FIROCOXIB 57 MG VETERINARY TABLETS

Degree Final Project

Daniel Cases Poley

Main Scope: Pharmaceutical Technology

Secondary Scopes: Biopharmacy and History and Legislation

UNIVERSITAT DE BARCELONA

Facultat de Farmàcia i Ciències de l'Alimentació

Universitat de Barcelona

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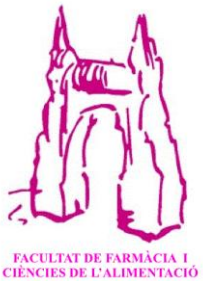


Abstract

This Degree Final Project is based on the bibliographical search of the active pharmaceutical ingredient (API) firocoxib from a pharmacological point of view including the mechanism of action, indications or contraindications among others.

Through a great search in biomedical literary bases such as PubMed and Scopus, the indications of this active pharmaceutical ingredient are supported with studies. In addition to investigating the new properties and indications that are currently being carried out and that are not described in its Summary of Product Characteristics.

Next, the formulation of Previcox® 57mg is studied in detail, the only veterinary medicine with the same dosage and pharmaceutical form indicated in this project. Moreover, a proposal of the industrial manufacture of medicine in a study is made. Detailing the composition for each component.

Finally, a new secondary packaging is designed. As a consequence, changes in primary packaging are produced. Resulting in a reduction of materials used and a more attractive design at an environmental level.

Se realiza este Trabajo de Final de Grado basado en la búsqueda bibliográfica del principio activo firocoxib desde el punto de vista farmacológico incluyendo el mecanismo de acción, indicaciones o contraindicaciones entre otros.

Mediante una gran búsqueda en bases literarias de ámbito biomédico como son PubMed y Scopus, se respalda con estudios las indicaciones de dicho principio activo. Además de indagar en las nuevas propiedades e indicaciones que se están llevando a cabo actualmente y que no se encuentran descritas en ficha técnica del producto.

Seguidamente se estudia con detalle la formulación de Previcox® 57mg, único medicamento veterinario con la misma dosis y forma farmacéutica indicada en este trabajo. También, se realiza la propuesta de fabricación industrial del medicamento en estudio. Detallando la composición por cada componente.

Por último, se diseña un nuevo envase secundario, como consecuencia se producen cambios en el envase primario. Dando como resultado una reducción de materiales utilizados y un diseño más atractivo a nivel medio ambiental.

Scopes involved

As the main scope, pharmaceutical technology is present in all parts of the project. But, it has the majority of implication in the dosage form, manufacturing process and packaging improvement.

As secondary scopes, biopharmacy and history and legislation. Pharmacokinetic and pharmacodynamic information of firocoxib are part of the biopharmacy field. This related information is explained in the section of the active pharmaceutical ingredient description. History and legislation are involved in firocoxib 57 mg chewable tablet project as laws and regulation of veterinary drugs by EMA (European Medicines Agency) and AEMPS (*Agencia Española del Medicamento y Productos Sanitarios*). History of NSAIDs is explained too. Strictly, it has no relation with the molecule of study but has a direct connection with the therapeutic group.

1 Introduction

The degree final project causes the student to see the large dimension of the pharmaceutical field and the areas covered by this knowledge. In particular, the work that I will present to you makes the student have a view from the molecule that produces the pharmacological action to the final product.

This subject (Degree Final Project) puts into practice the capacities of autonomous work, compression of articles and the search of them in a careful way and in reliable and credible pages. It also exposes the student to a situation that can be found in the professional world where it will be necessary for the realization and/or exhibition of projects.

The choice of this subject as my degree final project is based on the interest that I have in pharmaceutical technology. As the desire to continue specializing in this direction at the end of the degree.

It also integrates other subjects or areas such as biopharmacy and history and legislation. In the first, we will discuss drug related topics at the animal organism level. While the second material is crucial in all the pharmaceutical aspects, among which we find the packaging or product controls.

2 Objectives

The realization of this project is based on the below objectives:

- To review the pharmacology theory of analgesic drugs
- To delve into the subgroup coxib
- To search for veterinary studies
- Study of the drug market with the same indications at the state level
- To study the pharmaceutical form and its components.
- Proposing an industrial process of the active pharmaceutical ingredient firocoxib
- Making a new secondary packaging

3 Planning design

The project was carried out from the end of January until May of 2019.
During the months of January and February, the vast majority of searches of bibliographical references were carried out. These references belong to databases such as *PubMed* and *Scopus* as well as other reputable and reliable websites. All the notes related to the topics covered in this project were also located. The information collected was organized in folders according to the topics that they referred to. But not all of the information is included, as some documents were finally unrelated to the topics being attended.

The beginning of the writing process took place during the last week of February and the whole month of March and April, including some weeks of May. Until the delivery of the work, reviews, corrections or decoration of the document were made.

4 Pharmacological view

4.1 Pain

Pain is an unpleasant feeling that is conveyed to the brain by sensory neurons. Discomfort signals, actual or potential, damage the body. Also, the perception of pain gives information on the location of pain and its intensity.

4.1.1 Analgesic

Analgesic refers to any drug that reduces pain without blocking the conduction of nerve impulses, altering sensorial perception or affecting consciousness. This selectivity differentiates them from anaesthetics. Analgesic might be classified into two groups: anti-inflammatory drugs and opioids or narcotics. The first classified should be used for short-term pain and for moderate pain. The second group is related to severe pain, short-term or long-term either.

4.1.2 Anti-inflammatory analgesic

Most current anti-inflammatory analgesics are derived from three compounds discovered in the 19th century[1]:

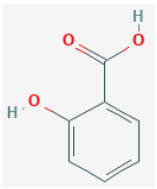


Figure 1: Molecular structure of Salicylic Acid [2]

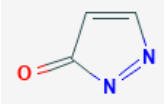


Figure 2: Molecular structure of Pyrazolone [3]

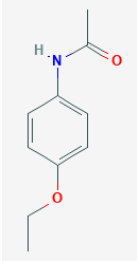


Figure 3: Molecular structure of Phenacetin [4]

A derivation of the first structure gives rise to develop acetylsalicylic acid. It is considered as the prototype for anti-inflammatory analgesic or non-steroidal anti-inflammatory drugs (NSAIDs).

4.1.2.1 Non-steroidal anti-inflammatory drug (NSAID)

NSAID reduces inflammation and is effective to treat pain and fever. Inflammation is the process of how the body protects against irritation or injury. Signs of inflammation such as redness, pain, swelling and warmth.

NSAIDs are used to treat several symptoms, for example osteoarthritis, muscle aches, tendonitis or rheumatoid arthritis.
NSAIDs inhibit the synthesis of prostaglandins (chemical product of inflamed white blood cells) that induce pain and inflammation. For this reason, it blocks cyclooxygenase (COX), an enzyme responsible for the synthesis of prostaglandins and related compounds[5,6].

Also, they must be differentiated of corticosteroids that are steroid hormones, with capacity to reduce inflammation in the body. These have a lot of side effects such as fluid retention, high blood pressure, headache or facial hair growth.

