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PILOCARPINE APPLICATION ON TREATMENT OF XEROSTOMIA: STATE OF THE ART

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ABSTRACT

To assess applications with patented active ingredient pilocarpine and discuss their implications for further research in drug development was realized a research in some patent databases including WIPO, Espacenet, USPTO and INPI using key terms which correlates pilocarpine and xerostomia. As results was found thirteen different innovative patented formulations, mainly tablets with different content and drug delivery technologies, but also liquid and semi-solid formulations. The tablets are commercialized on the market by MGI Pharma Inc. and were approved by FDA in 1994. It is the only option commercially available for use in xerostomia. Other forms of application as bioadhesives, chewing gum and gargling solutions are not available *yet al*though have been patented. There were twelve companies as patent assignees what shows how much the pilocarpine has been exploited. In this way is possible to conclude that innovative technology has been applied on development of pilocarpine pharmaceutical products although innovative marketed alternatives to treatment of xerostomia with this promising drug are still missing.

INTRODUCTION

Xerostomia is a symptom associated with quantitative and qualitative changes in the salivary flow, which is clinically relevant to be recognized and treated as a significant pathology because usually interfere in the quality of life causing oral dysfunction, dental destruction, atrophy and infection or ulceration of mucosa.[1,2] This is due to the lack of physiological salivary flow in xerostomia. Saliva, besides its importance during speaking, taste, mastication and swallow, is essential to maintain oral health against pathogenic microorganisms. This is achieved by mechanical lubrication besides cleaning and protecting of hard and soft oral tissues by antibodies present in that fluid.[1] Common causes of xerostomia include radiotherapy for head and neck cancer, Sjogren's syndrome and specific diseases, sarcoidosis, HIV disease (AIDS) and primary biliary cirrhosis. It is also an adverse effect of several commonly prescribed drugs. Over 500 medications have been associated with dry mouth, such as tricyclic antidepressants, antipsychotics, decongestants, antihistamines, mydriatic eye drops, drugs for urinary incontinence, antihypertensives, and the risk increases with the number of medications taken.[3] For the treatment of Sjogren's syndrome, we can find artificial saliva that is rarely used by patients because it leads to only few minutes of improvement, or bromhexine and anetholtrithione, that are often used to increase salivary secretion but never have been evidenced efficacy in randomized trial against placebo.[2] Therefore, the most recent data show that the only drugs with proven efficacy in production of saliva are the muscarinic receptor agonists, such as pilocarpine hydrochloride and cevimeline.[2] Several studies have demonstrated the sialogogue activity of pilocarpine hydrochloride in radiotherapy for head and neck cancer and Sjogren's syndrome patients, who have residual salivary gland function.[4-7] In fact, the salivary physiology has 2 components

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that are secreted by independent mechanisms. First, a fluid component that includes ions is produced mainly by parasympathetic stimulation; second, a protein component arising from secretory vesicles from acinar cells is released mainly in response to sympathetic stimulation. Excitation of both nerves stimulates salivary secretion but the effects of the parasympathetic result in a copious saliva of low protein concentration, whereas sympathetic stimulation produces little saliva but with high protein concentration, which may give a sensation of dryness, in this way.[8,9]

Though, despite its effectiveness the pilocarpine is associated with a high number of side effects when is administered orally. These include facial flushing, headache, sweating and increased urination. An alternative to these effects would be a local rather than systemic application of the drug.[10] On a crossover study comparing a spray of mucin-based artificial saliva and tablets of pilocarpine hydrochloride in the management of xerostomia in patients with advanced cancer, pilocarpine was found to be more effective than the artificial saliva in terms of mean change in visual analogue scale scores for xerostomia. However, pilocarpine was associated with mild side-effects that resulted in a representative amount of patients preferring to continue with the artificial saliva after the study. This happened due to the lack of side effects and mainly because the artificial saliva was in spray form, rather than a tablet.[11] Given the proven sialogogue activity of cholinergic agonists and low adherence to the use of tablets, besides the appearance of side effects with their use, there were several papers and patents on new dosage forms to such drugs. The aim of this study was to investigate in patent databases the status of technological development for formulations and presentations that treat xerostomia and contain pilocarpine as active ingredient. This will help the industries to produce new presentations and the researchers to develop new technological advances.

