution with it. On the opposite, if just a small amount of solvent is needed, it is better to add the binder dry. This will be later discussed. The binder also has to provide the tablet with enough strength to resist compaction stress.

As for the diluent or filler, there are two different types: the carbohydrates and the inorganic ones. Organic compounds are easier to digest for the system than inorganic substances. Microcrystalline cellulose could be used too for this purpose but adding some lactose (dryed by aspersion) could help with the digestion of the different ingredients (if the patient is not lactose-intolerant).

Another excipient is the disintegrant, which the cellulose also has the property to act as. To avoid lots of different products mixing which would make the process more difficult and the product more expensive, microcrystalline cellulose will act mainly as the binder and the disintegrant and as a filler it will be helped with lactose.

The next step is to select the anti-adherent lubricant and glidant. These are used when the packaging, like the blister, is tight and the particle size of the product is small. Adding these compounds can avoid the product sticking in the walls of equipment and package. Talc is commonly used in tablet formulation, as it is economic and can also act as a lubricant. It is water insoluble, like the other ingredients. The amount of talc has to be controlled, because an excess would reduce the product's bioavailability and alter its disintegration and the dissolution rates, as it would form a film cover over the granules. For the glidant, calcium, magnesium and silicon are used to reduce the granules friction, so they don't erode themselves or with the equipment. The selected compound according to the examples given would be calcium silicate in the form of powder. It is a hygroscopic substance.

Cremophor RH-40 or PEG-40 hydrogenated castor oil is a white doughy compound, water soluble, hydrophile surfactant that helps solubilize the API, so that it can be easier for the organism to absorb. Several of the cited articles conclude that the combination of this surfactant with lipophilic oils in high concentrations helps in the solubilization of testosterone undecanoate.

This lipophile compound could be oleic acid. The proportions between the cremophor and the acid should be above 1:4 respectively.

Lastly, for better sensorial experience, titanium oxide can be used to give the mixture a white color and salt (NaCl) can be added for flavor purposes, to lower the bitterness and the possible unpleasant odor. For the coating of the tablet, a beeswax solution can be used to mask odor and give the tablet a shiny/gloss surface, more appealing for touch and swallow. Film

coating is preferred as it does not increase the tablet's weight more than 3%, and allows the impression of a logo. Moreover, it is easily automated.

Table 6 has been elaborated to neatly summarize the selected compounds and their respective concentrations.

Table 6. Formulated tablet compounds and concentrations

1 tablet: 500 mg dosage			
Compound	Function	Concentration (%)	Weight/dosage (mg)
Testosterone undecanoate	API	8	40
Microcrystalline cellulose	Binder, Disintegrant, filler	25	125
Lactose	Filler	10	50
Propylene glycol	Plasticizer	1	5
Talc	Anti-adherent, lubricant	5	25
Calcium silicate	Glidant	1	5
Cremophor RH-40	Hydrophile solvent	10	50
Oleic acid	Lipophile solvent	40	200
Titanium oxide	Pigment (white)	<1	<5
Sodium chloride	Flavoring	<1	<5
Beeswax solution	Coating	<1	<5

For this composition, solubility and pH profiles should be analyzed. According to the existing formulations, which are similar in compounds and concentrations, both properties should be biocompatible and perform at the desired rates.

6 BASIC PROCESS DESIGN

Once the ingredients have been selected, it is time for designing the process of manufacturing of the product. There are five important steps in every production process which are depicted in Figure 4: pre-treatment, mixing, structure formation, post-treatment, and packaging. The first step is to obtain each one of the different ingredients via chemical reactions and then submit them to a pre-treatment, for example of concentration and purification, or heating and cooling, to condition them for the following steps. Next comes the mixing stage, where all of the ingredients are combined to obtain the final mix. Then they are given the desired structure or form and size. The product is finally put through one last treatment, which can be coating or sterilization. The ending stage consists in filling and packaging so the product can be distributed and commercialized.[42]

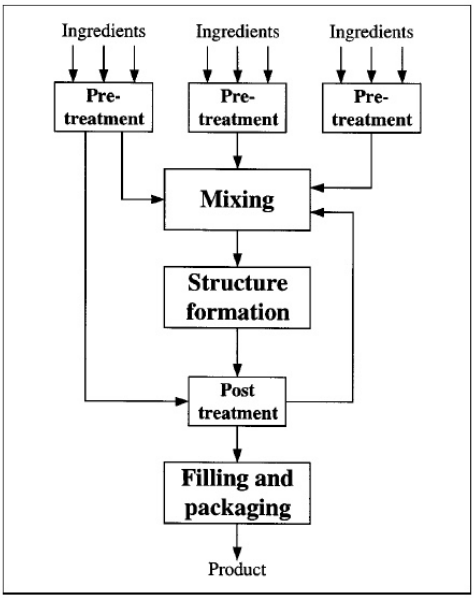


Figure 4. Generic flowsheet for product manufacturing processes [42]

6.1 SELECTION OF EQUIPMENT TO MANUFACTURE TESTOSTERONE GELS

As it has been mentioned before, the first step in manufacturing is to obtain each of the ingredients, staring with the API, in this case testosterone. The following process for the obtention of testosterone has been extracted from the patent found in *Notes and References 57*.