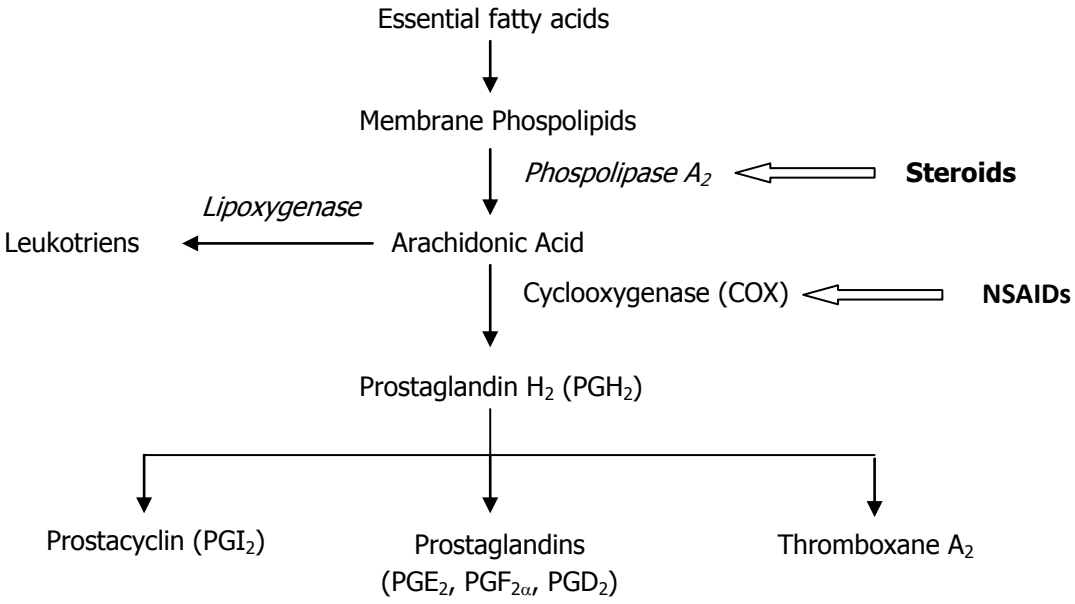


Figure 4: Prostaglandin synthesis [5]

Each prostanoid has a particular function[9]:

- TxA_2 (Thromboxane A_2): platelet aggregation, vasoconstriction.
- PGD_2 (Prostaglandin D_2): sleep/wake cycle, pain.
- $PGF_{2\alpha}$ (Prostaglandin $F_{2\alpha}$): reproduction and vasoconstriction.
- PGE_2 (Prostaglandin E_2): gastrointestinal protection, regulates body temperature, renal homeostasis, inflammation and pain.
- PGI_2 (Prostaglandin I_2 or prostacyclin): vasodilatation, inhibits platelet aggregation, renal homeostasis, inflammation and pain.

4.1.3 Cyclooxygenase enzyme

It is known that it has two different isoenzymes. Both COX isoforms use arachidonic acid as an endogenous substrate; however each one from a different source and form the same products by the same catalytic reaction[7, 8].

Properties	COX-1	COX-2
Proposed role	Physiological housekeeping	Inflammatory response
Amino acid homology within the same species	60%	60%
Intracellular localization	Endoplasmic reticulum membrane and nuclear envelope	Nuclear envelope and endoplasmic reticulum membrane
Regulation	Constitutive	Inducible
Range of expression	2 to 4 fold	10 to 80 fold
Tissue expression	Platelets, endothelial cells, stomach, kidney, smooth muscle, most tissues	Most tissues, especially inflammatory cells. Requires stimulation by growth factors, cytokines and hormones

Figure 5: Differences between COX-1 and COX-2 [8]

4.2 Mechanism of action and selectivity

Nowadays, NSAIDs can be separated into two groups: non-selective NSAIDs and selective COX-2 inhibitors.

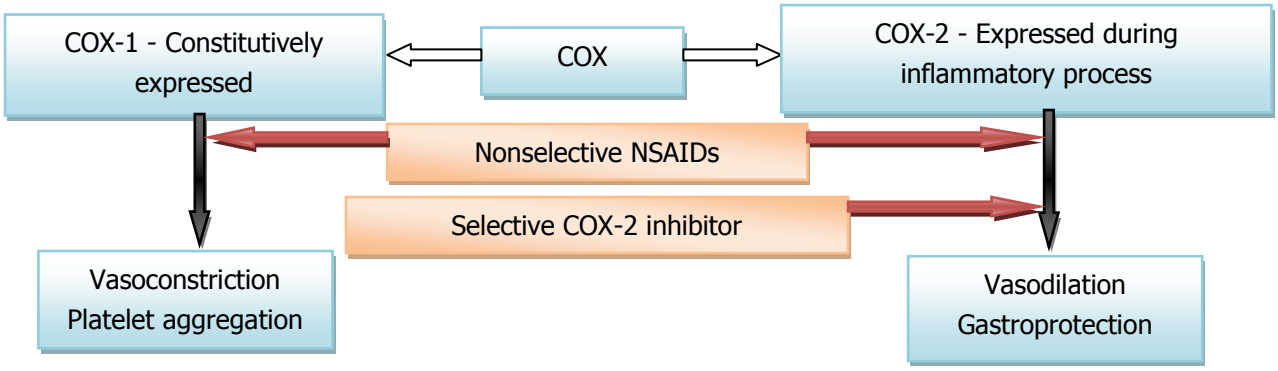


Figure 6: Mechanism of COX inhibition[10]

Also, COX inhibition produces adverse effects. In gastrointestinal mucosa, the COX- 1 inhibition reduces PGE_2 synthesis, as a result mucus and bicarbonate secretion decrease such as peptic ulcers and gastrointestinal bleedings. This situation can be worse if the person has an infection of *Helicobacter Pylori*, which increases developing duodenal ulcers.
Kidneys are mediated by COX-1 and COX-2, its block produces retention of water and sodium, hypertension and hemodynamic injury due to a reduction of vasodilator PGs of the afferent arteriole. Furthermore, this side effect reduces glomerular filtration rate (GFR).

At last, the cardiovascular system whose inhibition had a stroke and myocardial infarction is most common with COX-2 inhibition than COX-1. In the normal situation, a balanced effect between PGI_2 controlled by COX-2 endothelial and TXA_2 controlled by COX-1 platelet exists. PGI_2 produces vasodilatation and inhibits platelet activation. In contrast, TXA_2 produces vasoconstriction and platelet aggregation. When the balance is in favour of TXA_2, it happens after selective inhibition of COX-2 and vasoconstriction and platelet clumping can occur[11].

4.2.1 Coxib

Coxib is the suffix used to refer to of selective COX-2 inhibitors. It was researched to keep antiinflammatory and analgesic activities, reducing at the same time gastrointestinal pain due to no inhibition of COX-1. The large side effect is platelet aggregation.
In Spain, from 2002 to 2006 a health inspection visa for dispensing of these medicinal products was necessary. This produced a decrease prescription of coxib during these years. Furthermore, the *Agencia Española del Medicamento y Producto Sanitario* (AEMPS), the Spanish health administration, publish alerts with recommendations of risk and recommendable use of selective COX-2 inhibitors[12, 13].

Firocoxib

Firocoxib is a preferential COX-2 inhibitor for veterinary, 380 fold selectivity for this isoenzyme in the dog compared to COX-1 isoenzyme. The concentration of firocoxib required to inhibit 50% of the COX-2 enzyme (IC_{50}) is 0,16 (± 0,05) µM, whereas the IC_{50} for COX-1 is 56 (± 7) µM.

The molecular formula is $C_{17}H_{20}O_5S$, its IUPAC (International Union of Pure and Applied Chemistry) name is 3-(cyclopropylmethoxy)-5,5-dimethyl-4-(4-methylsulfonylphenyl)furan-2-one and the CAS (Chemical Abstracts Service) number is 189954-96-9, useful to search in DrugBank database.
The most relevant properties are molecular weight 336.402 g/mol, 0 hydrogen bond donor count, 5 hydrogen bond acceptor count and a logP of 2.98 (it has a low affinity for fat tissue). This drug satisfies Lipinski's laws[14, 15].
After oral administration firocoxib is rapidly absorbed and the time to maximal concentration (T_{max}) is 1,25 (± 0,85) hours. The maximal concentration (C_{max}) is 0,52 (± 0,22) µg/ml, area under the curve (AUC_{24}^{0}) is 4,63 (±1,91) µg·hr/ml, and oral bioavailability is 36,9 (± 20,4) percent.
The elimination half-life ($t_{½}$) is 7,59 (± 1,53) hours. 96 % of firocoxib is bound to plasma proteins. The steady state, after multiple oral administration, is reached by the third daily dose. Firocoxib is metabolised by dealkylation and glucuronidation in the liver. Elimination is principally in the bile and gastrointestinal tract[16].

