

**Technological prospection of Diminazene Aceturate, an Angiotensin II Converting
Enzyme activator, in front of diarrheic disorders**

**Prospecção tecnológica do Aceturato de Diminazeno, um ativador da Enzima
Conversora de Angiotensina II, frente a distúrbios diarreicos**

**Prospección tecnológica de Diminazene Aceturate, un activador de la Enzima
Convertidora de Angiotensina II, frente a los trastornos diarreicos**

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Abstract

Diarrhea, which is a gastrointestinal disease, has as its main characteristic the rapid passage of gastric contents through the intestine, which leads to the loss of water and electrolytes and consequent dehydration. The most common fluid replacement is the use of oral rehydration solution (ORS) together with the use of the drug loperamide. However, the use of this medication can cause severe bacteremia followed by sepsis and even death. Currently, there is no effective pharmacological treatment for diarrhea, therefore, it is noted the importance of seeking new therapeutic targets for the treatment of this disease. Thus, the aim of the present study was to conduct a research on the biological activities already described for Diminazene Aceturate with a special focus on antidiarrheal agents. For this, a survey was carried out,

through patent filing searches, in the USPTO, EPO, WIPO and INPI databases, using keywords and Boolean operators. Thus, it was found in the international patent databases the number of documents referring to the use of Diminazene Aceturate in several areas, mainly in the pharmaceutical industry, but with a relatively low number of documents regarding the description of possible antidiarrheal action of the compound under study, which reinforces the innovative character of research involving the use of Diminazene Aceturate as an antidiarrheal agent.

Keywords: Angiotensin; ACE II; Diarrhea.

Resumo

A diarreia, que é uma doença gastrointestinal, tem como principal característica a passagem rápida do conteúdo gástrico pelo intestino, o que leva à perda de água e eletrólitos e consequente desidratação. A reposição hídrica mais comum é o uso de solução de reidratação oral (SRO) juntamente com o uso do fármaco loperamida. Porém, o uso deste medicamento pode causar bacteremia grave seguida de sepse e até morte. Atualmente, não existe um tratamento farmacológico eficaz para a diarreia, com isso, nota-se a importância de buscar novos alvos terapêuticos para o tratamento dessa doença. Assim, o objetivo do presente estudo foi realizar uma pesquisa sobre as atividades biológicas já descritas do Aceturato de Diminazeno com foco especial nos agentes antidiarreicos. Para isso, foi realizado um levantamento, por meio de pesquisas de depósito de patentes, nas bases de dados USPTO, EPO, WIPO e INPI, utilizando palavras-chave e operadores booleanos. Assim, constatou-se nas bases de dados internacionais de patentes o número de documentos referentes ao uso do Aceturato de Diminazeno em diversas áreas, principalmente na indústria farmacêutica, mas com número relativamente baixo de documentos quanto à descrição de possível ação antidiarreica do composto em estudo, o que reforça o caráter inovador das pesquisas envolvendo o uso do Aceturato de Diminazeno como agente antidiarreico.

Palavras-chave: Angiotensina; ECA II; Diarreia.

Resumen

La diarrea, que es una enfermedad gastrointestinal, tiene como característica principal el rápido paso del contenido gástrico a través del intestino, lo que conduce a la pérdida de agua y electrolitos y la consiguiente deshidratación. El reemplazo de líquidos más común es el uso de solución de rehidratación oral (SRO) junto con el uso del fármaco loperamida, sin embargo, el uso de este medicamento puede causar bacteriemia grave seguida de sepsis e incluso la

muerte. Actualmente, no existe un tratamiento farmacológico eficaz para la diarrea, por lo que se destaca la importancia de buscar nuevas dianas terapéuticas para el tratamiento de esta enfermedad. Así, el objetivo del presente estudio fue realizar una investigación sobre las actividades biológicas ya descritas para el Aceturato de Diminazene con un enfoque especial en los agentes antidiarreicos. Para ello, se realizó una encuesta, a través de búsquedas de presentación de patentes, en las bases de datos de la USPTO, EPO, WIPO e INPI, utilizando palabras clave y operadores booleanos. Así, se encontró en las bases de datos internacionales de patentes la cantidad de documentos referentes al uso del Aceturato de Diminazene en varias áreas, principalmente en la industria farmacéutica, pero con un número relativamente bajo de documentos en cuanto a la descripción de la posible acción antidiarreica del compuesto en estudio. , que refuerza el carácter innovador de la investigación que implica el uso de Diminazene Aceturate como agente antidiarreico.

