METOPROLOL SUCCINATE 95mg EXTENDED-RELEASE TABLETS

Treball Final de Grau

ISAAC BORDAS PÉREZ

Main scope: *Pharmaceutical Technology*

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Facultat de Farmàcia i Ciències de l'Alimentació

Universitat de Barcelona

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FACULTAT DE FARMÀCIA I CIÈNCIES DE L'ALIMENTACIÓ

ABBREVIATIONS

AC: *adenylyl cyclase*

ACE-I: *angiotensin converting enzyme inhibitors*

AEMPS: *Agencia Española del Medicamento y Productos Sanitarios*

Alu/Alu: *blister made of two aluminium sides*

Alu/PVC: *blister made of one aluminium side and a polyvinyl chloride one*

AOP: *advanced oxidation processes*

API: *active pharmaceutical ingredient*

ATP: *adenosine triphosphate*

cAMP: *cyclic adenosine monophosphate*

EMA: *European Medicines Agency*

FDA: *Food and Drug Administration*

GHS: *Globally Harmonized System of Classification and Labelling of Chemicals*

HPMC: *hydroxypropylmethylcellulose*

NE: *norepinephrine*

PCI: *percutaneous coronary intervention*

PK-A: *cAMP-dependent protein kinase*

PVC: *polyvinyl chloride*

SR: *sarcoplasmic reticulum*

WHO: *World Health Organization*

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ABSTRACT

A bibliographical research about metoprolol succinate's pharmacology is conducted, by which the mechanism of action, indications, side effects and other generalities of this drug are explained, giving special attention to the extended-release properties that it has been formulated with.

Metoprolol succinate and metoprolol tartrate, two distinct salt variants of metoprolol, are compared. Differences in indication, posology and formulation between these two variants are explained.

With help of bibliographical examination, a manufacturing process for this medicinal product is proposed in a large-scale setting. The different stages of industrial production of extended-release tablets are explained in detail.

Also, and considering the importance of reducing the environmental waste derived from industrial activity, a new design for the packaging is proposed in order to make a more eco-friendly product, reducing waste of cardboard and plastic.

This dissertation intends to sum up knowledge about metoprolol succinate as the first necessity medication for developed countries that it is. Throughout this work, a glance regarding the whole process of transformation of metoprolol succinate is taken, from the molecule and through its galenic development to the environmental impact that it has.

Es desenvolupa una recerca bibliogràfica de la farmacologia del metoprolol succinat per tal d'explicar el seu mecanisme d'acció, les seves indicacions i efectes adversos, fent especial esmena a les propietats d'alliberació prolongada amb les que és formulat.

Es compara el metoprolol succinat i el metoprolol tartrat, dues variants en forma de diferents sals del metoprolol, i s'expliquen les diferències que hi ha entre elles pel que fa a indicacions, posologia i formulació.

Amb l'ajuda de la bibliografia consultada, es proposa un procés de fabricació per a aquest medicament a escala industrial per fer comprimits recoberts d'alliberació prolongada i s'expliquen les diferents etapes de producció.

Per últim, fent evident la necessitat de disminuir l'impacte ambiental de la producció industrial, es proposa un nou disseny de condicionament primari i secundari per tal d'oferir un producte més ecosostenible, reduint el consum de cartró i plàstic.

Vist en perspectiva, aquest treball intenta resumir el coneixement relatiu al metoprolol succinat, com a medicament de primera necessitat que és en països desenvolupats, a través d'una lectura transversal que comprèn des del procediment de transformació de la pròpia molècula activa fins a l'impacte ambiental que aquesta té, passant pel procés de fabricació industrial del medicament.

1. INTRODUCTION

The final monography of a degree *(Treball de final de grau)* is an academic work that challenges students to work autonomously in order to put in practise concepts, abilities and skills learnt through the development of the degree.

The pharmaceutical world is competitive and demanding in the same way that the degree is. In spite of all work and effort graduates must put to have a successful university experience, pharmacy covers many interesting knowledge areas.

In my humble opinion, one of the most fascinating topics of this degree has been learning and understanding the science by which a molecular compound with medicinal properties can be transformed into a pharmaceutical product.

We live in a moment of history where the world is globalised; technology has allowed an exponential growth in medicine, making medication accessible almost all around the globe.

Being interested in both pharmaceutical designing and technology, it is no wonder I made the decision of choosing pharmaceutical technology as the main area of study of my final dissertation project.

Integrating educational scopes:

The three major academic scopes of this essay are pharmaceutical technology, environmental managing and pharmacology.

The present work is a bibliographical exercise where I intend to expand my knowledge in pharmaceutical technology, industrial equipment and techniques, at the same time that I study the environmental impact that industrial production has and research the pharmacological properties of metoprolol succinate.

2. OBJECTIVES

The essay has several objectives:

- To review the pharmacological theory of beta-blockers and metoprolol in particular.
- To analyse the pharmaceutical dosage form of metoprolol succinate and study its excipients.
- To propose an industrial tablet manufacturing process for metoprolol succinate.
- To comment the impact that pharmaceutical products have upon the environment.
- To eco-design a new packaging for metoprolol succinate to create a more sustainable product.

3. WORKSHEET DESIGN

The organization of this dissertation has been planned along the first term of 2018.

The first ideas were born during the months of January and February as the result of a couple brainstorms. For example, these initial ideas included the design of an eco-friendly packaging, which has been materialized in the present work.

The major part of the research was made in the following weeks. It was a literature research with the support of books, articles, reports, web pages and other online documentation. The writing process began in April and was extended until the end of May, when the revision, correction and stylisation of the final document were done.

All consulted references are actualized and of a notorious scientific excellence.

4. A PHARMACOLOGICAL OUTLOOK

4.1 A quick view on β-blockers

4.1.1 Definition

Beta-adrenoceptor blocking agents are a class of drug that are widely prescribed for the treatment of cardiovascular disease, heart failure and hypertension. They were first identified by James W. Black in 1962, at the Imperial Chemical Industries in the United Kingdom[1], being propranolol the first beta-blocker with therapeutic use. Since then, beta-antagonists have been widely prescribed in cardiovascular medicine, reducing morbidity and mortality by as much as 90% in acute coronary syndromes.[2]

Black was awarded the 1988 Nobel Prize in Medicine jointly to *Gertrude B. Elion* and *George H. Hitchins* for *"their discoveries of important principles for drug treatment".*[3]

To later understand the mechanism of action of beta-blockers, we should first review some basic concepts:

4.1.2 Catecholamines

Catecholamines are organic compounds formed by a cathecol group and a side-chain amine that act as neurotransmitters or hormones.

In particular, epinephrine is an hormone released by the adrenal gland whereas norepinephrine is mainly released by neurons in the brain as a neurotransmitter, even though there is a small part produced by adrenal glands as well.[4,5]

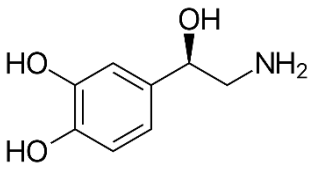


Figure 1: Molecular structure of norepinephrine (also known as noradrenaline) [5]

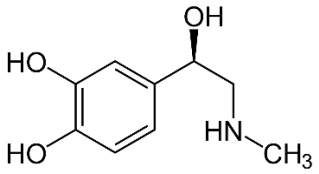


Figure 2: Molecular structure of epinephrine (also known as adrenaline) [5]

These two molecules play a crucial role in our body's sympathetic nervous system, in what it is known as the *fight or flight* response.

4.1.3 Fight or flight response

By binding to alpha and beta receptors, epinephrine and norepinephrine prepare the body to respond to a perceived harmful event, that can range from stressful situations to potential threats to survival.