Delta-4-androsten-3,17-dione ($C_{19}H_{26}O_2$) is dissolved in acetone-cyanohydrin (C_4H_7NO) while heating and shaking slightly so that androstendion-17-mono-cyanohydrin can crystalize. The solution is filtered, washed with petroleum ether and vacuum dried at atmosphere temperature. The product obtained is suspended in benzene (C_6H_6) and then distilled to get rid of possible humidity. The mix is then heated to 65ºC and the following compounds are added: ethyl orthoformate ($C_7H_{16}O$), ethanol (C_2H_6O), and hydrochloric acid (HCl). From this solution, a new product crystalizes: androstendion-17-mono-cyanohydrin's ether 3-ethyl-enolic. Once the crystallization is ended, the solution is cooled, and pyridine is added. The liquid is let to vacuum evaporate until the product is completely dry. The crystal is mixed with n-propyl alcohol and sodium is added in small amounts. Once the sodium is dissolved with the help of heat, HCl is poured to acidify the solution and boiling water dilutes the solution. Propyl alcohol is eliminated through a vacuum distillation, and the solution is left to cool and rest. Finally, it is filtrated, washed with water and dried to obtain crystalized testosterone. Table 7 shows the different equipment needed for the process to obtain the API. The obtention process of the rest of the ingredients will not be explained in here.

Gels are semi-solid products therefore are produced through dispersion processing. Liquid ingredients come directly from their production sites, while solids have to be pre-treated through bulk processing. Figure 5 schematizes the general manufacturing process for creams and pastes. Following it, the first step is to stablish which ingredients are insoluble and which will form the continuous and the dispersed phase.

The solvent selected is water. All ethanol 96%, carbomer, propylene glycol, triethanolamine and phytic acid are soluble/miscible in water, so they may form the continuous phase. These ingredients will be premixed in an agitated vessel (that requires less energy) and then heated to conditionate them for the mixing phase. By heating the mixture, the viscosity is decreased so that the components can be better mixed.

Isopropyl myristate is the only liquid component that is not soluble in water. It is neither soluble in propylene glycol. For this reason, it will make up for the dispersed phase in the form of droplets. Isopropyl will be heated to reduce its viscosity for the mixing phase. For testosterone, it is in a solid state and is not water soluble. It needs a pre-treatment for particle size reduction, where a crushing roll is selected.

Once all the different ingredients are conditioned comes the mixing phase. The continuous and the dispersed phase are not miscible, as well as the API is not soluble. A planetary mixer (Figure 6) is used to mix them. The dispersed phase will end up distributed as droplets, forming an emulsion. To minimize the droplet size, a homogenization process is done in a pressure homogenizer. The product is then cooled down and mixed again in an agitated vessel.

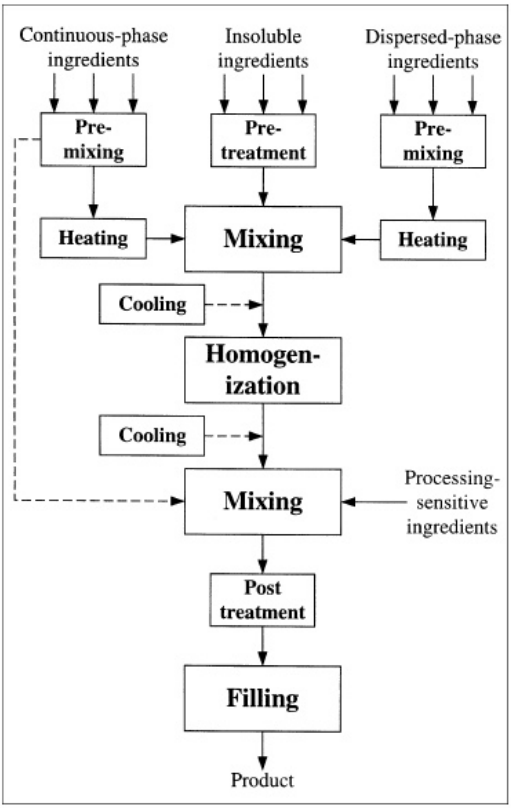


Figure 5. General structure of gels manufacturing process. [47]

For the mixing units, agitated vessels have been selected due to economic reasons. They consume less energy for mixing than other equipment. For the homogenization stage, a pressure homogenizer has been selected instead of an agitated vessel because it is the most important step for the components to be well mixed. In there, the feed flows through a narrow valve, creating high pressure that breaks the droplets and decreases their size (Figure 7).