Palabras clave: Angiotensina; ECA II; Diarrea.

1. Introduction

Diminazene Aceturate (DIZE) has been used as a treatment for animal trypanosomiasis. The drug was first introduced to the market as a trypanosomicide and babesicide for cattle. Because of its high therapeutic index and low incidence of resistance compared to other compounds, it has become the most used therapeutic agent for trypanosomiasis in cattle. Its chemical composition is basically formed by an aromatic diamidine with two aminophenyl moieties attached by a triazene bridge (Peregrine; Mamman, 1993).

For over 60 years, Diminazene Aceturate has been used as a treatment for animal trypanosomiasis. The drug was first introduced to the market as a trypanosomicide and babesicide for cattle. Because of its high therapeutic index and low incidence of resistance compared to other compounds, it has become the most used therapeutic agent for trypanosomiasis in cattle. Its chemical composition is basically formed by an aromatic diamidine with two aminophenyl moieties attached by a triazene bridge (Peregrine; Mamman, 1993; Da Silva Oliveira, 2015).

Recently, several studies have shown that Diminazene is responsible for interfering with various physiological processes in the rodent organism. The use of this compound is linked to the activation of Angiotensin II Converting Enzyme (ACE II). ACE II metabolizes

Angiotensin II (Ang II) into a metabolite called Ang- (1-7) thereby regulating some deleterious effects of the Ang II / AT1 pathway. (Velkoska et al., 2015)

Studies research has shown that administration of Diminazene Aceturate prevents chronic bouts of pulmonary hypertension in experimental models (Shenoy et al., 2013). In addition, DIZE has also been shown to have protective effects under different physiological conditions, including stroke, ischemia, glaucoma and heart disease and diabetic nephropathy. (Colafella et al., 2019; Malek et al., 2019; Velkoska et al., 2016) in the gastrointestinal tract its protective effect has been described in models of gastric ulcers induced by ethanol and acetylic acid (Kuriakose; Uzonna, 2014) gastric ulcer (Souza et al., 2016).

Thus, considering the modulatory effects of DIZE already described in the literature and focusing on its possible protective potential of the gastrointestinal tract, its use as an antidiarrheal agent is pending, but still pending scientific confirmation. In this sense, studies that seek to assert such antidiarrheal property of this compound would be contributing to the field of science in general and public health, considering that diarrhea, for many decades, has been recognized as one of the main causes of death, especially among women. socioeconomically disadvantaged populations in developing countries (Binder, 2019).

Among the most frequent clinical manifestations related to gastrointestinal diseases is diarrhea (Major; Gunn, 2019). This is a gastrointestinal disease that has as its main feature a rapid passage of gastric contents through the intestine, thus generating an increase in the number of bowel movements three or more times a day. As well as increased stool fluidity, possibly having the presence of blood and mucus, besides being accompanied by increased secretion and decreased absorption of intestinal fluid which leads to the loss of water and electrolytes and consequent dehydration (Das et al., 2018). Many factors may be related to the onset of diarrhea, including infectious agents, toxins, intestinal functional disorders, nutrient malabsorption, inflammatory bowel disease, and medications (Riddle et al., 2017).

One of the most severe is secretory diarrhea that can lead the patient to death (Brandt et al., 2017). Among them are those caused by the strains *Vibrio cholerae* O1 and O1.39 and enterotoxigenic *Escherichia coli* (ETEC), in which there is extensive fluid loss, with minimal or fecal mass formation, being called “rice water” (Hurst, 2019). Cholera caused by the bacterium *Vibrio cholerae* is still one of the major causes of morbidity and mortality in tropical regions (Di John et al., 2017).