This response involves physiological changes such as acceleration of the heart and lung action, dilation of blood vessels, inhibition of salivation, digestion and more.

To make it simple, this sympathetic reaction causes a higher heart rate and an increased blood flow (diverted from non-essential organs to the muscles and brain, supplying sugars and oxygen) and also speeds up the coagulation process (preventing excessive blood loss, in case of an injury). This last nuance will play a major role in the understanding of the treatments with beta blockers.[6]

4.1.4 Alpha and beta receptors

Adrenoreceptors are a class of G protein receptors that, when activated by norepinephrine and epinephrine, induce the sympathetic autonomous system and thus the *fight or flight* response previously explained.

There are two main types of adrenoreceptors, alpha and beta, and each one of these has its own subtypes: α_1, α_2 and β_1, β_2 and β_3.

In one hand, alpha-1 receptors are mainly found in smooth muscles, while alpha-2 are found in presynaptic nerves.

In the other hand, beta-1 are found in cardiac tissue, beta-2 in vascular and bronchial smooth muscle and beta-3 in fat tissue.[2]

β_2 –receptors are mostly involved in the *fight or flight* response in a muscular level, whereas β_1 are responsible for the increase of cardiac output. However, the heart also possesses β_2 receptors, even though β_1 are predominant.[7]

4.2 Mechanism of action of β-receptors

When norepinephrine binds to β-receptors in a cardiac myocyte, as shown in figure number 3, there is an increased amount of cAMP produced, consequence of the action of the adenylyl cyclase over ATP molecules.

This higher concentration of cAMP will result in an overexpression of PK-A, thus causing a greater flow of Ca^{2+} ions into the myocyte by phosphorylating calcium channels. The more amount of Ca^{2+} that enters to the cell during action potential, the bigger will be the amount of Ca^{2+} released by the sarcoplasmic reticulum. This action results in more contractions, leading to a higher heart rate.[1,7]

(Note that the arrow signalling the binding of NE with β_1 is thicker than the one with β_2).

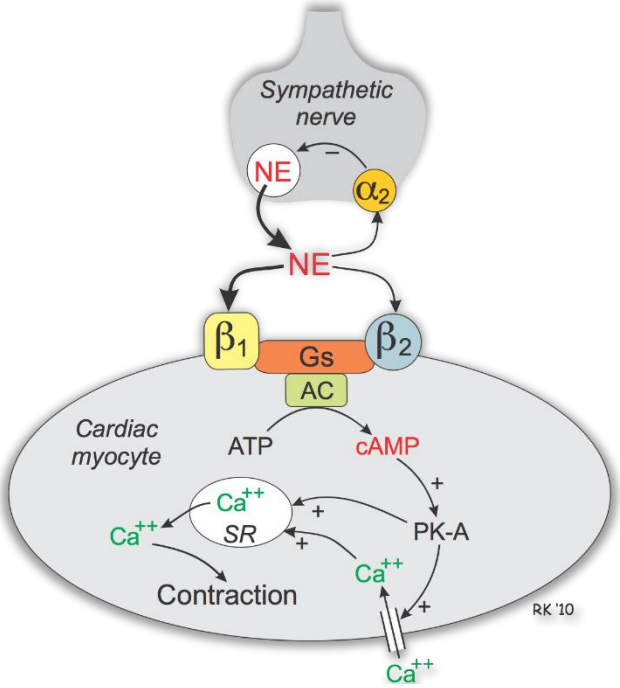


Figure 3: Beta-adrenoceptors coupled to Gs-proteins and cAMP formation in the heart. cAMP modulates cardiac myocytes' contractions.[7]

Abbreviations: NE, norepinephrine; Gs, G-stimulatory protein; AC, adenylyl cyclase; PK-A, cAMP-dependent protein kinase; SR, sarcoplasmic reticulum.

β-blockers

β-blockers, as we have seen before, act as competitive inhibitors of β-adrenergic receptors. Therefore, catecholamines may not properly bind to adrenoreceptors, meaning that their effect will be substantially reduced.

β-antagonists can be classified in 3 generations:

- 1st Generation comprises non-selective agents like propranolol and timolol.
- 2nd Generation consists of selective β_1 agents that act solely upon these receptors. In this group we find metoprolol and atenolol.
- 3rd Generation is made up of non-selective or β_1-selective agents that have vasodilation properties. In this group we find nebivolol and carvedilol.

Some of the main effects of these drugs are the reduction of heart rate (slowing down the sinoatrial node), the decreased formation of arrhythmias (due to a reduced contractibility) and a diminution of blood pressure (by dilation of cardiac artery).[4]

Metoprolol succinate

Metoprolol succinate is a second generation beta-blocker, as seen before. It acts binding selectively to β_1 receptors, antagonizing adrenergic effects.

The molecular formula of metoprolol succinate is $(C_{15}H_{25}NO_3)_2 \cdot C_4H_6O_4$, and its IUPAC name is butadenoic acid; 1-[4-(2-methoxyethyl)phenoxy]-3-(propan-2-ylamino9propan-2-ol.[8]

The molecular weight of this compound is approximately of 652.826g/mol.

It is one of the salt forms of metoprolol, alongside metoprolol tartrate. Being a salt makes this compound highly soluble in water. It is also considerably soluble in methanol, but it is practically insoluble in acetone or diethyl ether.

It is distributed as a powder, which must be stored at room temperature.

Accordingly to the Hazard and Precautionary Statements from the GHS, it is considered harmful if swallowed, damaging to organs and skin irritating, while it also hazardous to aquatic life with long lasting effects.[8]

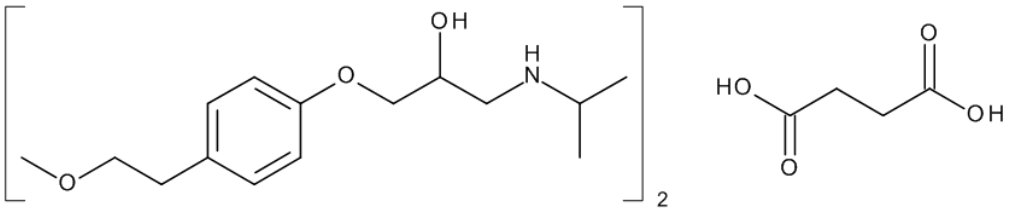


Figure 4: Metoprolol succinate's molecular structure.[8]

4.3 The clinical experience of *metoprolol succinate*

4.3.1 Indications

Metoprolol is a drug that can be presented both as metoprolol *succinate* and metoprolol *tartrate*. Even though the pharmacophore is the same, there are differences between the two API, and one of them is the indications they both have. [Those differences will be reviewed later in this document].

Metoprolol succinate is an EMA and FDA-approved drug for hypertension, angina and heart failure. At the same time, metoprolol tartrate is approved for hypertension, angina, and prevention of heart attacks.(9)

In the following sections we will see in detail the different indications of metoprolol succinate.

Heart failure

Heart failure is a chronic condition in which the heart muscles are progressively getting weaker and the body's oxygen and blood needs are not met, since not enough blood is bumped.

The body has some compensatory mechanisms, but in the long-term they are not enough to solve the problem. These mechanisms include developing more muscle mass and enlarging the heart (letting the heart pump strongly), diverting blood away from non-essential organs to the heart and brain and also hastening the heartbeat.(10)

Treatment for heart failure depends on its severity. Pharmacological treatment includes ACE-I (angiotensin converting enzyme inhibitors) and beta-blockers, usually in association. Exercising, quitting smoking and planning a healthier diet are recommended in all scenarios.(11)

Hypertension

Hypertension is a common diagnosed condition in which the blood pressure in the arteries is consistently elevated. It is a global health concern because it leads to a major risk for coronary disease, strokes, heart failure and other related pathologies.(12)

Lifestyle changes are the first recommended treatment for non-severe cases. However, since hypertension is one of the most prevalent conditions worldwide, millions of patients use medication to treat it.