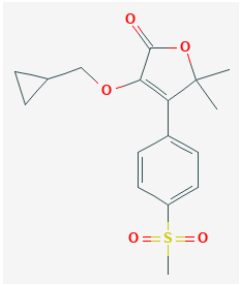


Figure 7: Molecular structure of Firocoxib[14]

No data relating to the use of firocoxib in humans were available. Adverse cardiovascular effects in humans have been considered with studies on firocoxib. In animals, studies don't show an increase in cardiac toxicity undergoing treatment with this molecule.
However, lower concentrations of residues in animal organisms are not expected to cause cardiovascular risk to public health[17].

Drugs can be divided by their selectivity for COX isoenzymes. The table below includes the most used NSAIDs in veterinary.

Selectivity	Drugs
Preferential or selective COX-1 inhibitors	Aspirin, Ketoprofen (cat), Vedaprofen, Tepoxalin, Flunixin (cow)
Non-selective COX inhibitors	S-Caprofen (horse), Flunixin, Ketoprofeno, Meloxicam, Phenylbutazone, Tolfenamic acid, Vedraprofen
Slightly or moderately selective COX-2 inhibitors	S-Caprofen (dog, cat), Deracoxib, Etodolac , Eterocoxib, Mavacoxib, Tolfenamic acid, Meloxicam
Highly or very highly selective COX-2 inhibitors	Cimicoxib, Firocoxib, Robenacoxib, Valdecoxib

Figure 8: COX inhibitors selectivity[18]

4.3 The clinical experience of firocoxib

4.3.1 Indications

Firocoxib was approved by EMA and FDA (Food and Drug Administration). The drug can be used in horses as an oral paste and for dogs as tablets.

In Europe, firocoxib has been approved following Directive 2001/82/EC on the Community code relating to veterinary medicinal product[19] with the aim to establish laws for authorization, manufacturing, supervision, sale, distribution and utilization of veterinary drugs in the European Union (EU).
However, this directive has suffered some modifications. Regulation (EC) No 596/2009[20], Directive 2009/53/EC[21], Regulation (EC) No 470/2009[22], Directive 2009/9/EC[23], Directive 2004/28/EC[24] and Regulation (EU) 2019/6[25].

Two indications were declared by firocoxib's producers focused on dogs. Firstly, relief of pain and inflammation associated with osteoarthritis. Secondly, relief of post-operative pain and inflammation associated with surgery of soft tissue, orthopaedics and dental.

Osteoarthritis

Osteoarthritis is a chronic disease characterized by loss of articular cartilage that has the function of protecting the ends of bones in joints of the body, as a result, bones don't friction among them. In dogs, osteoarthritis is the most common form of arthritis, affecting one of every four animals.

Different factors can affect the development of the disease (age, sex, obesity or breed). However, some studies demonstrated that there could be other predisposed factors:

- Males develop osteoarthritis in more level than female. This could be due to sex hormones or the differences of bodyweight[26].
- Neutered dogs have more predisposition to develop joint disease due to the reduction of gonadal hormones acting against osteoarthritis[27]. Another presumption is the association of neutering with weight gain[28].

In general, it appears as a second disease, being the first an orthopaedic disease such as hip dysplasia, elbow dysplasia, among others. The joints that principally are affected are the hip, stifle and elbow.
The most characteristic signs and symptoms are: normal activity reduction and stiffness, lameness or inability to jump can appear. And pain when a person manipulates, changes in its behaviour such as aggression or discomfort.
Osteoarthritis is commonly diagnosed when mobility is too affected. In general, more than 50% of diagnosed dogs are aged from 8 to 13 years[29,30].

Treatment consists of pain medication, physical modalities, exercise routine to lose extra-weight and nutritional support and physical rehabilitation as a way to improve mobility[31].

Postoperative pain

NSAIDs or coxib are safe and effective to treat this kind of pain. They should be administered to all cases unless specific patients in which administration is contraindicated. The use of these drugs help to decrease opioid requirements.
Which type of NSAIDs or coxibs is prefered depends on various factors such as cost effectiveness, duration and modality of administration. Neither side effects or complications are unusual in the postoperative period. Safety varies for each drug, dose and duration[32,33].

Soft tissue surgery

Soft tissue surgery refers to any surgery of muscle, fat, fibrous tissue or blood vessels, it can cause mild, moderate or severe postoperative pain. It depends on the severity of the postoperative condition and the localization and magnitude of the surgery.

Orthopaedics surgery

Orthopaedics surgery treats acute injuries, congenital and acquired disorders and chronic arthritis or overuse conditions of bones and joints.
Both indications (soft tissue and orthopaedics surgery) are very similar, NSAIDs are able to reduce pain in three levels: mild, moderate and severe. But, in major surgery or in a specific case it could be possible to add or replace it for another drug, for example opioid. Also, pain relief would need more or less dose. However, each post-operative surgery has its specific protocols [34].

Dental surgery

Oral or dental surgery is related to the tissues of the mouth, including teeth and gums. NSAIDs and OTC (Over The Counter) products that are prescribed by dentists could be a sufficient analgesic to treat the pain of postoperative surgery[35].

4.3.2 Firocoxib studies indications

Efficacy and Safety of Firocoxib for the Treatment of Pain Associated with Soft Tissue Surgery in Dogs under Field Conditions in Japan[36]

The study highlights the use of firocoxib to treat postoperative pain. A total of 131 dogs were divided into two different groups, one treated with firocoxib and the other non-treated with firocoxib. The evaluation of pain took place on Day 0 before the surgery through Day 2.

Firocoxib treatment consists of doses of 5mg/kg on Day 0 before the surgery and once daily through Day 2. 69 dogs took part in the study, 62 of these dogs are the group non-treated with the drug.

The success variable based on if the dog needed rescue medication (under pain assessment or Investigator's judgment) between the groups had a significant difference: firocoxib-treated ,16,4%, and non-treated, 50,0% (P=0,0031) was observed.

The effects of firocoxib (Previcox®) in geriatric dogs over a period of 90 days[37]

The study evaluated the effects of firocoxib administered to geriatric dogs with osteoarthritis over seven years of age for 90 days. Lameness and pain had been evaluated by the owner weekly in the first month and biweekly the last two months. At the same time, biochemical parameters have been controlled such as urea, creatinine or alanine transferase.

Initially, the study started with 45 dogs into the treatment group and 9 into the control group. Finally, it finished with 33 dogs in the treatment group and 8 in the control group.

Between days 0 and 90, bile acids and urea were significantly different in the treatment group. Furthermore, urea and creatinine on day 90 were significantly different between treatment and control group. As a conclusion, the study showed that firocoxib was effective to reduce pain associated with osteoarthritis for 90 days.

Long-term efficacy and safety of firocoxib in the treatment of dogs with osteoarthritis[38]

The study enrolled 29 dogs with osteoarthritis treated with 5 mg/kg, daily for 52 weeks. Finally, 25 dogs completed the study; the withdrawal rate associated with gastrointestinal adverse effects was 5,1%. At the end of the study, 96% of the 25 dogs that completed the study had improved under the owners' assessment.

Between day 90 and day 360, 48% of the 25 remaining dogs improved their lameness ($P<0.005$).