MATERIALS AND METHODS

Patent prospection was conducted based on the patent applications filed and issued in the databases of the European Patent Office – EspaceNet[12], World Intellectual Property Organization – WIPO[13], United States Patent and Trademark Office – USPTO[14] and the *Instituto Nacional de Propriedade Industrial* – INPI[15] of Brazil. All patents related to pilocarpine were analyzed, focusing on the use on pharmaceutical preparations developed for the treatment of xerostomia. An advanced search in titles and abstracts was done with the keywords pilocarpine*, xerostomia*, saliva* and mouth*. Patents with the same claims and inventors were discarded from the evaluation, wherein the priority dates were the same.
Data evaluation included research for formulations and published studies by inventors and assignees on patents in the scientific databases Web of Knowledge[16] and Scientific Electronic Library Online – Scielo[17]. Journal articles were classified according to the impact factor of Journal Citation Reports® 2010 – JCR 2010[16].

RESULTS

We searched patent databases for the terms pilocarpine, saliva, mouth, and xerostomia. A high number of patents was found with the pilocarpine term alone, most of them reported its base and salts, hydrochloride and nitrate, and their cholinergic agonist activity for the treatment of fibromyalgia, xerostomia, xerophthalmia, glaucoma, pharyngitis among other physiological disorders. They also referred to the methods for obtaining this alkaloid from plants of the genus *Pilocarpus* which is the only natural source of pilocarpine. Besides, they refer to the part that accumulates the highest content of this alkaloid, the leaves of the species *P. microphyllus* (jaborandi tree).[18]

However for the exclusive treatment of xerostomia and diseases caused by it, we found thirteen filed patents between 1979 and 2008 and published until 2011, wherein US, Japan and France were the main countries of filing, with five, two and two filed patents respectively. Among them are some innovations in its pharmaceutical form. Over the years, the greatest variety of innovations happened after the 1990s with the development of tablets, chewing gum and formulations that controlled release of pilocarpine (Table 1). All the patents who had contributions to this research were classified as dosage forms and was demonstrated that the main focus of the researchers was tablets (Figure 1), among them with immediate release, controlled release, dispersible and bioadhesive tablets. For example, Maruyama *et al.*[19] and Sun *et al.* [20] have patented two tablets showing the promising action of pilocarpine although with no particular innovation. Differently, Hamlar *et al.* [21] published a single article located in the scientific database Web of Knowledge[16] that contains a pastille, like a candy, although not patented.

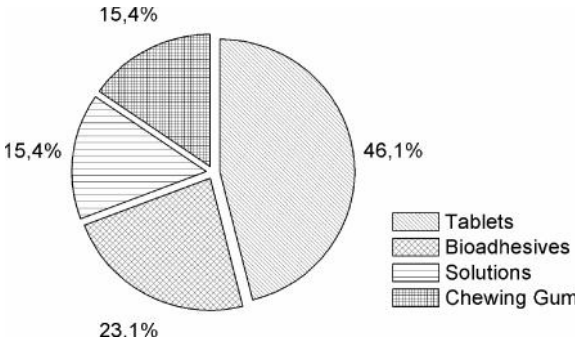

Figure 1. The number of pilocarpine patents useful to treat xerostomia by dosage form

Companies involved in filing patents were analyzed too. In general were represented by pharmaceutical industries or universities (Table 2). MGI Pharma Inc. is the owner of the only patent of pilocarpine hydrochloride (Salagen, MGI Pharma Inc., Minnesota, US) approved by Food and Drug Administration (FDA) for xerostomia treatment. No other company has approved drug product from different dosage forms nor has more than one patent issued with pilocarpine. Beyond the patents found there were sixteen published articles from the same authors located in Web of Knowledge[16] and Scielo[17] (Table 3), including preclinical and clinical studies with pilocapine. Three of these had no abstract available.

DISCUSSION

The patent prospection is a good tool for new products development both in industries and universities. In this way, it is possible to market products already patented or to research and discover new products not yet patented.

Table 1. Patented dosage forms of pilocarpine for xerostomia

Dosage form	Inventor(s)	Patent No.	Priority date
Mouth-wash solution	Mikhail	US Patent 4209505[22]	03/04/1979
Controlled release tablet	Acharya	World Patent 9401108[27]	02/07/1992
Percutaneous absorption preparation	Hori & Sato	Japanese Patent 7330602[31]	13/06/1994
Chewing gum	Ryu & Lee	Korean Patent 9606319[34]	30/06/1994
Immediate release tablet (Salagen®)	Muscoplat	French Patent 2737661[36]	08/08/1995
Buffer system for chewing gum	Singh *et al.*	US Patent 2003084515[45]	01/04/2002
Bioadhesive to buccopharyngeal tissue	Perovitch *et al.*	French Patent 2864901[46]	09/01/2004
Dispersible tablet	Hayward	US Patent 2007087053[47]	14/10/2005
Antiseptic bubble gargler	Su *et al.*	Korean Patent 2008012700[48]	04/08/2006
Bioadhesive sticker tablet	Brama *et al.*	European Patent 2027852[49]	24/08/2007
Oral gel composition	Grégio	Brazilian Patent 200805520[44]	01/12/2008

Table 2. Assignee companies for pilocarpine patents useful to treat xerostomia.