Amongst the most frequently prescribed drugs for hypertension we find ACE inhibitors, calcium channel blockers, diuretics and beta-blockers.(13)

Angina

Angina is the name given to the chest pain caused when the heart muscle does not receive enough oxygen. The feeling of discomfort feels like a pressure or squeezing in the chest and can also be extended to arms, shoulders, neck or back.[14]

Angina can be classified depending on the pattern:

- Stable angina (also known as *angina pectoris* or *chronic angina*): is caused when the heart is working more than what it usually does, for example doing some physical activity like exercising. Since it has a regular pattern it can be predicted and sometimes avoided. Resting can alleviate stable angina, and even though the most common pharmaceutical option is nitroglycerin, beta-blockers such as metoprolol are also considered.
- Unstable angina: unlike stable angina, unstable angina shows itself with no apparent pattern and it can even occur during rest. It is considered far more dangerous, because it can be a sign of immediate or potential heart attack and rest or medication do not relieve it. In severe cases, surgical procedures like a percutaneous coronary intervention (PCI) or a coronary artery bypass graft surgery are performed.[15]
- Pinzmetal's angina (also known as *variant*) and microvascular angina are two types of angina characterized by an abnormal narrowing of the blood vessels without being led by a coronary disease. Nitrates and calcium-antagonists are the mainstays of these angina's treatments.

4.3.2 Contraindications

Metoprolol succinate is not suitable for everyone. It should not be prescribed if the patient is prone to have bradycardia or hypotension, second- or third-degree atrioventricular block, blood circulation problems, arrhythmias or in case of allergy to any of the components. It is not meant to be used in patients with unstable coronary artery disease nor in cardiogenic shock, either.

Also, in case of asthma, emphysema or any other respiratory distress disease and in renal insufficiency, dosage should be individually calculated and monitored. [16–18]

4.3.3 Adverse effects

Common side effects of metoprolol succinate, that are dose-dependent, include: dizziness, tiredness, drowsiness, headache, diarrhoea, itching or rash and nausea.

Unusual cases include: depression and paraesthesia.

Rare cases include: visual, auditive and olfactive alteration, anxiety and memory loss. [16–18]

5. A PHARMACEUTICAL TECHNOLOGY PERSPECTIVE

In the previous unit of this academic work, we reviewed the pharmacological aspects of metoprolol. This section will be focused on the technological aspects involving *metoprolol succinate*.

For that, we will first take a glance on the medicinal products containing *metoprolol succinate 95mg* that have been approved by the AEMPS administration.

There are only two options available in the Spanish market:

- *BELOKEN RETARD® 95 MG EXTENDED-RELEASE TABLETS* [16]
- *METOPROLOL KRKA RETARD 95MG EXTENDED-RELEASE TABLETS* (generic product)[17]

5.1 Selecting the adequate dosage form

Oral administration is generally the most accepted and used route of drug delivery. A few of the reasons for that are that the administration is easy, it is well accepted by patients, and that its manufacturing process is usually cost effective.

Amongst all the available options, tablets are one of the most common. Not only because of the advantages that these dosage forms have per se, but also because they are more stable compared to other dosage forms.[19]

In addition, tablets can be formulated in a way that allow an extended or modified-release. This is probably the reason why this dosage form was chosen for metoprolol succinate.[20,21]

Metoprolol, as we have reviewed before, can be found in a *tartrate* or a *succinate* structure. Both of these structures make metoprolol a salt, which means their solubility in water is very high.

Instead, what sets these two salts apart is the way they are released into the bloodstream, thus making their clinical indications slightly different.

Metoprolol tartrate is a drug indicated in hypertension and angina (just like the succinate variant) but is also a treatment in post-myocardial infarction.

This difference is explained by the drug's concentration levels through time. Metoprolol tartrate offers an immediate release of the active ingredient, which means the concentration of the drug in the blood will peak. Instead, metoprolol succinate will extend the release in a constant manner and its effects will last longer.[22]

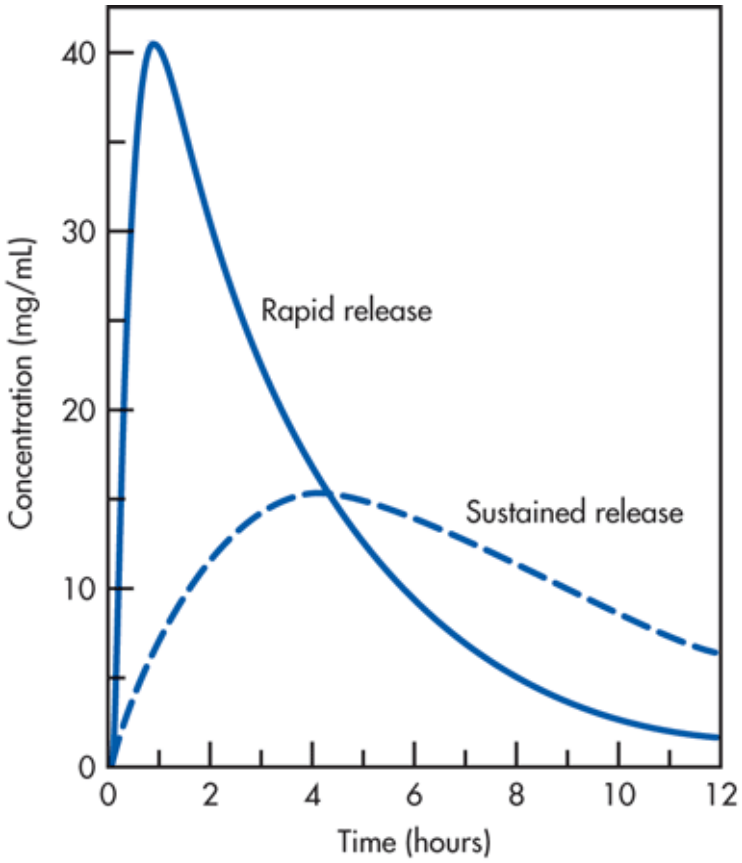


Figure 5: Graphic representation of the difference between immediate-released and extended-released drugs in plasma concentration through time. [23]

In comparison to metoprolol tartrate, the extended-release metoprolol succinate reaches plasma levels of one-fourth to one-half the peak reached by conventional metoprolol and also has a lower peak to trough variation.[24]

For these reasons, the extended-release formulation of metoprolol succinate makes the posology of this medication be just one tablet a day.

5.2 Studying the excipients of the formulation

The generic medicinal product of metoprolol succinate commercialized in Spain is *Metoprolol succinato retard 95mg KRKA*. The aim of this section is to display information regarding the excipients used for its tablet manufacturing.

All these excipients are used in different formulation applications, but we will only describe uses in tableting, since metoprolol succinate is only commercialized as a tablet.