Cholera toxin seems to work by stimulating the transepithelial secretion of chlorine by crypt cells, thereby increasing fluid secretion by its osmotic effect (Yamasaki et al., 2017.). Recent WHO data show that the incidence of cholera has been increasing globally, making it

a serious public health problem among people in developing countries. Still today cholera is still considered a highly lethal disease, it is one of the leading causes of morbidity and mortality in the world, with an estimated 2 to 3 million cases. Over 100,000 deaths are estimated each year (Phelps et al., 2017).

Currently, there is no effective pharmacological treatment for diarrhea and the available treatment is not specific, having only palliative action to reduce the discomfort, dehydration and inconvenience caused by frequent bowel movements. Therefore, the search for therapeutic alternatives that may be able to remedy diarrheal diseases and especially with minor side effects has seen the no specificity of current therapy.

In this sense, technological prospection, which patents showing the properties already described of Diminazene Aceturate compound, with a special focus on its antidiarrheal activity, represent a very useful tool, as they constitute systematic means of providing scientific information that assume an important background information role to guide in the development of new technologies, aiming at a better quality of products, services and life (Cuppen et al, 2019). In this context, this study aims to conduct a research on the biological activities already described of Diminazene Aceturate with special focus on possible applications of these substances as antidiarrheal agents, performing a search for articles and patent applications at national and International.

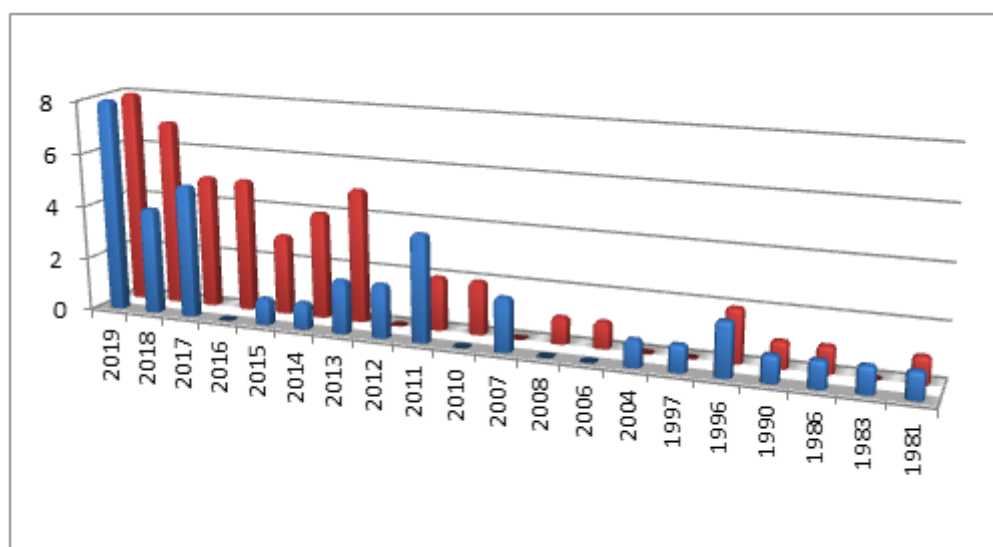
2. Methodology

This study was based on a survey of patent applications filed in the main databases: european patent office (EPO), world intellectual property organization (WIPO), united states patent and trademark office (USPTO) and in the database. from the national institute of industrial property (INPI) of brazil. The survey was conducted in December 2019, and all patent documents available for consultation were investigated until the date of this research (10/12/2019). Searches were performed using keywords such as Diminazene aceturate alone or combined with the term diarrhea, MAS receptor, diarrhea treatment (Table 1), together with the Boolean operator “and”, possibly associating the terms with the use of quotation marks or parentheses. Documents with these terms in the abstract and/or title were considered valid. The technical procedures applicable to data collection concern the search for patents and collections and official databases that provide information about analysed parameters were carried out according to the methodology relevant to this type of research (Pereira et al., 2018).