After the final mixing follows the post-treatment. In this case, a chilling unit is needed for the semi-solid to rest and become gel. The last step is the filling of the sachets with the product. The final product is viscous, causing high stress to the equipment that manipulates it. The selected filling machine fills the sachet and seals it with heat. Table 8 summarizes the different equipment needed for the process to obtain the gel.

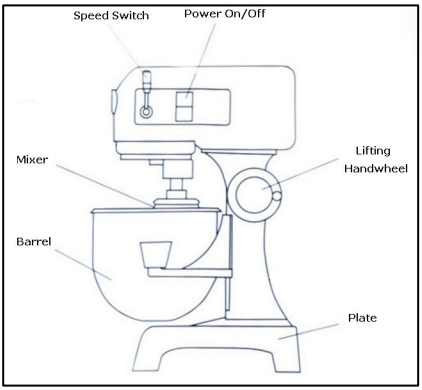


Figure 6. Planetary mixer. [59]

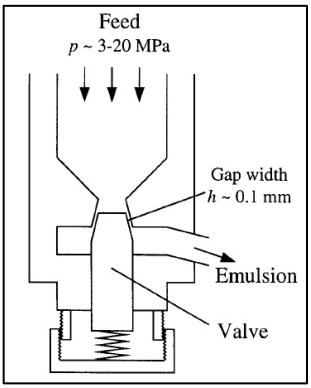


Figure 7. Pressure homogenizer. [47]

Table 7. Equipment to obtain testosterone.

Process	Operation	Equipment
Reactive mixing	Dissolution	Agitated vessel
Crystal separation	Filtration	Filter
Crystal purification	Drying	Vacuum dryer
Benzene mixing	Suspension	Agitated vessel
Water elimination	Distillation	Distillation column
Heat to 65ºC	Heating	Heat exchanger
Mixing	Dissolution	Agitated vessel
Cooling	Cooling	Heat exchanger
Mixing	Dissolution	Agitated vessel
Drying	Evaporation	Vacuum evaporator
Mixing	Dissolution	Agitated vessel
Alcohol elimination	Distillation	Vacuum distillation column
Crystal separation	Filtration	Filter
Crystal purification	Drying	Stove

Table 8. Equipment to manufacture testosterone gel.

Process	Operation	Equipment
Premixing continuous phase	Dissolution	Agitated vessel
Conditioning continuous phase	Heating	Heat exchanger
Conditioning disperse phase	Heating	Heat exchanger
Solid size reduction	Grinding	Crushing roll
Mixing immiscible phases	Emulsification and dispersion	Planetary mixer
Droplet size reduction	Homogenization	Pressure homogenizer
Conditioning	Cooling	Heat exchanger
Final mixing	Homogenization	Agitated vessel
Resting	Gelling	Chilling unit
Filling	Fill and seal	Filling machine

A flowsheet for the process is depicted in Figure 8.