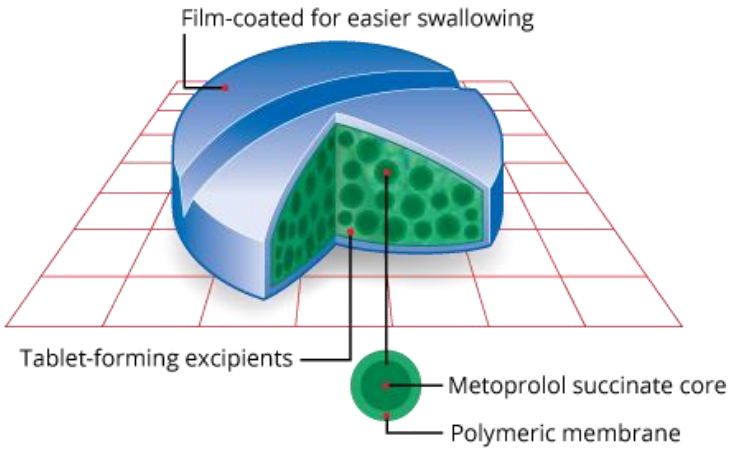


Figure 6: Visual representation of metoprolol succinate's film-coated tablet formulation. The active substance is protected by a polymeric membrane made of tablet-forming excipients. The tablet is coated with other excipients that make swallowing easier and also help in the extensive-releasing properties.[18]

5.2.1 Compressed nucleus

- **Colloidal anhydrous silica**

Colloidal anhydrous silica (also known as colloidal silicon dioxide or *Aerosil®*) is a micronized silica of approximately 15nm particle size. It is a non-coloured, tasteless and odourless white powder that is often used in the formulation of tablets because it improves flow properties of other excipients in the form of dry powder. It can act as an adsorbent, as an anti-caking agent and as a tablet disintegrant.[25,26]

- **Microcrystalline cellulose**

Microcrystalline cellulose, also known as Avicel®, is a semipolymerized purified cellulose that is mainly applied as a diluent in oral tablet formulations, used in both direct-compression and in wet-granulation processes. Additionally to being used as a filler, it can also be applied as disintegrant and dry binder in tablet formulations. It is a tasteless, odourless, crystalline white powder.[25–27]

Note that all excipients have been named following the current British Pharmacopoeia standards.

- **Hypromellose**

Hypromellose (also known as hydroxypropylmethylcellulose or HPMC) is a white granular powder, which is tasteless and odourless, that is often used in oral products as a coating agent, as a tablet binder and as a polymer for extended-release formulations.[25,26]

In the case we are presenting, HPMC in a compressed nucleus is applied as a tablet binder and a polymer.

- **Sodium lauryl sulphate**

Sodium lauryl sulphate is a pale coloured powder –it can also adopt a flake or crystalline form- that has a bitter taste and smooth feel. It is an anionic surfactant used as a tablet lubricant.[25,26]

- **Polysorbate 80**

Polysorbate 80 (sometimes also referred as Tween® 80) is a yellow oily liquid that is used as a emulsifying and wetting agent in tablets and other pharmaceutical dosage forms, like emulsions.[25,26,28]

This surfactant acts improving the wettability of the interior of the tablet, which promotes its disintegration.

- **Glycerol**

Glycerol, also known as glycerine, it is a substance used in a wide variety of formulations. In tableting it is used as a humectant solvent, preservative and as a sweetener. It is a clear, viscous liquid. It has a sweet taste, but it does not have colour or any odour.[25,26]

- **Hydroxypropylcellulose**

Hydroxypropylcellulose is a pale yellow, tasteless and odourless powder that is used in oral formulations as a film-coater, as a tablet binder and as a modified-release matrix former. Depending on the concentration of this substance, it can be used in direct-compression tableting or in the production of extended-release tablets.

It is known that the quickness of the release is inversely proportional to the viscosity of hydroxypropylcellulose. It is also remarkable that if an anionic surfactant (like sodium lauryl sulphate, whose application we have already described) is added into a formulation containing hydroxypropylcellulose, the viscosity of the cellulose increases, thus the release of the drug is extended.[25,26]

- **Ethylcellulose**

Ethylcellulose is an ethoxylated-cellulose, tasteless and colourless, that is commonly used as an excipient in oral formulations. Although its primarily use is being a coating product, masking an unpleasant taste or improving the stability of tablets, it can also act as a matrix former in extended-release tablets.[25,26]

- **Sodium stearyl fumarate**

Sodium stearyl fumarate is a commonly used tablet lubricant at 0.5-2.0% concentration (weight/weight, w/w). It is a fine, white powder that usually contains agglomerated particles, in a flat and circular-shaped form.[25,26]

5.2.2 Coating film

- **Hypromellose**

HPMC, as presented previously, is a granular powder used as a tablet binder or as a coating agent.

In the case we are presenting, HPMC is used as a binder for the core of the extended-release tablet of metoprolol succinate and as a coating agent in the process of film-coating the nucleus of the tablets.[25,26,29]

- **Titanium dioxide**

Titanium dioxide (TiO_2) is a white tasteless and odourless powder used as a white pigment and opacifier in film-coated tablets. [25,26]

- **Talc**

Talc is a very fine crystalline powder used as a tablet lubricant and glidant. It has a white to light-grey colour and it is odourless. It has a soft touch, being almost impalpable and unctuous.[25,26]

- **Propylene glycol**

Propylene glycol is a colourless clear, viscous liquid with a sweet, acrid taste that is commonly used as a plasticizer in film-coating tableting. It can also act as a humectant and as an antimicrobial agent.[25,26]

5.3 Proposing a manufacturing process

Given that the access to bibliography regarding the specific manufacturing process of metoprolol succinate is limited, this section of the dissertation will be an attempt to recreate the fabrication process based on theoretical information found in books and articles. Note that since no bibliography regarding formulation, proportion of excipients or batch sizes was found, no comments on that aspect will be done. This is an exercise that requires analysing the theory and synthesising the acquired knowledge, and might not represent faithfully the way this medicinal product is industrially manufactured.

Once that statement is made, it is important to emphasise that the list of excipients reviewed previously will be the cornerstone of the exercise.

In the current time in industry, big firms often possess advanced technology in their manufacturing process. Even though the cost of large machinery is high, the results are more efficient, reliable and of a great quality and improved safety.[20] The process of tableting can be done by three different mechanisms: direct compression, dry and wet granulation.

Direct compression is the simplest, most straightforward way to produce tablets since it has fewer process stages than granulation options, leading to a faster production. The choice to use direct compression will be determined by a few factors. Excipients must have the exact flow and compression characteristics. The process of direct compression involves weighting the excipients and the active substance, milling and mixing them, in order to later compress them altogether.[30]

Alternatively, on the one hand there is dry granulation, a form of oral dosage production wherein small particles are adhered together to form granules that will make compression easier, all in fewer steps than in wet granulation.[31] Those steps include: weighting, milling the powders, blending them, compacting the mix of powders through a roller compactor to form sheets of compressed material, which are then milled into granules, lubrication of granules and final stage compression. Compared to wet granulation, there are no humectant liquids involved in the procedure.[30]

On the other hand, wet granulation involves similar steps but also includes a step in which humectants and wetting agents are added to a pre-mixture to increase the binding of the excipients that form the granules. After the liquid is added, granules are dried so their intrinsic humidity is removed.[20]

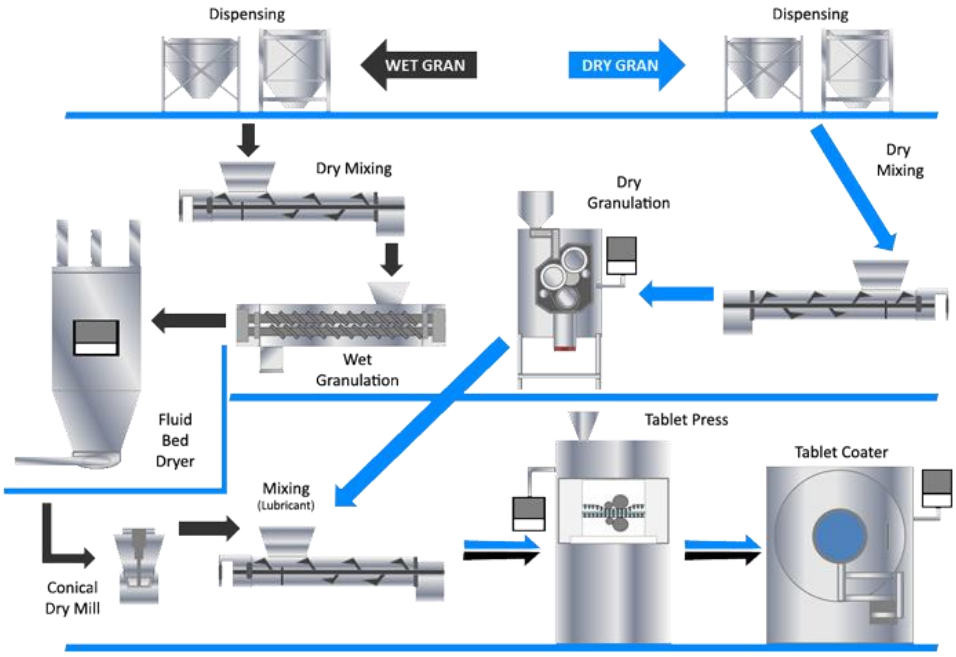


Figure 7: Different work flow process for wet and dry granulation.[31]