4.3.3 Firocoxib studies comparison

Comparison of the effects of firocoxib, carprofen and vedaprofen in a sodium urate crystal induced synovitis model of arthritis in dogs[39]

This study compares different NSAIDs after induced synovitis at three and seven hours. Firocoxib, carprofen and vedaprofen will be compared. This comparison is formed by two evaluations: peak vertical ground reaction force as the most important variable and the punctuation of lameness extremity.

Administration of a very selective COX-2 inhibitor, like firocoxib, decreases the pain produced by synovitis and improves significantly the capacity to support the weight at doses that the manufacturer recommend (≥5,0 mg/kg).

As a conclusion of the study, firocoxib has significant differences with carprofen and placebo, but not with vedaprofen.

Post-operative analgesic effects of butorphanol or firocoxib administered to dogs undergoing elective ovariohysterectomy[40]

Comparison between butorphanol or firocoxib as analgesic medication post-surgery. Twenty-five dogs were enrolled in the study, 12 of them in the butorphanol group and the rest in the firocoxib group. Animals were treated with respective drug after surgery and their pain evaluated using the dynamic and interactive visual analog scale (DIVAS). Rescue analgesia was morphine and firocoxib if DIVAS> 50.

As a result of the study, firocoxib group had significantly lower pain scores than the butorphanol group ($p<0,05$). Rescue analgesia was used to 11/12 in the butorphanol group and 2/13 in the firocoxib group ($p<0,05$).

Comparison of the analgesic efficacy of perioperative firocoxib and tramadol administration in dogs undergoing tibial plateau leveling osteotomy[41]

Administration of tramadol, firocoxib or tramadol-firocoxib were evaluated for signs of pain and limb function. Thirty dogs enrolled in this study, they were divided between three possible treatments (10 in each group).

As a result, treatment with firocoxib or the combination firocoxib-tramadol is useful to reduce the pain as it could be seen in lower pain scores. Furthermore, limb function was better than dogs which received only tramadol. The use of tramadol only may not provide sufficient analgesia to treat post-operative orthopaedic pain in dogs.

4.3.4 Contraindications

Firocoxib should not be administered during gestation and lactation. Neither in dogs with less than 10 weeks of life or less of 3kg of weight. It should not be used in animals with some of the following diseases: gastrointestinal bleeding or bleedings disorders and dyscrasia. Or if the animal has a treatment with another NSAIDs or corticoids[16].

4.3.5 Interactions

Treatment with firocoxib needs to avoid administration at the same time with other NSAIDs. For this reason, animals have to maintain a period of 24 hours without any other treatment. The administration of both medications could aggravate or side effects could appear.

There will be interaction when administered with molecules that action renal flow, such as diuretics or angiotensin-converting enzyme inhibitors (ACEI). Also, nephrotoxic active pharmaceutical ingredient must be avoided because it can increase the risk of renal toxicity. Firocoxib has a high degree of protein bindings, concomitant administration with a drug that has a high degree of binding can produce toxicity effects due to a fact of competition between them[16].

4.3.6 Side effects

Generally, emesis and diarrhoea are transitory and reversible when withdrawing the treatment. In rare occasions, it can produce nervous system disorders. In very rare occasions, it can produce hepatic and renal disorders.

If one or more of the following side effects occur the use of the product must be left off: vomiting, repetitive diarrhoea, hidden blood in the stool, spontaneous loss of weight, anorexia, lethargy and alteration of parameters biochemistry renal and hepatics[16].

4.3.7 Precautions for humans

In SmPC (Summary of Product Characteristics) of Previcox® it is possible to see a specific paragraph that contains the precautions for the person who gives the medicine or comes into contact with the animal. These precautions are[16]:

- If the person ingests the medicine as an accident, this person should be visited by a physician and show the package leaflet or the label.
- Wash hands after manipulating the product.
- Use gloves to take the tablet. Avoid contact with skin or eyes. If it occurs, wash the area with water.

4.4 The last advances with firocoxib

Although firocoxib and selective COX-2 inhibitors have shown having chemotherapy characteristics, it doesn't appear in SmPC.

4.4.1 Mechanism of action

The inhibition of COX-2 produces an increment of arachidonic acid that stimulates the conversion of sphingomyelin to ceramide, a mediator of apoptosis. Also, it can produce apoptosis by the alteration of prostaglandins production and diminution of angiogenic factors. The mechanism is no dependent of the cyclooxigenase, it includes the inhibition of the activation of transcriptional factor NF-κB, interference of the union of nuclear hormonal receptor PPAR and the diminution of antiapoptotic gene expression BCL-XL.
In mouse experimental tumoral study, after administration of coxib, cell proliferation decreases and the apoptosis increases [42].

4.4.2 Studies

Combination of radiation therapy and firocoxib for the treatment of canine nasal carcinoma[43]

Twenty-four dogs were randomized to administrate the combination of firocoxib and radiotherapy (Group 1) or placebo and radiotherapy (Group 2). Dogs were monitored and pet owners completed a quality-of-life questionnaire monthly.
As a result, not having differences statistically significant between the two groups in terms of median progression-free interval and overall survival. However, quality of life, which was evaluated with questionnaires, was significantly improved in Group 1 (P=0,008). As a conclusion, firocoxib combination with radiotherapy is safe and enhanced life quality.

Adjuvant therapy for highly malignant canine mammary tumours: Cox-2 inhibitor versus chemotherapy: a case-control prospective study[44]

Twenty-eight dogs were enrolled and evaluated the disease free survival and overall survival. Dogs were randomized into two treatment groups mitoxantrone or firocoxib. As a conclusion, firocoxib's treatment had significantly higher disease-free survival (P=0,0015) and overall survival (P=0,048) than control dogs.

Randomized trial of cisplatin versus firocoxib versus cisplatin/firocoxib in dogs with transitional cell carcinoma of the urinary bladder[45]

Forty-four dogs were enrolled in this study and randomized in three groups to receive cisplatin, firocoxib or a combination of both. Assessing tumor size, renal function and toxicoses.

As a result, the remission rate of the combination (57%) had a significantly difference (P=0,021) in comparison with cisplatin alone 13%. Renal and gastrointestinal toxicoses didn't show significant differences between dogs which received cisplatin or cisplatin/firocoxib. As a firocoxib alone, partial remission was of 20% and stable disease was of 33%.

Firocoxib alone can be useful as a palliative treatment for dogs with transitional cell carcinoma.

Canine malignant mammary gland neoplasms with advanced clinical staging treated with carboplatin and cyclooxygenase inhibitors[46]

Twenty-nine female dogs enrolled in this prospective study and dogs were treated with different protocols: surgery, chemotherapy and cyclooxygenase inhibitors. The goal was to compare overall survival periods of dogs that were diagnosed with advanced mammary tumors. The overall survival of females with high COX-2 scores was shorter than females with low COX-2 scores. In a similar way, adjuvant treatments associated with surgery shared longer overall survival in comparison with surgery alone.

5 Pharmaceutical technology

As appears previously, firocoxib 57mg tablets was approved by EMA and AEMPS. It is commercialized under the name of Previcox® 57 mg chewable tablets for dogs in Spain. But, the brand of firocoxib is Previcox® in all kinds of presentations, oral paste for horses or chewable tablets for dogs.

5.1 Study of marketing authorizations

In AEMPS web site it is possible to search drugs that have been approved in Spain. Through the use of *Centro de Información online de Medicamentos Veterinarios de la AEMPS* (CIMAvet[47]), which is a tool in Spanish drug regulatory page to know the situation of veterinary medication. After a slow search, firocoxib is compared with other medications with the same indications and for dogs that are approved by AEMPS. But their situation can be discontinued temporally or provisionally for different reasons, such as administrative causes or risks for public health, animal health or environment, or marketed[34, 47, 48].