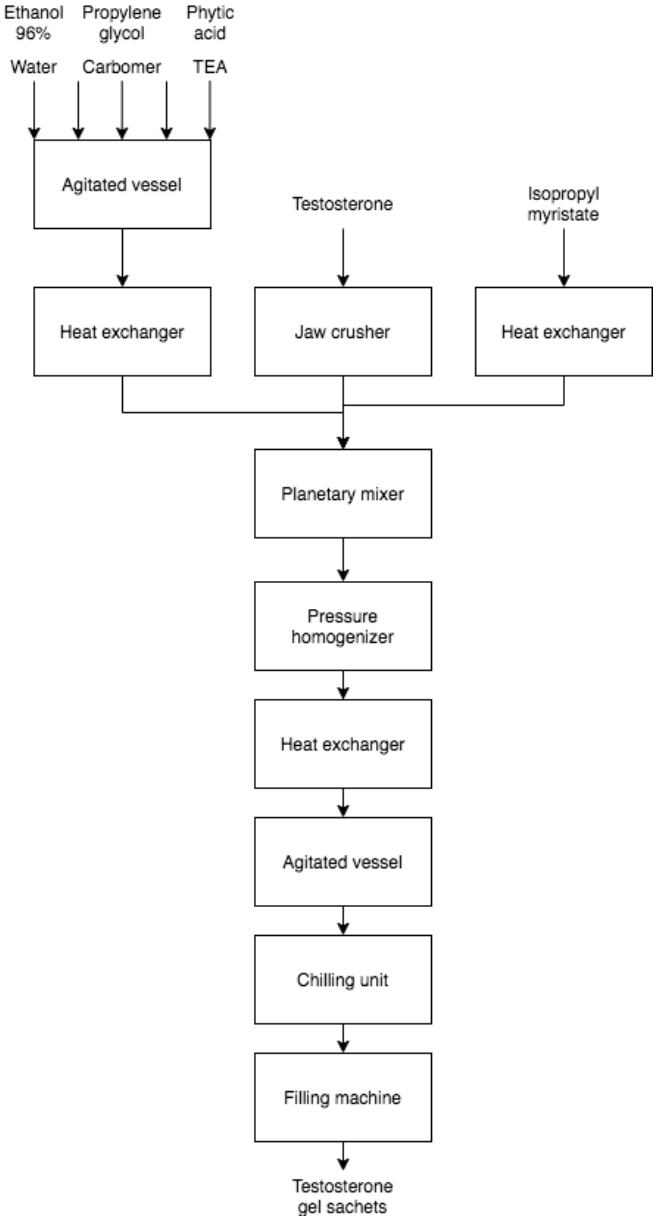


Figure 8. Flowsheet for manufacturing testosterone in gel.

6.1.1 Selection of equipment suppliers

The list of required equipment for both the obtention of testosterone and the manufacturing for the gel is listed below:

- 7 agitated vessels
- 5 heat exchangers
- 2 distillation columns
- 2 filters
- 1 crushing roll
- 1 planetary mixer
- 1 pressure homogenizer
- 1 vacuum dryer
- 1 vacuum evaporator
- 1 stove
- 1 chilling unit
- 1 filling machine

As the product is for pharmaceutical use, a supplier (Pflauder[60]) provides glass-lined equipment, that has sanitary properties that are optimal for pharmaceutical industry. This same provider manufactures customized reactors according to the client's needs. The provided vessels can work from 4 to 80000 L, the capacity range is high so it can be adequate for all 7 agitated vessels that this process needs. The glassy structure will not cause problems because the temperatures in the process are not elevated enough. The same provider sells columns from the same material that can work for the process too. A wiped film evaporator is offered, and it is specially destined for viscous and heat sensitive products.

In the case for heat exchangers, glass is not the best material as it is worse conducting heat than metals. Aguilar y salas[61] is a local provider and is selected as the heat exchangers' provider, as it has a large catalog.

Another local provider is Bachiller.[62] It provides filters (Filtro Nucha, FNB) from 19L to 15000L and also offers secondhand products. It also has a sanitary vacuum dryer from 50L to 10000L that suits the desired conditions.

Ünal[63] produces roll crushers that can reduce particles to 0.5 mm with a 2500 kg/h flow.

Spxflow[64] can provide the planetary mixer.

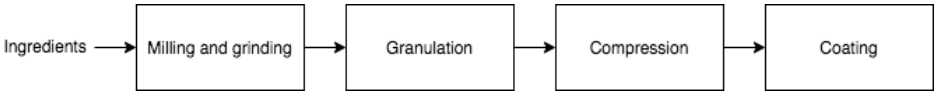
BEE international[65] can provide the homogenizer with a 50-6000 L capacity and is special for pharmaceutical industry.

In *Appendix 3: Equipment* images for the selected equipment from their respective providers are presented.

6.2 SELECTION OF EQUIPMENT TO MANUFACTURE TESTOSTERONE TABLETS

Like in the previous case, the first step in manufacturing is to obtain each of the ingredients, staring with the API, in this case testosterone undecanoate. The process is the same, but this time the hydrogen in the hydroxyl group has to be substituted by an undecane with a carbonyl group in the first carbon (esterification). So, the equipment necessary to obtain testosterone undecanoate is the same as the one in Table 7 but including the equipment necessary to do the esterification of testosterone, usually a fractional column.

Powders and granules are solids, so they are treated like bulk solids processing. The diagram below represents the generic steps to follow when manufacturing tablets: [54]



It is a lineal process, where one unit follows the other. The first one consists on reducing the particle size to the desired specifications. Solid ingredients are crushed. In this case, those ingredients are testosterone undecanoate, microcrystalline cellulose, lactose, talc, calcium silicate, titanium oxide and sodium chloride. As there are several ingredients that need to be perfectly mixed, a small size of particle is required. It also helps with further processes like compression. In consequence, a fluid jet mill will be selected to crush the solid ingredients. The smaller the size, the easier it gets absorbed in the system and the more effect the pill has. All of the solid ingredients are mixed together in a helical ribbon blender except for titanium oxide (the pigment) and sodium chloride (the flavoring).