As reviewed before, the generic version of metoprolol succinate approved by the AEMPS contains three liquid excipients (*propylene glycol*, *glycerol* and *polysorbate 80*), in which the first is used in the coating step and the last two are used in the granulation process.

Because of that, the most suitable option for the manufacturing of tablets in this particular case is wet granulation.

Needless to say, every single step of the manufacturing process has to follow GMP (Good Manufacturing Practices), not only because it is legally required but also because it is the best way to ensure pharmaceutical quality and safety.[32]

WEIGHING

The proposed manufacturing procedure starts with the weighing of the active substance and excipients. All compounds must comply the expected quality in order to guarantee the safety and efficacy of the potential tablets. To do so, excipients will be sent to a weighing room where trained operators will carefully weigh all of them with the adequate scales and later store them in tagged containers.[20]

GRANULATION

Subsequently, some excipients are used in what it is the first phase of granulation.

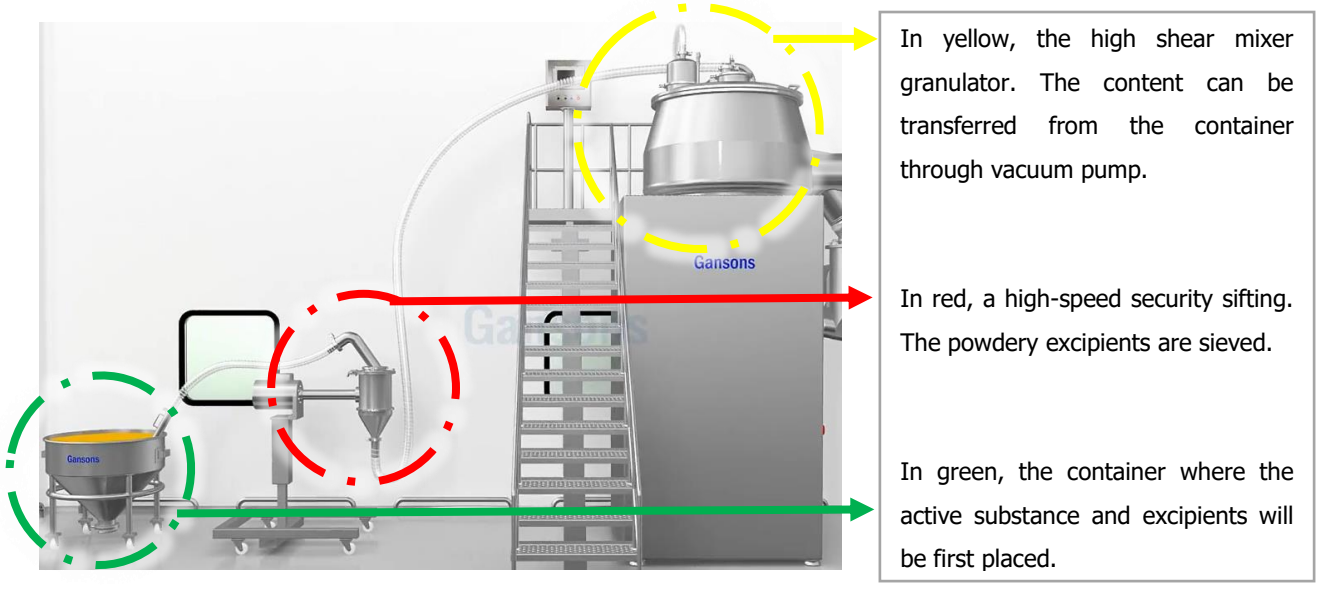


Figure 8: Industrial manufacturing process often use lined-up sets of equipment to improve efficiency.[33]

In order to do so, the active substance and the first excipients are placed in a container. The material is then charged into a high shear mixer granulator with previous sifting to uniformize particle size.

The excipients that will be used in the first phase are: ***colloidal anhydrous silica***, ***microcrystalline cellulose***, ***hydroxypropylcellulose*** and part of ***hypromellose*** (a certain amount will be used in the coating process).[27]

Once in the high shear mixer, these compounds will be vigorously mixed by an agitator (n_2) and a chopper (n_1). *(See Figure 9)*

An industrial mixer might be represented by the following diagram. The powdery excipients are transferred through the charging canal and the liquid binders are added with a sprayer after a set time. Molecular nitrogen is added to facilitate the mixing procedure right before the binders are added.

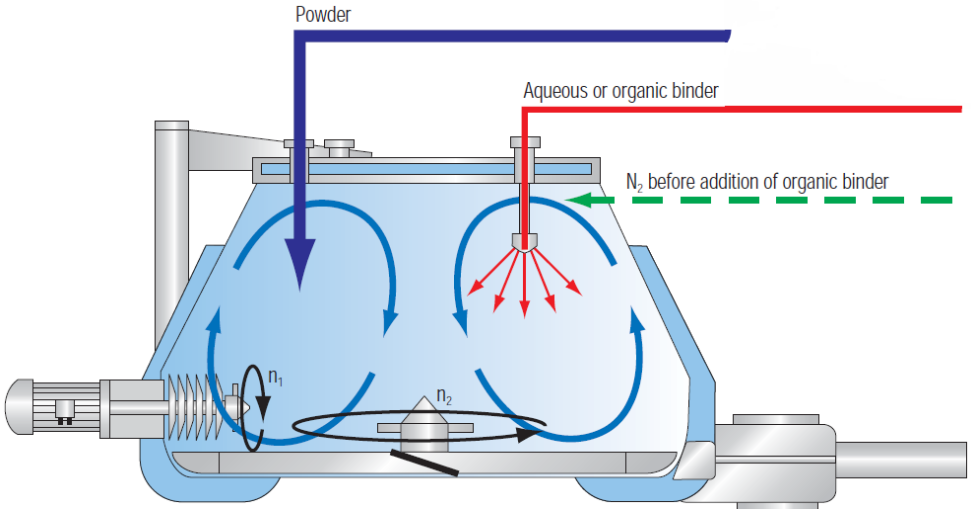
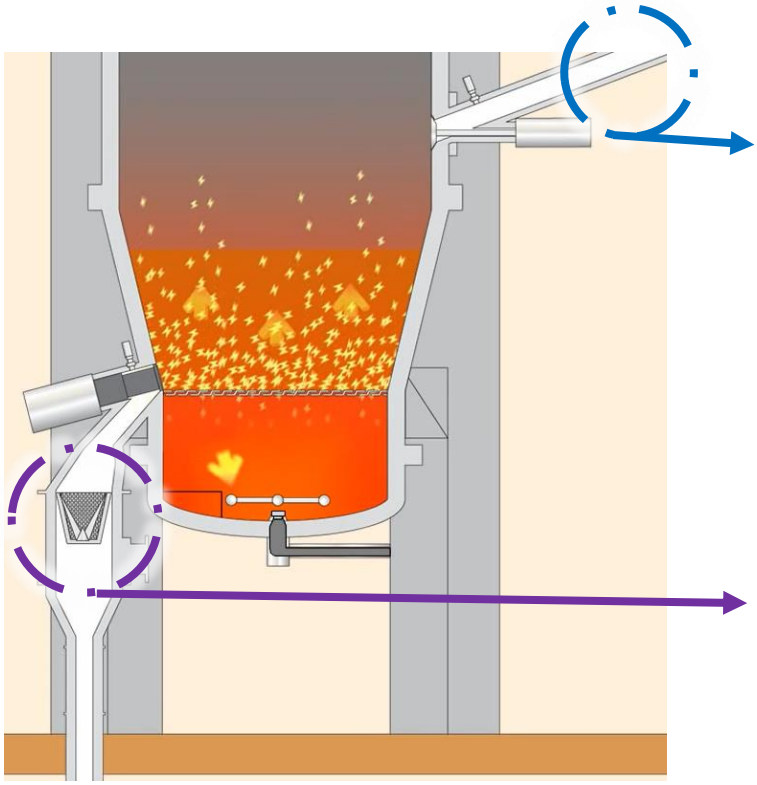