All of them take part from list the ATCvet QM01A. Anatomical Therapeutic Chemical Classification System (ATC) is a drug classification system that classifies by active pharmaceutical ingredient in accordance with the organ or system where it produces its therapeutic effect related to pharmacological and chemical characteristics. In the case of veterinary drugs, it receives the name of ATC veterinary or ATCvet.

In the following table NSAIDs that have been approved with the same indications than Previcox® appear. Cimicoxib and mavacoxib are highlighted due to both are selective COX-2 inhibitors and have the same presentation as firocoxib.

Drug	Trade Name	Licensed formulation	COX-2 selectivity
Carprofen	Canidryl / Carprox VET / Norocarp / Rycarfa	20, 50 or 100 mg tablets	Partial
	Carporal	40 or 160 mg tablets	
	Carprodyl (discontinued)	20, 50, 100 mg tablets	
	Carprodyl Quadri	50 or 120 mg chewable tablets	
	Norocarp	20, 50 or 100 mg flavoured tablets	
	Dolocarp Sabor / Rimadyl	20, 50 or 100 mg chewable tablets	
	Carprofelican / Carprogesic/ Norocarp / Rimadyl / Rycarfa / Carprox (discontinued)	50 mg/ml solution for injection	
Cimicoxib	**Cimalgex**	**8, 30 or 80 mg chewable tablets**	**Yes**
Firocoxib	**Previcox**	**57 or 227 mg chewable tablets**	**Yes**
Ketoprofen	Ketofen (discontinued)	5, 10 or 20 mg tablets	Partial
	Ketofen (discontinued)	10 mg/ml solution for injection	
Mavacoxib	**Trocoxil**	**6, 20, 30, 75 or 95 mg chewable tablets**	**Yes**
Meloxicam	Acticam (discontinued) / Inflacam / Loxicom / Metacam / Rheumocam	1 or 2,5 mg chewable tablests	Partial
	Acticam / Inflacam / Loxicom / Meloxidolor / Meloxidyl / Metacam / Rheumocam	5mg/ml solution for injection	
	Adocam / Inflacam / Loxicom / Melosus / Meloxidyl / Meloxoral / Metacam / Rheumocam	1,5 mg/ml oral suspension	
	Inflacam	1mg chewable tablets	
	Loxicom / Metacam (discontinued)	0,5 mg/ml oral suspension	

Robenacoxib	Onsior	10, 20 or 40 mg tablets	Yes
	Onsior	20 mg/ml solution for injection	
	Onsior (discontinued)	5 mg tablets	
Tolfenamic acid	Tolfedine	6, 20 or 60 mg tablets	Partial
	Tolfedine / Tolfedol	40 mg/ml solution for injection	

Figure 9: study market of NSAIDs in Spain [34, 47, 48]

5.2 Previcox® dosage form

The formulation as a chewable tablet must be adequated to the hardness that is the necessary power to break the tablet, the disintegration that is the time for break up into small particles in more cases it is an important factor to prevent gastrointestinal obstructions, and dissolution which is essential a correct pH. Also, it should be palatable and an appropriate size and shape[49].

Palatable dosage forms improve compliance and convenience of animals that are voluntarily accepted. In the case for dosage forms that are too chewy might not be consumed so freely even with complex palatants. The addition of aroma in the dosage form can help it to be more attractive to dogs.
Palatable means the property of being acceptable to the mouth. There are two different types of palatability: acceptance (choice to consume or not) and preference (choice between two dosage forms).
The studies will be carried out with chewable tablets without active pharmaceutical ingredient. The most critical test is the acceptance test, it is a direct measure of compliance of consuming the medication. Acceptance palatability compares four different complex palatant with placebo. The aim was conducted to investigate whether the addition of an aroma component improves acceptance. Sugar placebo is assumed to not have a high palatability. As a result, dosage form which included complex palatant with the goal to enhance the taste and smell approximately doubled the acceptance. When it compares the rate of partial or none consume with full consume, either of them was higher in placebo than complex palatants. Furthermore, treatment was not well accepted when the tablet was too chewy. To sum up, the mouth feel can also play a significant role.
Moreover, in the acceptance study, the addition of aromatic ingredients did not increase significantly the prehension or the full consumption. Although, in preference study, choice of a tablet with aroma was, in general, more often than the control (sugar placebo)[50].

Firocoxib is a chewable tablet with tan-brown colour and it has round, convex and engraved scored tablets. It must be administrated orally.
For dogs with osteoarthritis, the veterinary has to administrate 5mg/kg once daily. The laboratory recommends care and regular control when it will be administrated for more than 90 days. Post operatory pain administrate 5mg/kg once daily for three days, it can be necessary to start two hours prior to surgery.
For orthopedic surgery, it would continue with the same dosage after the first three days. With veterinary acceptance[16].

Body weight	Number of chewable tablets by 57 mg	mg/kg range
3.0 – 5.5	0.5	5.2 – 9.5
5.6 – 10	1	5.7 – 10.2
10.1 – 15	1.5	5.7 – 8.5

Figure 10: dosage of Firocoxib 57mg[51]

The laboratory gives this schedule for this dosage. For dogs with a body weight over 15 kg it recommends to administrate the dosage of 227mg.

5.3 Excipients of Previcox®

- **Silica, Colloidal anhydrous**
  Colloidal anhydrous silica (known as colloidal silicon dioxide or Aerosil® too) is a microscopic silica with an approximately particle size of 15nm. Its characteristics are a bluish-white-coloured, tasteless, amorphous, light, loose and odourless powder. It is used in pharmaceutical formulation of tablets or capsules due to its small particle size but the large surface area that improves the flow properties of dry powder. It can act as many functions as an adsorbent, an anti-caking agent, an emulsion stabilizer, a suspending agent, a viscosity-increasing agent and a tablet disintegrant[52].

- **Hydroxypropylcellulose**
  Hydroxypropylcellulose is a light yellow, tasteless and odourless powder. It is used in oral formulations as a binder, a film-coating and an extended-release matrix former. In concentrations of 2-6%, it is used in wet or dry granulation and in direct compression tableting processes as a binder. Moreover, in concentrations of 15-35%, it is used to produce extend-release drugs. The velocity of the release and viscosity of this substance are inversely proportional. Also, the addition of an anionic surfactant produces the increase in the viscosity of hydroxypropylcellulose resulting in a decrease in the release of the drug. To film-coat tablet, this may be used too, as a solution of 5%. Other properties of this substance are that it can be used in microencapsulation processes and as a thickener agent[52].

- **Cellulose, Microcrystalline**
  Microcrystalline cellulose (known as Avicel® too), is a purified cellulose and partially depolymerized. Its appearance is an odorless, tasteless, crystalline and white powder. Depending on porous particle sizes its properties and applications will be different. The most used property is as a diluent and blinder. Both of them can be used in wet-granulation and direct compression processes of oral tablet or capsule. Also, this excipient has a lubricant and disintegrate behaviour that are good properties for tableting[52].

- **Lactose Monohydrate**
  Lactose monohydrate appears as a variety of isomeric forms, it depends on the crystallization and conditions. The stable crystalline forms of lactose include lactose monohydrate conformation α. Lactose looks like white crystalline particles or powder. It is sweet-tasting and odorless. Lactose monohydrate is used as a filler and diluent. Fine grades of lactose are commonly used in the wet-granulation method or when milling, due to its size it allows better mixing with the other substances and utilizes the binder with better efficiency[52].

- **Croscarmellose Sodium**
  Croscarmellose Sodium appears as a white or light gray and odorless powder. It is used as a disintegrate for capsules, tablets or granules. In the second case, carmellose sodium might be used either direct-compression or wet-granulation[52].

- **Magnesium Stearate**
  Magnesium stearate is a very fine, precipitated or milled, light white, impalpable powder with a low density. It has a characteristic taste and odor. Also, it adheres to the skin and for handling it has a greasy feel. It is used as a lubricant in capsules or tablets[52].