The next step is granulation. It is required when the different streams to mix have different densities, because it avoids segregation in the following steps. Granulation also increases the flowability of the product, so that the equipment is not damaged. Granulating is not needed when the particles are rounded, which is not the case. The selected granulator is a high shear mixer granulator (Figure 9). It is simple, allows liquid phases and is recommended when one of the phases is viscous. This is important because during this step, the liquid ingredients are added: propylene glycol, cremophor (viscous) and oleic acid.

After the granulation, the product is left to dry. It is crushed again, this time in a hammer mill, that leaves the particles to millimeter range, whereas the fluid jet left them to microns size. To

make sure the particle size is correct, a vibrating screen is used to separate the desired sizes from the bigger ones, that are recirculated to the granulator. The rest of the excipients (titanium oxide and sodium chloride) are added and blended with the granules, again with a ribbon blender. The product is now ready for the final steps of the process.

Compression comes next. The selected tableting machine is the rotatory tablet press, which bibliography says is the most common. [54]

The last step consists on coating, that in the present process is done with a beeswax aqueous solution. Based on heuristics (found in Appendix 2, Table E), perforated coating pan or fluidized-bed coating should be selected. The first one requires less control, hence why it is selected. Table 9 sums up the different equipment used to manufacture the tablets. A flowsheet for the process is depicted in Figure 10.

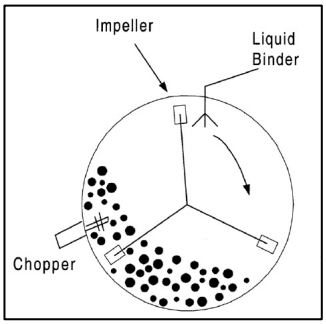


Figure 9. High shear mixer granulator. [54]

Table 9. Equipment to manufacture testosterone tablets.

Process	Operation	Equipment
Particle size reducing	Grinding	Fluid jet mill
Mixing solids	Blending	Ribbon blender
Particle size enlargement	Granulating	High shear mixer granulator
Particle size reducing	Grinding	Hammer mill
Mixing solids	Blending	Ribbon blender
Tableting	Compression	Rotatory tablet press
Shiny appearance	Coating	Perforated coating pan

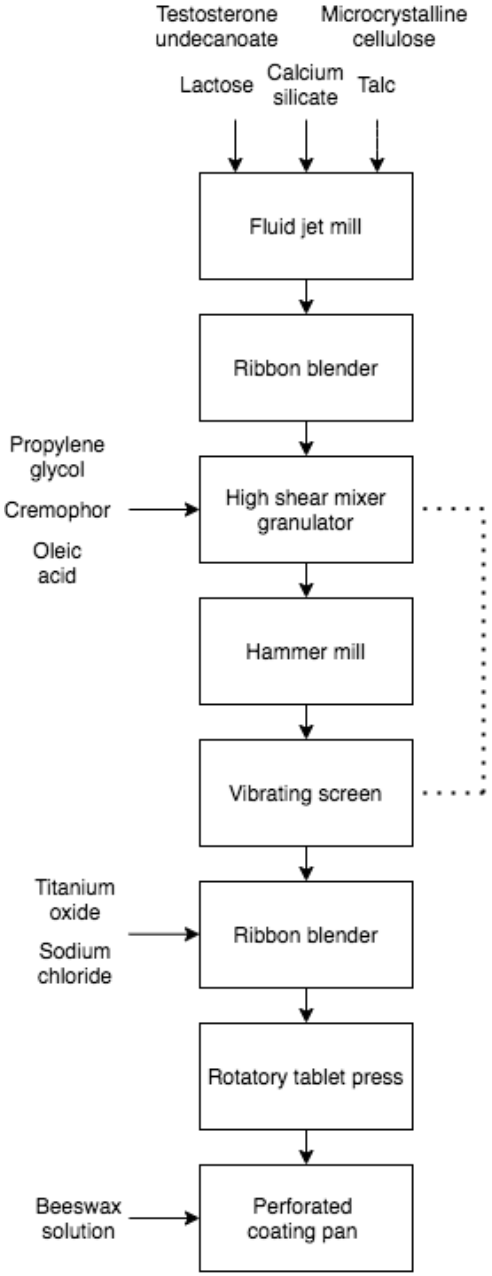


Figure 10. Flowsheet for manufacturing testosterone in tablets.