Figure 9: Shear mixer internal structure; powder gets mixed by a chopper (n_1) and an agitator (n_2). Binders are sprayed while the mixture is being conducted.[31]

In our case, the liquid components are ***polysorbate 80*** and ***glycerol***, acting as humectants and wetting agents.

After the mixture finishes, the wet granules formed are discharged with a wet sieve to homogenize particle size and are later sent into a dryer.

Usually, for the drying of granules it is used a fluidized bed dryer. This is an equipment that reduces the moisture content from granules and powders. Hot air is introduced at high pressure through a perforated plate, lifting the granules and keeping them suspended in an airstream. The heat vaporizes the liquid particles that the wet granules have and then they are carried away by the airflow.[31,34–36]



The mixed wet granules are transferred from the high shear mixer to the fluid bet dryer, going through a second sieve.

The heated airflow makes granules move and lose their moisture. The excess of humidity is then removed through bag filters and finally the granules get dry.

Once the product is dry, it is sift for a third time and sent to an other last mixer.

Figure 10: Fluid bed dryer. Warm airflow suspends granules and dries them by removing the moisture that they contain. The humidity loss of these granules is cleared by filters. After a set time, when granules are dried, they go through a sieve to homogenize particle size. [20]

The dry granules go through a sieve and are transferred to a final mixer, where there will also be added the lubricant substances. In our case, those are ***sodium stearyl fumarate*** and ***sodium lauryl sulphate***.

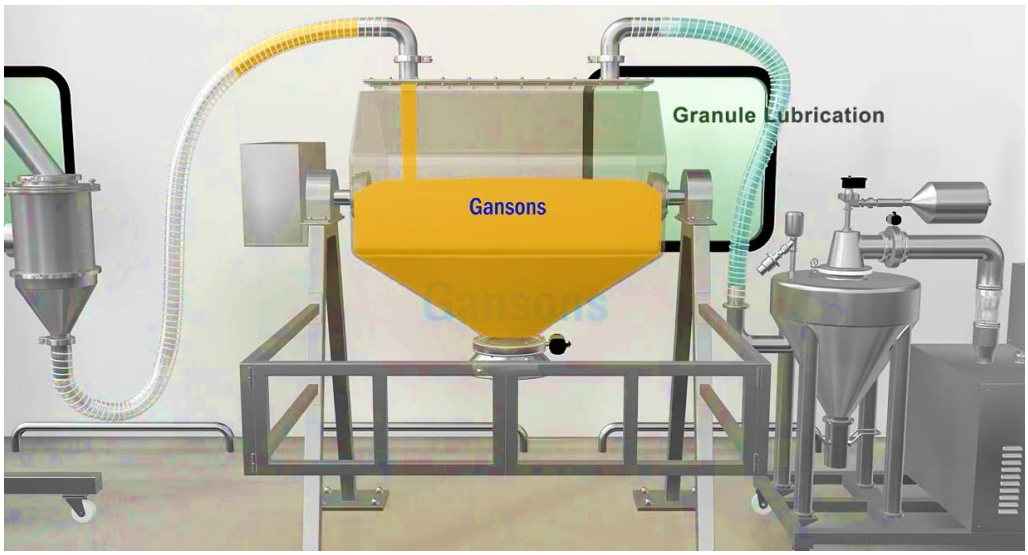


Figure 11: Lubrication container. Non-lubricated granules and lubricating excipients are placed in a rotary container that will mix both of them.[33]

With that, lubricants will stick to the formed granules, giving them better flowing properties and a better compressibility. Finally, the product obtained from the granulation will be compressed.

COMPRESSION

Compression is the process in which the previously formed granules are pressed at high pressure to compact them together and create a tablet.

The most used tablet press in industrial settings is the rotary press, while eccentric presses are usually used in the primary phases of pharmaceutical development. Rotary tablet press machines allow large productions and can have an output as high as 450,000 tablets per hour.[37]

It is formed by an automated rotating turret that contains a double set of punches across it (the upper section of the turret holds the upper punches and vice versa), a set of dies for each couple of vertical punches, the feeder, the compression rolls and the ejection site. Additionally, these machines usually have control mechanisms by which parameters like weight, centrifugal velocity, and applicable pressure can be regulated depending on the situation.

Precompression is the process where punches exert a first amount of pressure to remove traces of air that are trapped within the powder. In the main compression a higher pressure is applied in order to compact the granules into tablets with the desired hardness. In both of these situations, punches move by the compression rolls; upper punches will move down because of it and compression will take place. After the upper and lower punches lose contact with the compression rolls, the upper punches will be lifted by the upper cam and at the same time the lower punches will be moved by the ejection cam and tablets will be pushed out of the die cavity and discharged.[38]

Usually, the number of tablets obtained per revolution coincides with the number of dies that the turret has.[37] It is also worth pointing out that punches are one of the most crucial and delicate pieces of the tablet press. They can be specifically design for every type of tablet and they characterize the form of the resulting tablet.

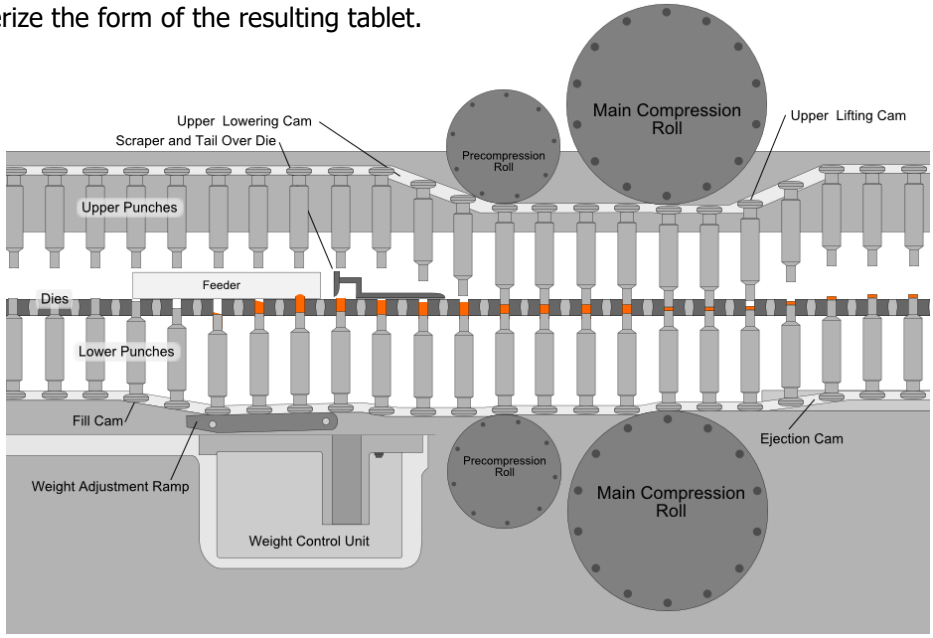


Figure 12: Rotary press internal system. In orange, granules are pressed to form a tablet.[39]

COATING

The last step of the manufacturing process of tablets is coating.