3. Results and Discussion

The results obtained in the present technology research refer to all patent filings made on the subject in question, considering, for patent filings, the country and year of filing as well as the International Patent Classification (CIP). The USPTO database search found 35 patent document results covering the term “Diminazene Aceturate” and 49 results for the term “MAS receptor” and 140 documents associated with the term “diarrhea treatment” (Figure 1). Results obtained for the search for the term “Diminazene Aceturate” in the USPTO patent base for the years of filing of patent applications.

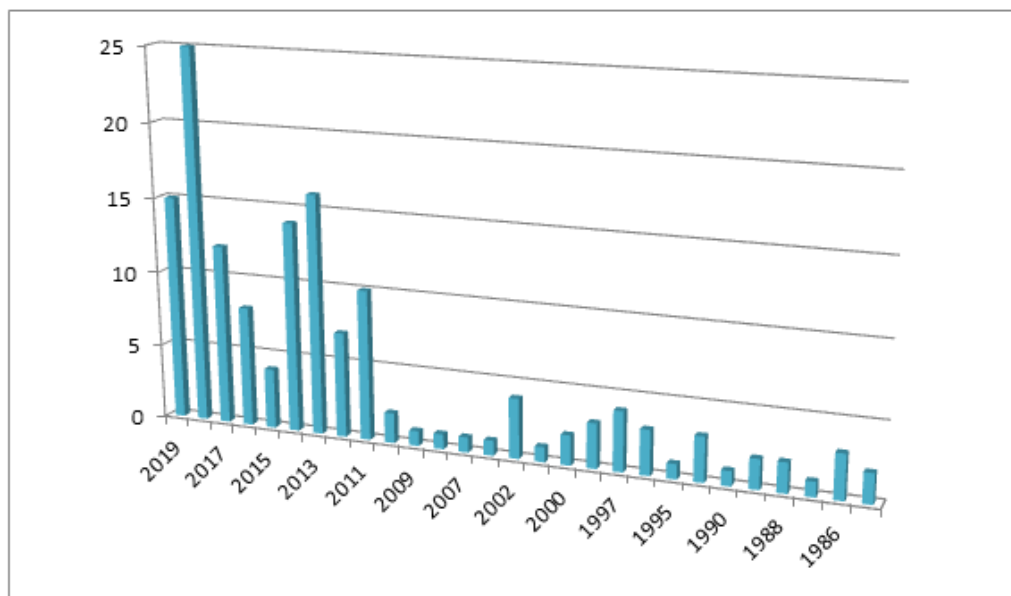
Figure 1. Results obtained for the search term “Diminazene Aceturate” and “MAS receptor” in the USPTO patent database for the years of filing of patent applications.



Source: Prepared by the authors from USPTO (2019).

We can see from the result obtained in this database that this compound is very old, used since the 80's, and most patents refer to its antiparasitic activity only in recent years has been observed a change in patent patterns that now also opening compositions with analgesic and anticancer anti-inflammatory formulations. For the search for the term “MAS receptor we can observe from the graph that they were the same patents for Diminazene, is showing that this pathway is well described and has been much studied of said compound. When the search for the term “diarrhea treatment” was performed it can be observed that in recent years there has been a growing increase in the search for therapeutic alternatives for the treatment of diarrhea with a peak of 25 patents only in 2017 (Figure 2).