6.2.1 Selection of equipment suppliers

The list of required equipment for the manufacturing of the tablets is listed below:

- 2 Ribbon blenders
- 1 fluid jet mill
- 1 hammer mill
- 1 high shear mixer granulator
- 1 vibrating screen
- 1 rotatory tablet press
- 1 perforated coating pan

The ribbon blenders could be supplied by Ross Mixers[66]. The rotation speed is 300 fpm.

Local supplier Riera Nadeu[67] provides fluid jet mills that can reduce particles to micrometers and can also do particle coating. As there are no grinding devices, it is more difficult for the product to be contaminated.

Andritz[68] will be the provider for the hammer mill. It has a wide range of capacities and has a patented rotor that saves up to 20% in energy.

GEA[69] supplies granulation technology for pharmaceutical applications. So it is a good option for the high shear mixing granulator.

GN Separation[70] will provide the vibratory screen for the filtration of big particles. It has different models, even a vacuum one.

7. CONCLUSIONS

As shown in the project, it is concluded that testosterone is of great significance in the treatment of hypogonadism so that adult males can live a normal life without low sexual hormone symptoms. Testosterone treatments can also improve the life of transgender males by giving them the physical features they feel comfortable or they identify with.

As for the product presentations, gels are one of the most common forms of testosterone supplements. Therefore, their ingredients are well studied, and the properties and quality factors are already optimized. Testosterone gels use ethanol as the emulsifier, and carbomer is frequently used as a thickener, having other functions. Water is always the solvent, while propylene glycol is commonly the penetrator.

With tablets, the crushing of the ingredients' particles to reduce their size is the most important step, along with the granulation. Heuristics have been taken into account when selecting the necessary equipment to manufacture the product.

Finally, it has been shown that this pharmaceutical products have simple, linear production lines, there are not recirculation, excepting from one in the tablets processing.

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ACRONYMS

SHBG: sex hormone binding globulin

TRT: Testosterone replacement therapy

THT: Transgender hormonal therapy

API: Active pharmaceutical ingredient

FDA: Food and Drug Administration

TEA: triethanolamine

EDTA: ethylenediaminetetracetic acid

PEG: polyethylene glycol

APPENDICES

APPENDIX 1: CHEMICAL STRUCTURES

The following chemical structures have been created with ChemDraw.