Even though it is an optional step in conventional tablets, in our case proposing a manufacturing process for metoprolol succinate it is necessary.

As reviewed before, four excipients of the formulation are involved in the film-coating of the tablets

Hypromellose, not only used as a tablet binder but also as a coating agent, and ***propylene glycol*** are going to be used as the two major coating components. Both ***talc*** and ***titanium dioxide*** are excipients that will grant extra quality attributes. Titanium dioxide is a powder that gives a white pigment and opacifies tablets, while talc grants the best lubrication and gliding.

In order to start the coating procedure, the batch of compressed tablets will be loaded into a drum coating system. The drum will start spinning, slowly moving tablets around. Warm air will flow continuously and eventually the rest of the excipients (mixture of liquid and powders) will be sprayed. The combination of parallel spraying and spinning results in a uniformed coating. Once the coating is uniform, there is a drying lapse and a posterior cooling-down of the machine.[20,36] Tablets will now be coated.

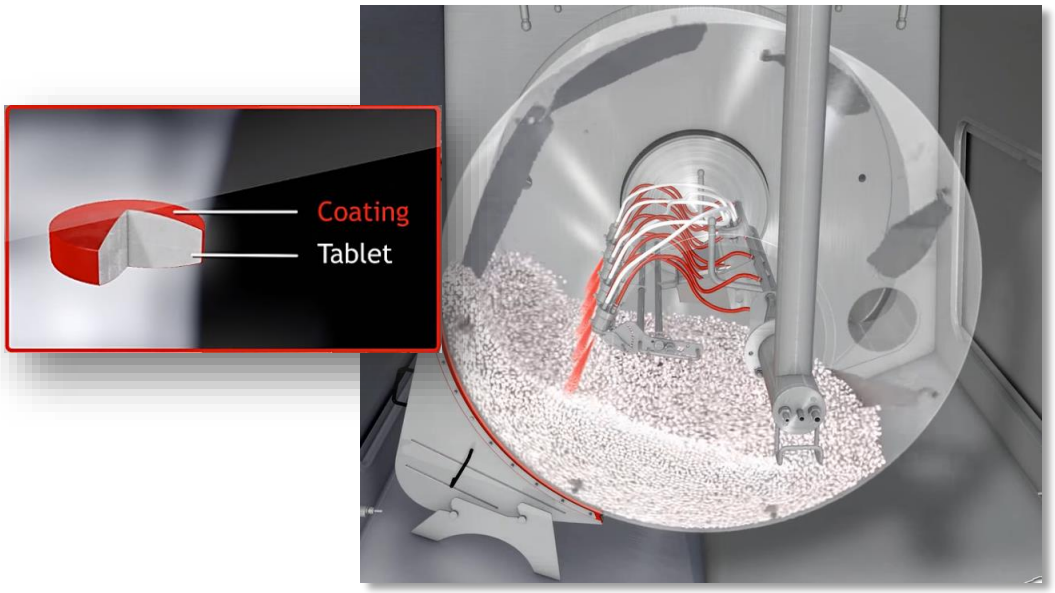


Figure 13: Representation of the coating process. The charged drum spins moving tablets around at the same time that the coating substances are sprayed upon them.[31]

PACKAGING

After the manufacturing of the tablets, packaging is what follows.

Some tablets will be used as samples to analyse the lot quality; if tests are successful, the rest of the tablets will be stored in the designed packaging.

The primary packaging of a medicinal product consists in the protection of the pharmaceutical dosage form. In our case, the primary protection is a blister, even though other options could be considered. The main goal of creating this primary packaging is maintaining the integrity of the product.

The blistering procedure is also highly mechanized, since the portion of tablets produced in one lot is usually very large. The equipment used contains stationary and moving parts that are meant to help produce the blister sets. Through many electromechanical movements, the machine produces cavities on mouldable web materials, fills those cavities with the tablets and covers them with the adequate material.[40]

Blisters from *metoprolol succinato 95mg KRKA* are made of Alu/PVC (one aluminium side and a polyvinyl chloride, plastic one). For this packaging, large rolls of PVC are placed in the feeding rollers. Those rollers will make them move and undergo through a heating box that will form bubble-like cavities. After that, tablets are going to be placed in the formed pockets with the help of automated and synchronized mechanisms.

Right after, the blister is formed after a seal station covers the tablets in their pockets with the second material used. Sealing is accomplished with applied temperature, that differs depending on the material used. Once the blister is sealed, it is moved to the printing station, where important information is engraved. There is usually information about the product, the dosage and the manufacturer, but the expiry date and the lot identification number are always printed. Then, blister packs are moved into the last station, where they are trimmed into individual units and ejected from the machine line.[40,41]

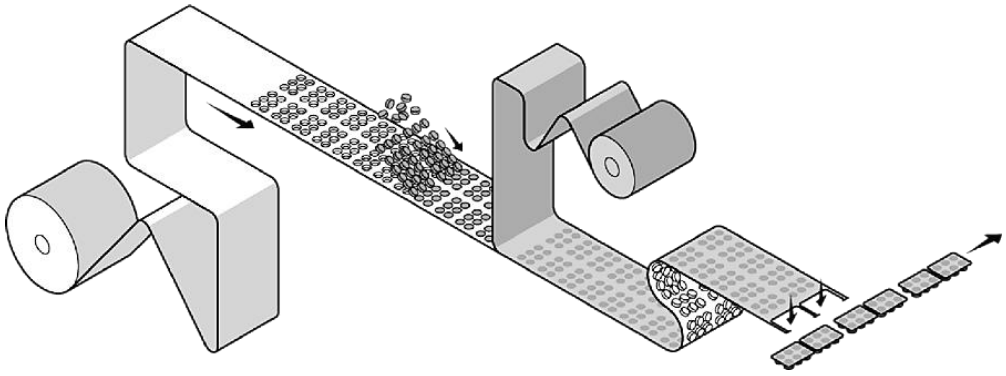


Figure 14: Schematic representation of the blistering procedure: cavity formation, tablet filling, sealing and trimming.[40]

6. PROSPECTS ON ENVIRONMENTAL MANAGEMENT

6.1 The impact of emerging contaminants

Pharmacokinetically, metoprolol succinate's absorption is fast and almost complete. Its plasma half-life ranges from 3 to 7h. However, plasma levels achieved after oral administration are variable interindividually.

It is metabolized by the liver and a 5% of the dose is recovered unchanged in the urine.[24] This unaltered percentage of metoprolol and other metabolites are excreted through urine, thus making their way to the sewage.

Just like metoprolol, there are many medicinal products that end up in the sewage. Most of them can be considered *emerging contaminants*, which can be defined as a group of compounds that raise toxicological concern for the environment and are not yet legislatively regulated but might be in a future.[42] They are candidates to undergo studies on their effect upon aquatic life forms and the environment.

Pharmaceutical products are not always removable in residual water treatment plants with the conventional treatments.

Alternative treatments such as advanced oxidation processes (AOPs) might work best to treat medicinal products.[42]

The number of contaminants reaching wastewaters does not exclusively come from households, but also from hospitals, from production plants of pharmaceutical industries and from livestock treatment waste.