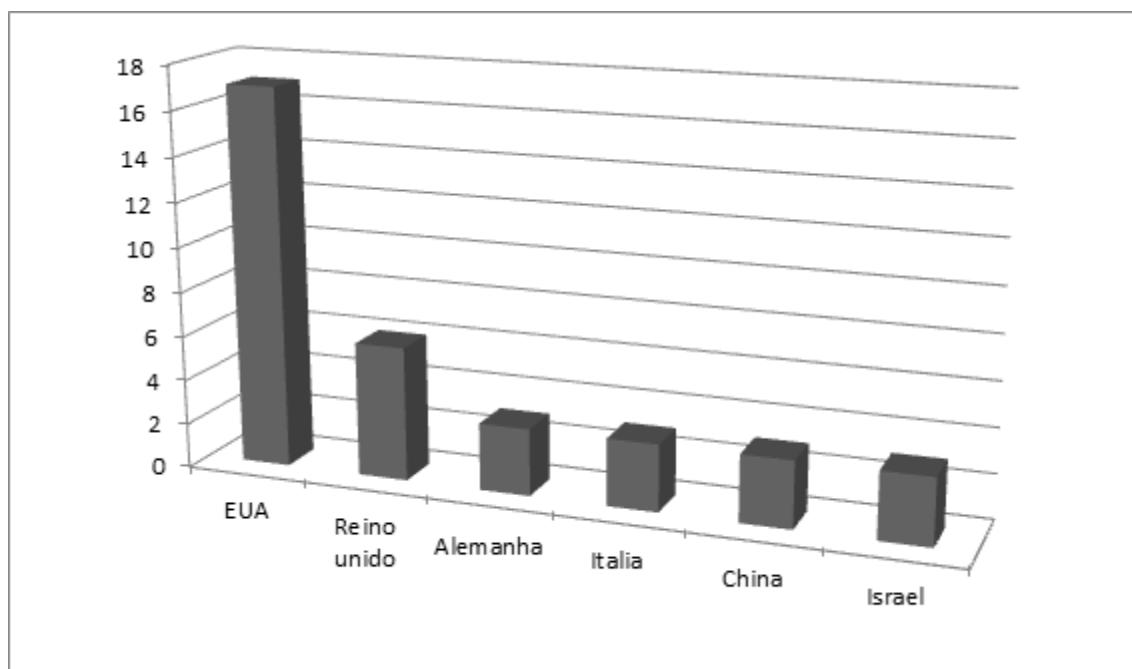
Figure 2. Results obtained for the search for the term “diarrhea treatment” in the USPTO patent database for the years of filing of patent applications.



Source: Prepared by the authors from USPTO (2019).

However, when the combination of the terms Diminazene aceturate alone or combined with the term diarrhea, MAS receptor, diarrhea treatment was performed, the search returned no results. This reinforces the technological innovation in the use of these compounds to treat such disease. When looking at the nation of origin of the patents associated with the term “Diminazene Aceturate”, it was found that the United States is the largest holder with 17 filing applications, followed by the United Kingdom with two, plus a filing application in Japan, Germany, Italy and Israel (Figure 3). Analysing the distribution of patents in the database, there was an increase in the number of filings from the year 2010, demonstrating an advance in studies and research investments in relation to this material in recent years.