- **Iron Oxides**
  A quite variety of iron oxides exist, its appearance depends on the particle size and shape, and crystal structure. It can be yellow, red, black or brown powder. Iron oxides are used as colorants and UV absorbents in pharmaceuticals formulations. In some countries, the quantities that may be consumed are restricted[52].

- **Caramel**
  Caramel is used as a food colouring. Four different types exist E150a, E150b, E150c and E150d in Europe and Caramel Colors I, II, III, IV in America. E150d means caramel ammonium sulphite and it is the darkest of all the caramels. It is necessary to differentiate caramels for colouring and caramels for flavouring[53].

- **Chartor Hickory Smoke Flavour**
  Aroma of smoked nut.

5.4 Manufacturing process

Excipient	Function	Percentatge	Weight for tablet
Silica, Colloidal anhydrous	Glidant	0,5%	1,2mg
Hydroxypropylcellulose	Binder	4,0%	9,6mg
Microcrystalline Cellulose	Diluent	48,0%	115,2mg
Lactose Monohydrate	Diluent	15,0%	36,0mg
Croscarmellose Sodium	Desintegrant	3,0%	7,2mg
Magnesium Stearate	Lubricant	2,5%	6,0mg
Iron Oxides	Colorant	0,1%	0,24mg
Carmel	Flavour	0,15%	0,36mg
Chartor Hickory Smoke Flavour	Aroma	3,0%	7,2mg
Firocoxib	NSAID	23,75%	57,0mg
Total weight			240mg

Figure 11: formulation of Firocoxib 57mg[16, 51, annexes]

List of excipients deduces that direct compression is the best way to produce firocoxib 57mg chewable tablets due to the fact that lactose monohydrate and microcrystalline cellulose are used in direct compression tablet.

But hydroxypropylcellulose as a binder is used in wet granulation too. The use of binder in the direct compression process, enhances the capacity of flowability and compressibility[54].

The manufacturing process consists of a sequential addition of the excipients and the active substance, with direct compression of the desired chewable tablet weight[17].

Direct compression has many advantages such as cost effectiveness that direct compression requires few operations as a result of less equipment, lower source consumption, less space and time. It is an important type of compression when active pharmaceutical ingredient (API) needs to maintain the stability that it could not keep up with wet or dry granulation.

Drugs that are produced by direct compression have a faster dissolution due to the fact that API disintegrates directly to particles instead of granules. Also, direct compression avoids the high pressure by slugging or roller compaction.

And for a short period of time, less chance for contamination or cross contamination making it easier to satisfy Good Manufacturing Practices (GMP). At the same time, reducing the quantity of documentation that is required. No use of water decreases the possibilities to be contaminated by microbial growth.

Figure 12: direct compression process[55]

Weighting

The process starts with the weighting of all components (API and excipients) for producing a batch with a specific size. Previously, components must have passed quality controls to comply with the security and efficacy expected.

Weighting takes place in an independent room where qualified operators use adequate scales to weigh every component and tag them. They will be stored in containers or bags[55].

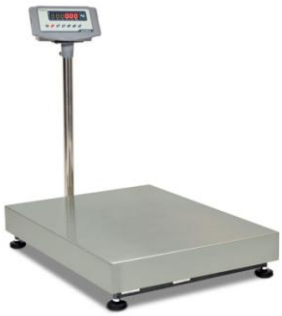


Figure 13: Scale Baxtran TMM of 30 to 600KG[56]

Sieving

Firocoxib and excipients should have similar size, for this reason, all components have to use sieve machine to homogenize particle size. Components can be passed through a mesh of a specific size or through a cascade of decrease size. In general, for compression sieving is used as an optional step, but it is useful to do it since it reduces the possibility to have granules and little mass with a bigger size than the others. These machines use a vibrating system to sieve the substance.

Nowadays, some machines incorporate mill and sieve steps. It has good advantages in contrast with conventional machines: it reduces process time, faster clean because one machine has to be cleaned not two, less lost components, among others. This system uses rotational harms to crash the granules and to ease the sieve process[55].

Figure 16: vibratory sifter diagram[57]

Figure 17: oscillating sieve[58]

Figure 18: mill-sieve machine diagram[59]

Mixing

In this point is when all the components of Previcox® get in touch. Except for the magnesium stearate that will be added a few minutes before the end of the mixing process. If it is added at the first moment, it could give problems of disintegration because magnesium stearate creates a coating that does not allow contact between water and mixing mass. Mixing machine is based on rotation movement to facilitate a homogenous mix powder.

In the market a variety of mixers for the pharmaceutical industry exist, but three types of mixers are widely used.

- Double Cone blender is a symmetric machine in its transverse and sagittal plane. It is usually used for the mixing of dry powders and granules homogeneously.
- "V" shape blender is a symmetric machine in its sagittal plane. It is commonly used to mix powders. With rotational movement, the powders separate and come together, in contrast with double cone blender, where powders go together all the time.
- Eliconomix is a vertical cone container inside a vertical screw that runs all the volume of the cone, producing an upward flow of product.

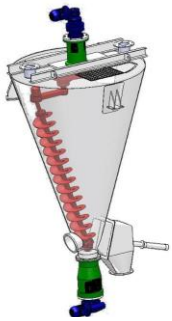


Figure 18: eliconomix[60]

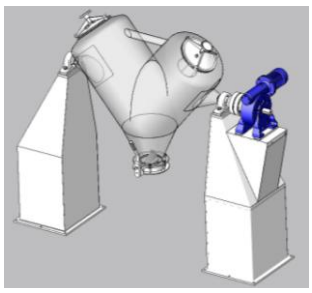


Figure 19: "V" shape blender[60]

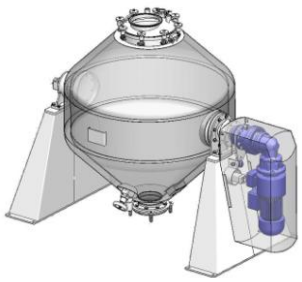


Figure 20: double cone blender[60]

Mixers can include a system called "Clean-in-place" which means it cleans itself. This technology has a lot of advantages such as reducing the quantity of water and detergents in comparison with hand clean, it is an automatic system and it minimizes the cleaning time.
The few disadvantages are the cost to install it and the technology that the system uses as professional staff to operate it is necessary [55].

Compression

The compression process uses high pressure to compact all components to create a tablet. Eccentric press and rotary press take part in this stage.

On the one hand, the eccentric machine is used in pharmacy or in the first part of the development of the drug due to the fact that a big quantity of tablets is not necessary. On the

other hand, the rotary press is more extended used in pharmaceutical industry because of its power to manufacture a huge number of tablets per hour.

The rotary press consists of a rotating system of punches, each station has a pair of punches oriented vertically (upper and lower). The modification of a parameter of purchase can change pressure, weight or hardness. Also, it could be possible to change the velocity of the system.

Stages of compression:

- Powder filling. It is a pre-compression stage. The powder will be charged in the hopper to feed the tablet press.

- Powder metering. It consist of the precise filling of powder in the die cavity. It should be as precise as possible because excess powder can cause incidents in the following stages.
  Immediately after the filling, the punches of lower turret moves to a determined level and the excess of powder will be removed from the surface. This determined level has the function to fill the exact volume and weight of powders for compress and pass controls of tablet parameters.

- Pre-compression and compression process. Pre-compression means to remove the air that has been trapped within the powder. For doing it, punches exert pressure but a little amount in comparison with the compression process. In the compression process, powders will be completely compressed in a tablet applying huge pressure for having the desired hardness.
  This stage takes place through pre-compression and compression roll. Either of them, upper punches go down to compress the powders. After compression, upper punches come back to their initial position.