Metoprolol is classified as "dangerous for the environment".[43] It can be found in wastewater treatment plants and even in rivers[44] and they must be treated accordingly to prevent potential environmental damage.

However, water pollution is not the only environmental concern to consider. Water consumption, plastic use and paper waste are also material goods whose usage must be reduced in any circumstance.

The protection of the environment has become increasingly transcendental and pharmaceutical industries are facing the challenge of reducing and preventing environmental pollution without compromising their activity.[45]

6.2 Eco-friendly designing

As an example of a plan proposed to reduce waste in a pharmaceutical perspective, I have re-designed the secondary and primary packaging (cardboard and blister format, respectively) of metoprolol succinate. The model for the comparison has been, like in other sections of this dissertation, *Metoprolol succinato retard 95mg KRKA*.

According to the World Health Organization, efforts should be made to reduce the surface and weight of packaging materials and to use eco-friendly, recyclable or degradable materials.[45]

-THE "*OLD*" AND THE "*NEW*" DESIGN

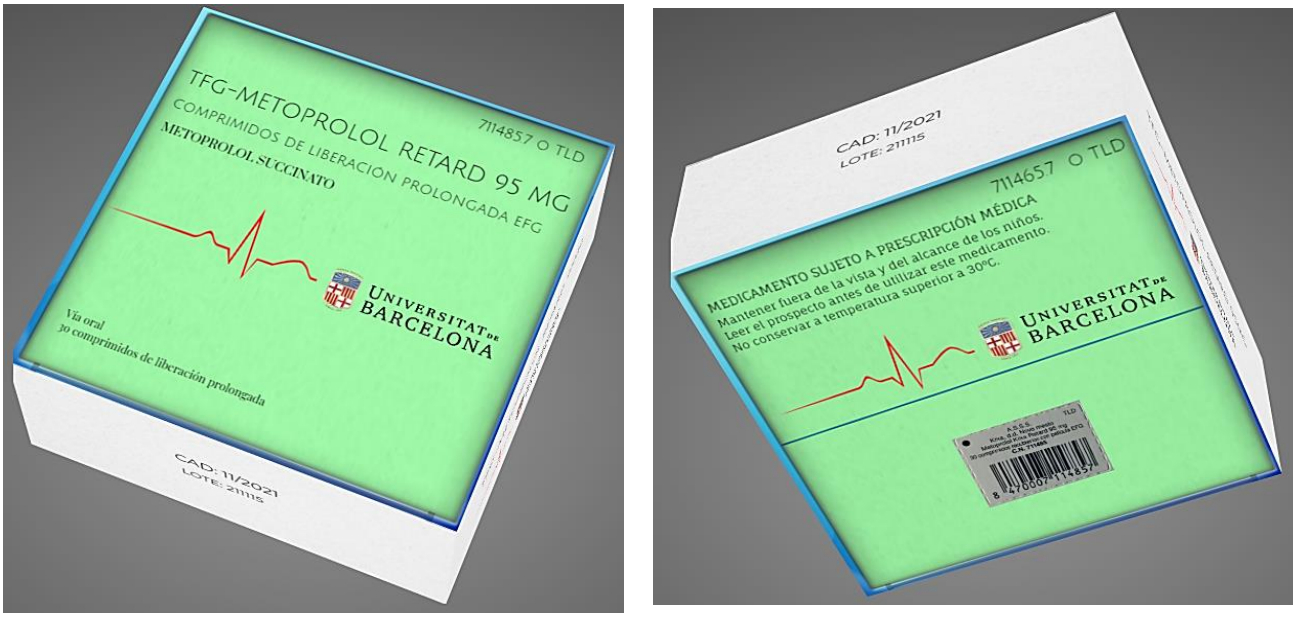
The current packaging looks like this:

Figure 15: Picture of Metoprolol succinate KRKA. (Own content)

Length: 11.5 cm
Width: 7 cm
Depth: 2.5 cm
Area: 253.5 cm^2

Even though its packaging is not excessively large, there is still room for improvement.

In the new design dimensions are slightly changed.



Length: 8.5 cm

Width: 8.5 cm

Depth: 1.5 cm

Area: 195.5 cm^2

Figure 16: Different angles of the new designed packaging for metoprolol succinate. Own creation using Packwire.

-CLAIMED IMPROVEMENTS

The length is reduced to 8.5 cm and the width is also 8.5cm, making the packaging squared; also, depth is reduced to 1.5cm, since the number of blister sets is minimized from 3 (containing 10 tablets) to 2 (containing 15 tablets). Overall, the area of the new design is 195.5 cm^2.

The new design is indeed more packed but it can be handled nonetheless, even by geriatric patients.

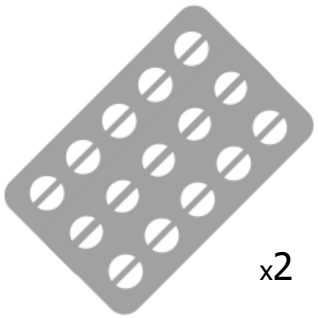


Figure 17: Representation of the proposed 15-tablet blister set. (Own creation)

The new packaging is designed to contain only two blister sets, instead of three. This is why the depth of the packaging has diminished.

Another eco-friendly feature that has been proposed is to substitute the blister being Alu/PVC to Alu/Alu. Aluminium can be more easily recycled than plastic materials, therefore the option of using blisters Alu/Alu has been chosen.[45]

Comparing the areas of the two designs, the new one is 23% smaller. The amount of cardboard used and the weight of the packaging have been considerably reduced. The area of the new packaging represents a 77% of the current version (23% smaller).

$$\frac{area_1\ 108.375\ cm^3}{area_2\ 201.25\ cm^3} \times 100 = 77\%$$

No data bibliography has been found regarding how many people use KRKA's metoprolol succinate.

In spite of that, the obtained numbers will be extrapolated to understand the impact made by the new design's area diminishment.

In the event of manufacturing 100,000 units, the amount of cardboard reduced in cm^2 would be:

$$100{,}000\ new\ packaging\ units\ \times\ (253.5\ -\ 195.5 cm^2) =\ 5{,}800{,}000\ cm^2 =\ 580 m^2$$

A hundred thousand units represent 580 m^2 fewer cardboard. At first, it may not seem a huge difference, but if eco-design was adopted by all pharmaceutical companies the reduction of cardboard, aluminium and plastic used would make a great, positive impact on the environment.

7. CONCLUSIONS

- Metoprolol succinate is a medicinal product with extended-release properties given by a special formulation, which has been thoroughly commented in the present work.

- Because of the fact that this medication has a sustained release, patients only need to take one tablet per day, thus improving therapeutic adherence. Only two options are available in the Spanish market: *Beloken Retard ® 95mg comprimidos de liberación prolongada* and *Metoprolol KRKA Retard 95mg comprimidos de liberación prolongada EFG.*

- Metoprolol succinate differs from metoprolol tartrate, another salt form of metoprolol, and for that reason they have different posology, physical properties and indications. The first is used as a treatment for pathologies such as hypertension, angina and heart failure.

- For an academic purpose, scientific and commercial literature has been reviewed and all the acquired knowledge has resulted in a synthesised proposal of a continuous, industrial tablet production line, since nowadays most pharmaceutical industries use advanced technology.

- Even though this dissertation is mostly a bibliographic work, a great amount of time and effort were destined to redesign the packaging for this medication to make it more eco-friendly. To contribute to diminish resource waste, the new packaging has been designed to contain a 23% less amount of cardboard, at the same time that blisters are no longer made of Alu/PVC but exclusively of Alu/Alu, making it easier to recycle.

- Furthermore, writing an entire essay in a non-native language has also put my language abilities at stake and has pushed me off my comfort zone.

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