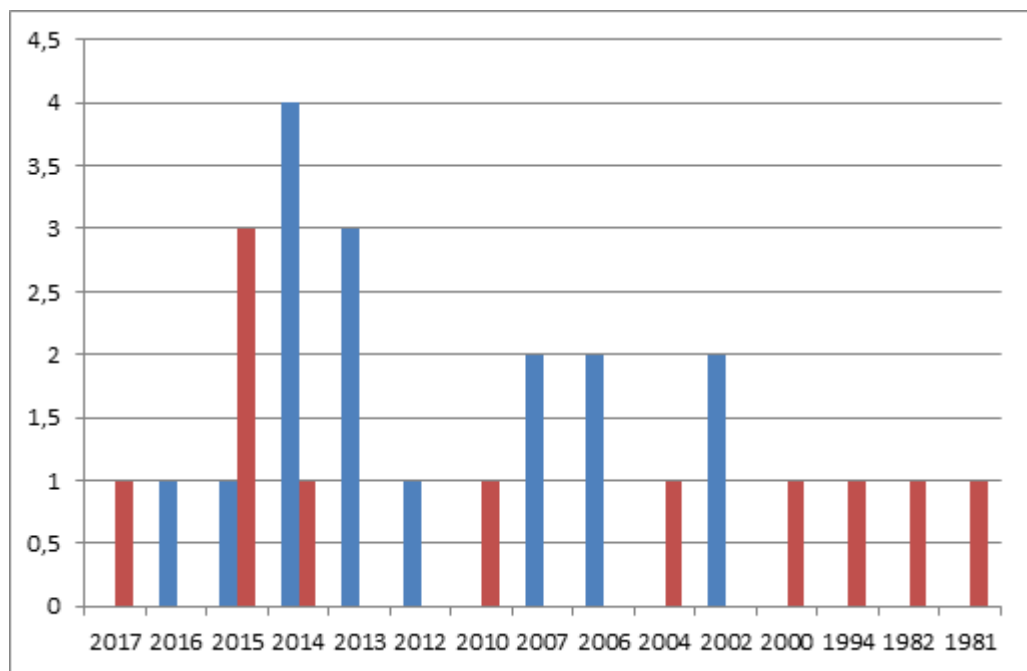
Figure 3. Results obtained for the search for the term “Diminazene Aceturate” in the USPTO database, for countries filing applications based on patent quantities.



Source: Prepared by the authors from USPTO (2019).

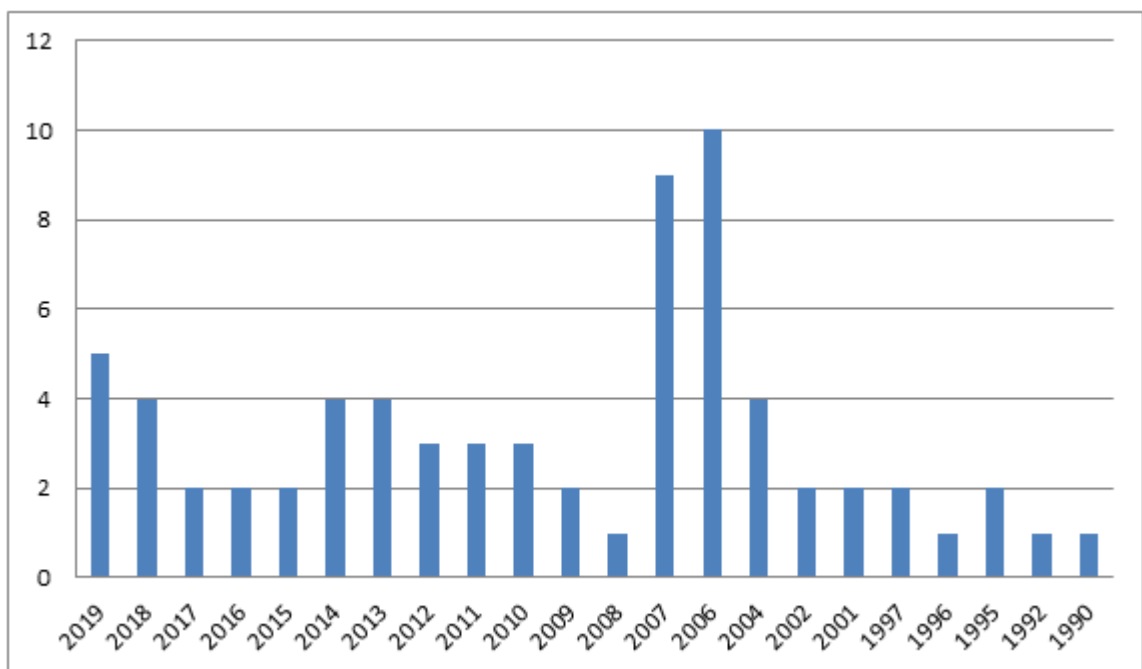
In the EPO database 12 patent documents were found for the term “Diminazene Aceturate”. The search for the term “MAS receptor” reported 16 results, and the search for the term “diarrhea treatment” reported 69 results, as in the other database A large increase can be observed in recent years of Diminazene patents and the specific receptor pathway (Figure 4). In addition, patent applications from the Patent Cooperation Treaty (PCT) were significant, which simplifies and reduces the initial cost in patent application procedures in member countries. These data show that the pharmaceutical industry has been interested in this area and that patents are constantly being required for the manufacture of new drugs. On the other hand, when the combination of the terms Diminazene aceturate combined with the term diarrhea, MAS receptor, diarrhea treatment was performed, the search returned no results. Showing that the study of such pathways and the compound in question is innovative and to date there are no patents on this subject.