- Tablet discharged. Lower punches were already lifted up, pushes tablets out of the die cavity. Then, the scraped will remove the tablet to the discharge chute.

The process of compression is continuous in which turret moves in a rotary way. In general, a complete revolution should match the number of tablets produced and the number of dies in the turret. If it is not equal, press machine maybe has had a problem with filling, compress stage or purchase, among others[55,61].

Figure 21: compression machine XL400MFP/SFP Korsch[62]

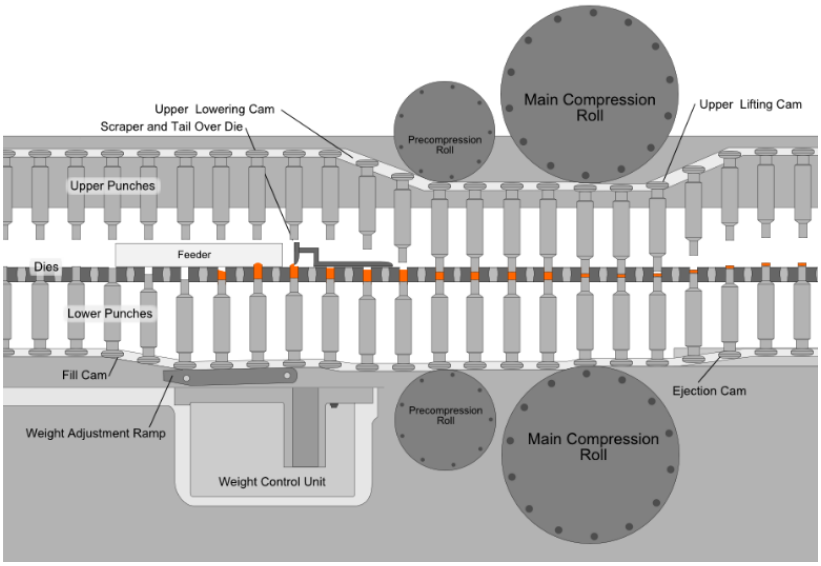


Figure 22: tablet making process machine[61]

Quality Control

When the manufacturing has finished, finished product quality controls take place. The dosage form of firocoxib is chewable tablets that have the same quality control test than tablets. But, the disintegration test is not necessary. These tests are listed below :

- Organoleptic evaluation: tan-brown, round, convex, engraved scored tablets, slotted and smell of smoked walnut.
- Content of active ingredient
- Uniformity of content of active ingredients:
- Uniformity of weight: as maximum two chewable tablets out of range 95-105% and none out of range 90-110%. If the average weight is 240 mg, the range of 95-105% is 228-252 mg and the range of 90-110% is 216-264 mg.
- Dissolution
- Diameter
- Friability: it is acceptable if it has a maximum loss of 1% of the weight and none of the tablets have been broken. In chewable tablet different specifications can be accepted.
- Hardness: pharmacopeia accepts the results when the values are higher than 60N, for chewable tablets these values will be minor due to its dosage form and administration.
- Uniformity of weight of slotted tablet (half-tablet)
- Blister tightness

If tablets pass all this quality control, they could be distributed and marketed after being packaged. At the moment that batches fail the quality control and specifications, an OOS (Out Of Specifications) will be opened and started an investigation to resolve the causes of this mistake. Also, the possibility to apply CAPA (Corrective Actions Preventive Actions) to reduce the number of future mistakes in the manufactured process[49,55,63,64].
Moreover, this manufacturing process maybe includes in-process quality control. In-process quality controls allow to find out OOS in less time and reduce economic impact. In firocoxib's manufacturing, weight and hardness would be these parameters. However, it is important to have a strict follow up of the times in which these quality controls will be carried out[55, 65].

Packaging

It should be differentiated in primary and secondary packaging. The primary packaging product has the function of protection and keeps the integrity, for example, it could be a blister or a jar. The secondary packaging means the box where the primary packaging is introduced, it has to satisfy its corresponding law.

Nowadays, it is easy to see an automatic process of packaging at the end of manufacturing chain medicine. Automatic blister machines are composed by a set of stages that will be defined below.

Firocoxib 57mg (Previcox®) blisters are made of Alu/PVC, it means one side is aluminium and the other side of polyvinyl chloride. PVC will be defined as the forming film that forms the base of the blister pack and aluminium as the lidding material that covers the content of the cavity. Their locations in the machines are different because the PVC roller will be located at the beginning and the aluminium roller in the middle of the blister process.

The forming film will then move to a heating station where the lower and upper plates form a uniform and consistent heating to carry the next stage on. Pocket forming consists to use either plates or compressed air to form cavities. After that, these should be cooled to form a rigid plastic cavity. The next stage is the filling with tablets, manual or automatic, and checking that all cavities are empty. Followed by the coverage with the lidding material and the sealing with the application of temperature, it will be different depending on the material. The next station is an important stage because the information that will be printed in the blister occurs at this moment. Usually, the information that is engraved is information about the product such as dosage, expiry date, lot identification, route the administration and the name of the medicine as a manufacturer. Finally, the trimming stage pack products into individual units and eject from the machine[55,66,67].

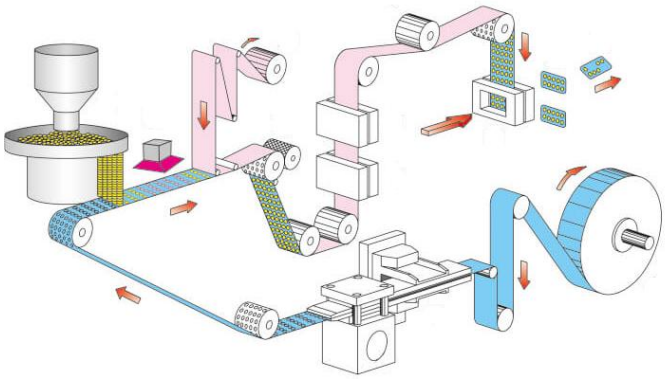


Figure 22: flow chart of automatic packaging machine[67]

Figure 23: SaintyCo Blister Packing Machine[66]

6 Packaging improvement

Old design

The dimensions of the packaging of Previcox® 57 mg 10 tablets (the choice of this presentation is because it is the most practical in comparison with the other and for the owners it is the cheapest) are 11 cm x 4,8 cm x 2,3 cm (length x width x depth):

Figure 22: Previcox 57 mg 10 tablets (Owner)

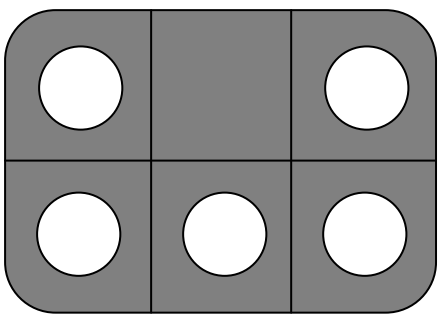
If the finality is to design new packaging that improves the current one, it is necessary to know how the blister was manufactured. Previcox® 57 mg 10 tablets only consist in one blister with the following dimensions: 10,2 cm x 4 cm x 0,5 cm.

Figure 23: Previcox 57 mg 10 tablets (Owner)

The first enhance of this product is to include expiry date and lot identification in every tablet because each one can be trimmed and separated from the rest of the blister.

New design

To design a new one it could be easy to reduce the depth of secondly packaging and make it tighter than the older. In the box, the information appears in three languages: English, Spanish and Greek. Keeping Spanish and English it is possible to reduce the length and modify the disposition of the blister in two blisters with five tablets each.