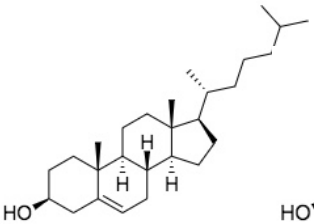

Figure A. Cholesterol

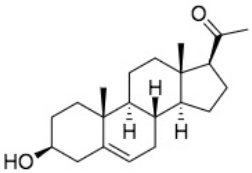

Figure B. Pregnenolone

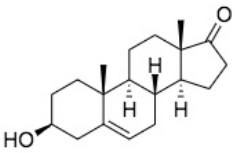

Figure C. Dehydroepiandrosterone

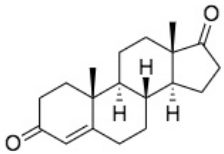

Figure D. Androstenedione

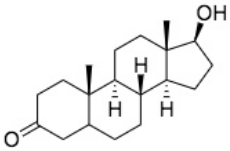

Figure E. Androstanolone

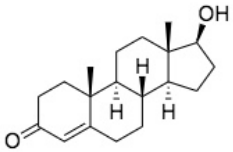

Figure F. Testosterone

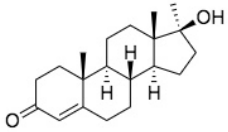

Figure G. Methyltestosterone

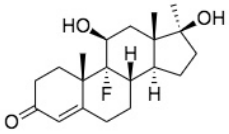

Figure H. Fluoxymesterone

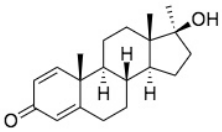

Figure I. Metandienone

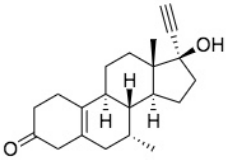

Figure J. Tibolone

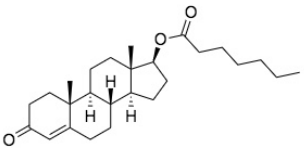

Figure K. Test. enanthate

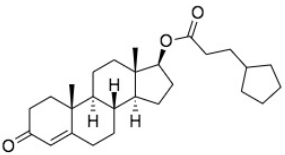

Figure L. Test. cypionate

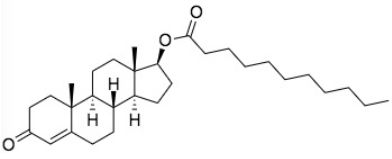

Figure M. Test. undecanoate

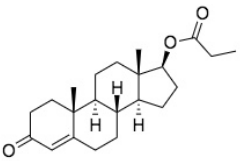

Figure N. Test. propionate

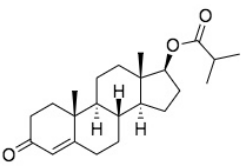

Figure O. Test. isobutyrate

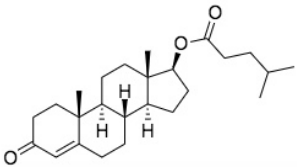

Figure P. Test. isocaproate

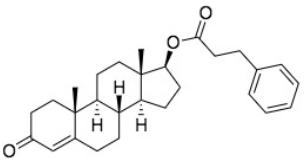

Figure Q. Test. phenylpropionate

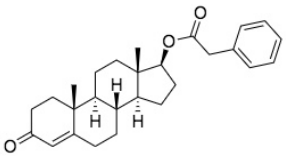

Figure R. Test. phenylacetate

APPENDIX 2: TABLES

Table A. Testosterone levels in human system

Age	Male		Female	
	Free (pg/mL)	Total (ng/dL)	Free (pg/mL)	Total (ng/dL)
Premature	-	59-198	-	5-22
Newborn	-	75-400	-	20-64
1 week	-	20-50	-	-
First months	-	60-400	-	-
Until puberty	0.1-0.6	3-10	0.1-0.6	<10
7-9 years	0.1-0.8	0-8	0.1-1.6	1-12
10-11 years	0.1-5.2	1-48	0.1-2.9	2-35
12-13 years	0.4-79.6	5-619	0.6-5.6	5-53
14-15	2.7-112.3	100-320	1.0-6.2	8-41
16-17	31.5-141.6	200-970	1.0-8.3	6-53
>18	44.0-244.0	350-1080	Not apply	Not apply
20-39	-	400-1080	Not apply	Not apply
40-59	-	350-890	Not apply	Not apply
>60	-	350-720	Not apply	Not apply
Premenopausal	Not apply	Not apply	0.8-9.2	10-54
Postmenopausal	Not apply	Not apply	0.6-6.7	7-40

Table B. Ingredients in gel formulation from Patent ES 2693745 T3 (%p/p)

Series	Testosterone	Alcohol 95%	Isopropyl myristate	Carbomer 980	NaOH 0.1M	Water
1	1.665	74.3	0.75	1	7	15.3
2	1.665	72.5	0.50	1	7	17.3
3	1.665	76.1	0.50	1	7	13.7
4	2.000	74.3	0.50	1	7	15.2
5	1.330	74.3	0.50	1	7	15.9
6	1.330	76.1	0.75	1	7	13.8
7	2.000	74.3	1.00	1	7	14.7
8	1.665	74.3	0.75	1	7	15.3
9	1.330	74.3	1.00	1	7	15.4
10	2.000	72.5	0.75	1	7	16.8
11	1.665	76.1	1.00	1	7	13.2
12	2.000	76.1	0.75	1	7	13.2
13	1.665	72.5	1.00	1	7	16.8
14	1.330	72.5	0.75	1	7	17.4
15	1.665	74.3	0.75	1	7	15.3

Table C. Analytic results for the different formulations from Table B

Series	pH	Viscosity (Pa·s)
1	5.79	23.567
2	5.76	26.900
3	5.82	23.000
4	5.75	26.700
5	5.76	25.467
6	5.69	30.233
7	5.78	24.733
8	5.79	24.767
9	5.76	24.300
10	5.72	26.133
11	5.82	20.700
12	5.83	19.733
13	5.72	26.033
14	5.69	28.267
15	5.77	23.233

Table D. Typical excipients used in tablets, capsules and powders. [54]