Figure 4. Results obtained for the search for the term “Diminazene Aceturate”, “MAS receptor” in the EPO database, regarding the years of filing of applications based on patent quantities.



Source: Prepared by the authors from EPO (2019).

Figure 5. Results obtained for the search for the term “diarrhea treatment” in the EPO patent database for the years of filing of patent applications.

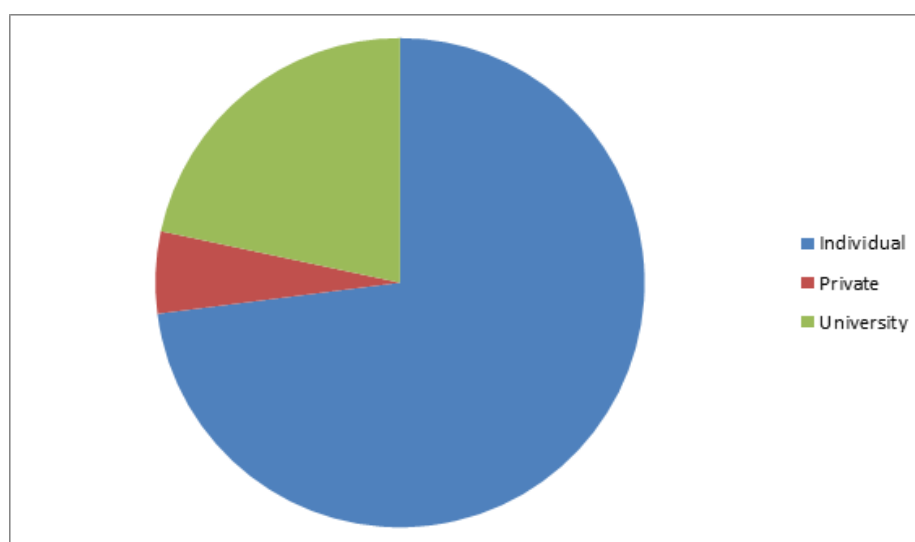


Source: Prepared by the authors from EPO (2019).

The search in the WIPO database regarding patent documents already filed involving the subject in question returned 10 results involving the term “Diminazene Aceturate”. Being predominantly according to the following IPC categories: A61 (health, lifesaving, medical or veterinary science and hygiene). It should be noted, however, that such results mostly refer to the protection of analytical methods, as well as their use as a trinaposomycid drug in large animals, and formulation for their use in the treatment of malaria.

When searching for the term MAS receptor the search returned 3 results one of the patents one of the patents being on pharmaceutical compositions containing Ang- (1-7) or another MAS receptor agonist in combination with Pi3k/Akt inhibitors for anticancer therapeutic treatment, the second is about Ang 1-7/MAS receptor pharmaceutical compositions for treating eye conditions and the third is about stem cell differentiation showing that this pathway is still very recent and has much to explore. We found 35 results for searching for the term “diarrhea treatment” (Figure 6) where most are under the responsibility of private companies showing their interest in researching alternatives to diarrhea treatment. As noted in the other databases, the search for terms Diminazene Aceturate combined with the term diarrhea, MAS receptor, diarrhea treatment search not returned results.

Figure 6. Results obtained for the search for the term “diarrhea treatment” in the WIPO patent database for the type of patent filer.