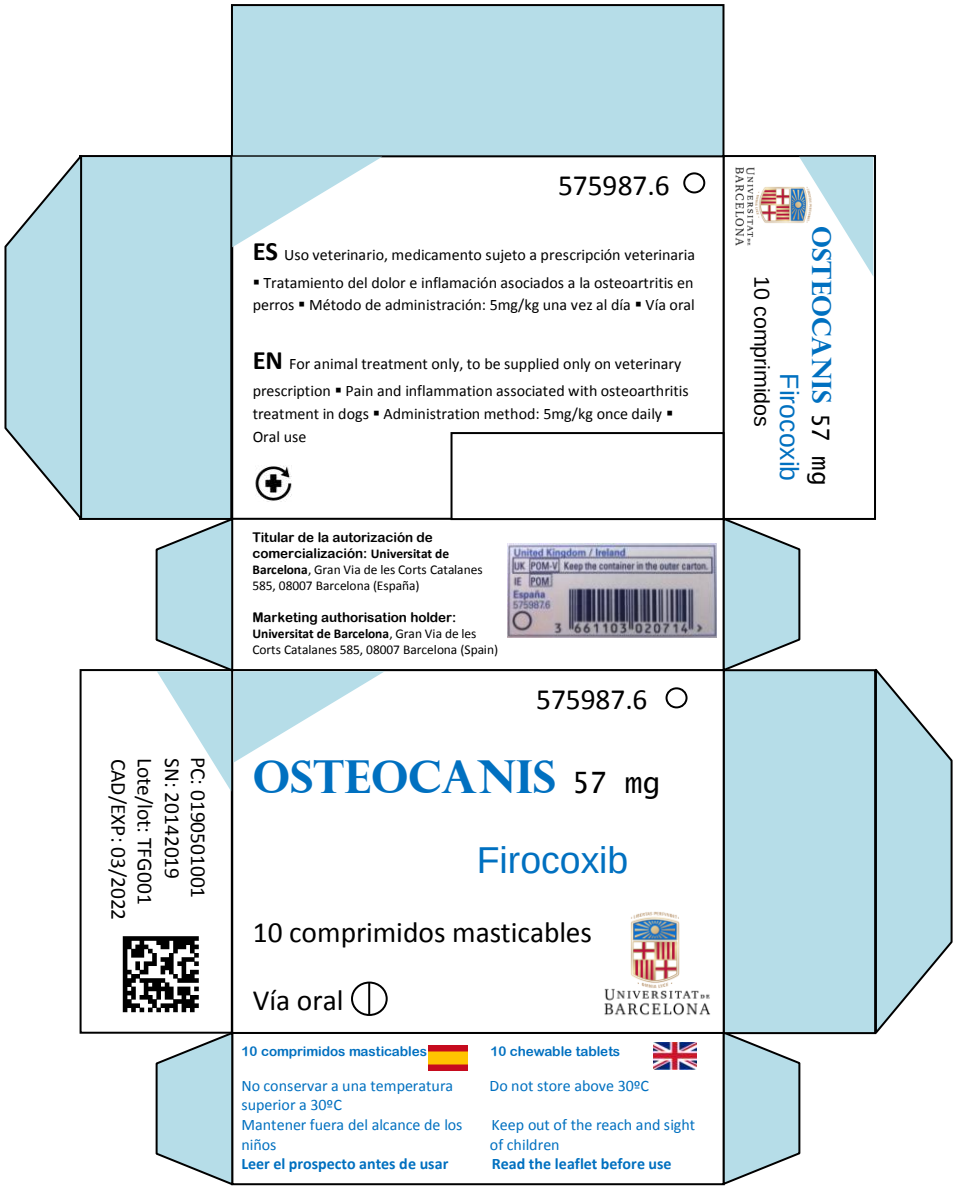
Dimensions: 5,7 cm x 4 cm x 0,5 cm

The width of the current design is 1,0 cm larger than the width of the blister to ease its handling. In the new design, it can be useful to keep the same distance between the box and the length of the blister. For calculating the depth it is indispensable to remember that now the presentation consists of two blisters. For this reason, the depth of one of them needs to be multiplied by two and leave space for the leaflet. As the information of the product, in the box, the languages of the leaflet will be reduced from three to two, discarding Greek. Finally, the dimensions of the secondary packaging will be 6,5 cm x 4,8 cm x 2 cm.

	Old design	New design	Reduction
Length	11 cm	6,5 cm	40,91%
Width	4,8 cm	4,8 cm	0%
Depth	2,3 cm	2,0 cm	13,04%
Area	178,28 cm^2	107,6 cm^2	39,65%

It would be considered an eco-friendly improvement since the reduction of paperboard in comparison with the old design. Another environmental-friendly action would be the change of blister material, changing Alu/PVC for Alu/Alu. Aluminium is one of the materials that has been extensively recycled. In contrast, if the PVC combustion is not complete, it causes an increase in the level of dioxin in the atmosphere[68].

The new design that is adequate with the regulations[25] is presented below.


575987.6
ES Uso veterinario, medicamento sujeto a prescripción veterinaria ▪ Tratamiento del dolor e inflamación asociados a la osteoartritis en perros ▪ Método de administración: 5mg/kg una vez al día ▪ Vía oral
EN For animal treatment only, to be supplied only on veterinary prescription ▪ Pain and inflammation associated with osteoarthritis treatment in dogs ▪ Administration method: 5mg/kg once daily ▪ Oral use
OSTEOCANIS 57 mg
Firocoxib
10 comprimidos
Titular de la autorización de comercialización: Universitat de Barcelona, Gran Via de les Corts Catalanes 585, 08007 Barcelona (España)
Marketing authorisation holder: Universitat de Barcelona, Gran Via de les Corts Catalanes 585, 08007 Barcelona (Spain)
United Kingdom / Ireland
UK POM-V Keep the container in the outer carton.
IE POM
España
575987.6
575987.6
PC: 0190501001
SN: 20142019
Lote/lot: TFG001
CAD/EXP: 03/2022
OSTEOCANIS 57 mg
Firocoxib
10 comprimidos masticables
Vía oral
Universitat de Barcelona
10 comprimidos masticables
No conservar a una temperatura superior a 30ºC
Mantener fuera del alcance de los niños
Leer el prospecto antes de usar
10 chewable tablets
Do not store above 30ºC
Keep out of the reach and sight of children
Read the leaflet before use

7 Conclusions

- Firocoxib belongs to the subgroup coxib within the NSAIDs. It is only used in veterinary medicine and is formulated as a chewable tablet.
- Previcox® 57mg is the only drug marketed in Spain that contains firocoxib as an active pharmaceutical ingredient. Despite this, there are a wide variety of drugs marketed with the same indications.
- The main indication is the treatment of osteoarthritis as well as postoperative pain. Although new indications of this drug are currently being discovered.
- The dosage of this medicine depends on the pain that the animal suffers and its duration. As a general rule, the amount to be administered is directly proportional to the weight: more weight more doses.
- Through the study of excipients and their functions, it is determined that the industrial process performed is a direct compression. Developing all the steps that will be carried out, using new and last technology.
- Design of a new packaging that allows a positive evolution, promoting the reduction of materials used as an approach to a responsible packaging with the environment. The primary packaging will also undergo changes to favor an eco-friendly attitude by changing the blister of Alu/PVC by another one exclusively of Alu/Alu.
- I have decided to present this work in English because it is the communicative vehicle established in global communication.

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9 Annexes

To give an approximate quantity of each compound that has a single tablet the ten chewable tablets that the littler box of Previcox® contains were weighted in an analytical balance. The results are below:

Balance: Santorius BP310P				
0,241g	0,240g	0,245g	0,237g	0,236g
0,242g	0,240g	0,240g	0,237g	0,243g
$\bar{x}$= 0,240g		SD=2,846·10-3		

Before weights, the balance has been calibrated and regulated. As shown in the following pictures.

Figure 24: weight process (Owner)