Excipient*	Desired Function	Typical Examples	Typical Amount
Diluent/Filler (T, H, P)	Make up tablet size, capsule size or the required powder dosage	Microcrystalline cellulose Calcium sulfate dihydrate Sucrose Lactose Starch	20–90% — — 65–85% 5–75%
Binder (T, H, P)	Increase cohesiveness of powder and hold them together to form granules	Sucrose (Solvent: Water) Microcrystalline cellulose Pregelatinized starch (Solvent: water) (Dry addition) Povidone (Solvent: Water or Water-alcohol solution) Alginic acid (Solvent: Water)	2–25% 5–20% 2–5% 5–10% 2–5% (5–10%)† (1–5%)
Filler-Binder (T)	Use in direct compression	Spray-dried Lactose Starch 1500 Microcrystalline cellulose	> 80% — 10–25%
Disintegrant (T, H, P)	To facilitate the breakup of tablet or granule	Starch Microcrystalline cellulose Cross-linked povidone Alginic acid	5–20% 5–15% 0.5–5% 5–10%
Lubricant (T, H, P)	Reduce friction during tablet ejection or facilitate drug transport to filling machine	Magnesium stearate (I)‡ Talc (I) Starch (I) Magnesium lauryl sulfate (S) Polyethylene glycol (S)	0.25–2% 5–10% 5–10% 1–3% 2–10%
Anti-adherent (T)	Reduce sticking of tablets to the punches or die wall	Talc Magnesium stearate Microcrystalline cellulose	1–5% 0.25–1% 5–10%
Glidant (T, H, P)	Promote flow of granules or powders by reducing friction between them	Calcium silicate Silicon dioxide Magnesium stearate Starch	0.5–2% 0.1–0.5% 0.2–2% 1–10%
Pigment (T, P)	Add color to tablet or powder	Titanium oxide	q.s.
Flavoring (T, P)	Add taste to tablet or powder	Flavor oils Sweeteners Salt	q.s.
Surfactant (T, H, P)	Wetting agent	Sodium lauryl sulfate	q.s.
Plasticizer (T, H, P)	Add to binder solution to increase binder efficiency	Glycerol Propylene glycol	q.s.
Salt (T, H, P)	Modify aqueous solubility of API	Hydrochloride Citrate Tartrate	q.s.
Cosolvent (S)	To aid in the preparation of solutions incorporated in soft gelatin capsules	Water and alcohol Glycerin and polyethylene glycol	Up to 5% Up to 10%
Suspending agent (S)	To prevent the settling of solids and to maintain homogeneity	Paraffin wax Polyethylene glycol Acetylated monoglycerides	5% 1–15% 5%

*T = tablet, H = hard gelatin capsule, S = soft gelatin capsule, P = powder.
†Concentration in parentheses represents dry mixing of binder (that is, mix with powder in blender and solvent is added in granulator).
‡I = water insoluble, S = water soluble.

Table E. Heuristics for coating equipment selection[54]

	Drying Efficiency	Low → High				
Level of Control	Coating Equipment	Sugar Coating	Film Coating (VOC Solvents)	Film Coating (high drying Efficiency Solvent)	Aqueous Film Coating	Film Coating of Powders
Low ↓ High	Conventional coating pan	✓	✓			
	Immersion sword	✓	✓	✓		
	Perforated coating pan	✓	✓	✓	✓	
	Fluidized-bed coating		✓	✓	✓	✓

APPENDIX 3: EQUIPMENT

Figure S. Heat exchanger (Photo from Aguilar y Salas)[61]

Figure T. Distillation column (Photo from Pflauder)[60]

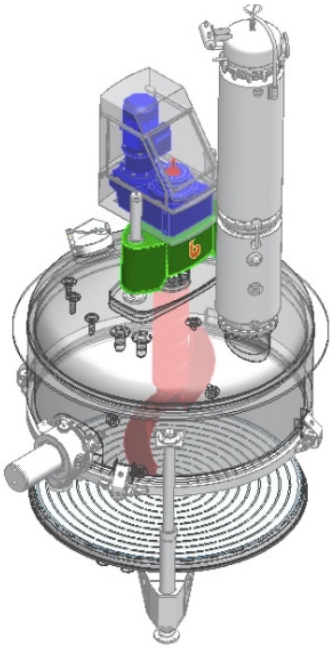

Figure U. Filter Nucha (Photo from Bachiller)[62]

Figure V. Roll crusher (Photo from Ünal)[63]

Figure W. Pressure homogenizer (Photo from BEE International)[65]

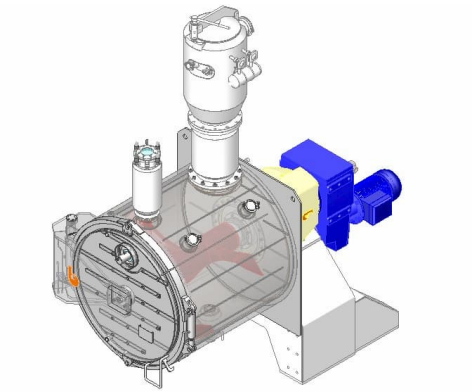

Figure X. Vacuum dryer (Photo from Bachiller)[62]