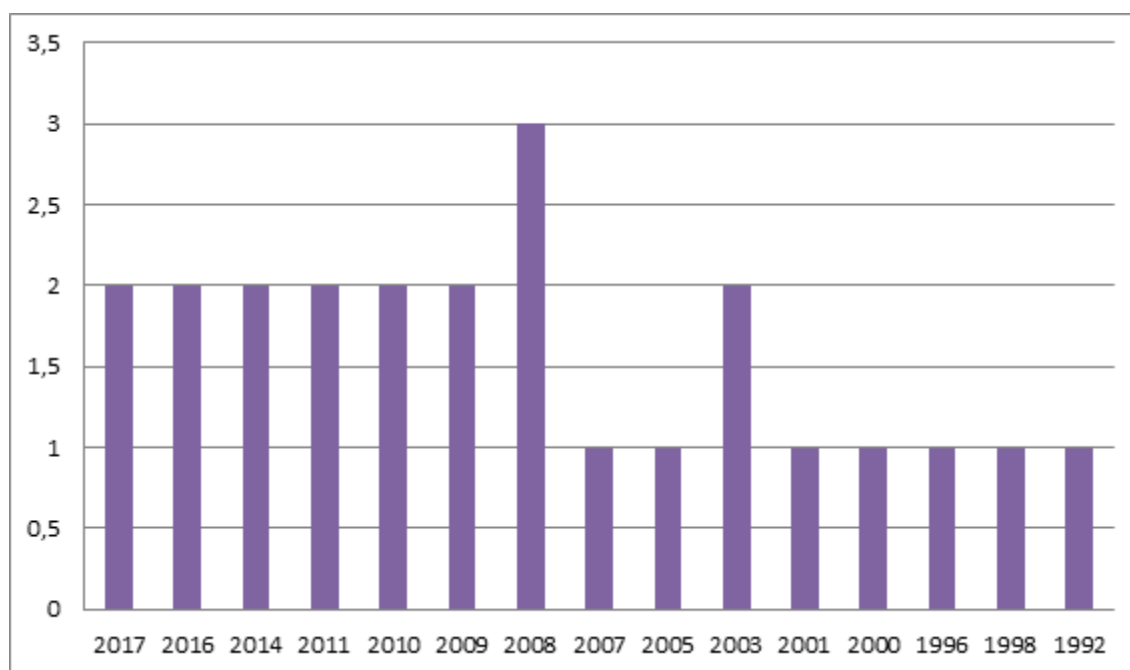


Source: Prepared by the authors from WIPO (2019).

The INPI national patent search resulted in a total of 24 patent filings for the term “diarrhea treatment”, which aimed to protect formulations for new drugs, vaccine

preparations, treatment for bowel syndrome. irritable, enteritis and colitis were also in the results, in addition to other pharmacological applications. In this search, it is still possible to point out that no patent deposits were found when the term “Diminazene Aceturate” was used. The search performed for the combination of the terms “Diminazene Aceturate” and “Diarrhea” returned no results.

Figure 7. Results obtained for the search for the term “diarrhea treatment” in the INPI patent base for the years of filing of patent applications.



Source: Prepared by the authors from INPI (2019).

4. Conclusion

Based on the analysis of the data presented, it is noted that in recent years there has been a growing patent filing for the use of Diminazene Aceturate in several thematic areas, especially the pharmaceutical industry. Such data represent the technological advance achieved in the last decade. As is the interest of the pharmaceutical industry in therapeutic alternatives for the treatment of diarrhea. However, the associated terms in patent searches have yielded scant results, which reinforces the innovative character of research involving the use of Diminazene Aceturate as an antidiarrheal agent.

Suggestion

This study may suggest the application and use of the use of Diminazene Aceturate in several thematic areas, especially in the treatment of diarrheal diseases and gastrointestinal disorders, and which may be a good pharmacological target for the treatment of these diseases, since the interest of pharmaceutical industry in therapeutic alternatives for the treatment of diarrhea.

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