Patente No.	Company	Business activity
World Patent 9401108[27]	Theratechnologies Inc.[29]	Pharma – Endocrinology and metabolism
	Oramed Inc.[30]	Pharma – Biotech
European Patent 2027852[49]	Axiomedic Ltd.[50]	Pharma – Diverse
Brazilian Patent 200805520[44]	Assoc. Paranaense de Cultura[51]	University
US Patent 2007087053[47]	EffRx Inc.[52]	Pharma – Drug delivery
Japanese Patent 7330602[31]	Nitto Denko Corp.[53]	Patches Industry
	Lederle Japan Ltd.[32]	Pharma – Diverse
Japanese Patent 2007176906[18]	Kissei Yakuhin Kogyo Co. Ltd.[54]	Pharma – Diverse
French Patent 2737661[36]	MGI Pharma Inc. (Eisai)[35]	Pharma – Diverse
US Patent 2003185884[45]	TransOral Pharmaceuticals Inc.[55]	Pharma – Neuro
Korean Patent 2008012700[48]	Sh Pharmaceuticals Ltd.[56]	Pharma – Diverse
Chinese Patent 101229155[19]	Qingdao University[57]	University

Table 3. Journal articles submitted by inventors/assignees of pilocarpine patents useful to treat xerostomia

Year	Author	Objectives	JCR 2010
1993	Johnson *et al.*[37]	Prospective, randomized, double-blind, placebo-controlled trial to evaluate the treatment of radiation-induced xerostomia with pilocarpine	53,486
	Leveque *et al.*[38]	Randomized, double-blind, placebo-controlled, multi-center clinical investigation to determine the efficacy and safety of pilocarpine for symptomatic relief of postradiation xerostomia	18,970
1996	Lockhart *et al.*[28]	Assessment of safety, efficacy, duration of action, multiple dose tolerance, and side effects of a controlled-release formulation of pilocarpine	1,417
1998	Chambers *et al.*[39]	Assessment of salivary flow and functional improvement in cancer patients with oral pilocarpine	3,773
1999	Vivino *et al.*[7]	Multicenter, double-blind, placebo-controlled trial to assess the safety and efficacy of Salagen® on dry mouth or dry eyes in patients with Sjogren syndrome	10,639
2001	Asari *et al.*[58]	Assessment of prophylactic effects of pilocarpine on xerostomia models induced by either single or repeated X-ray irradiation in rats	1,960
2002	Asari *et al.*[59]	Sialogogic mechanism triggered by pilocarpine in X-ray irradiation-induced rat xerostomia model	-
2003	Omori *et al.*[60]	Assessment of the effects of muscarinic receptor agonists on salivary secretion from the submandibular/sublingual glands in normal rats and in rats with xerostomia induced by X-ray irradiation	53,486
	Takagi *et al.*[61]	Investigation of the mechanism of radiation-induced dysfunction in rat submandibular glands	2,578
2006	Li *et al.*[62]	Study on the effect of pilocarpine on the ion channel activity, cytoplasmic free Ca2+ concentration and aquaporin expression	2,451
	Inoue *et al.*[63]	Assessment of the effects of single and repeated administrations of pilocarpine on salivary secretion in a model for Sjogren's syndrome	2,260
2009	Asari *et al.*[64]	Examination of the muscarinic receptor subtype mediating pilocarpine-induced parotid salivary secretion and the contributions of ion transporter systems and aquaporin-5 translocation to this response in parotid glands in irradiated-induced xerostomia	1,960
	Silva *et al.*[65]	Assessment of the effect of antidepressants on the size, mass, cellular volume, of rat parotid salivary glands and salivary flow rate, as well as the secretagogue action of pilocarpine on this flow	1,603
	Zaclikevis *et al.*[66]	Measurement of salivary flow rate of rats under chronic treatment with benzodiazepine and verification of effects of pilocarpine in glandular parenchyma and in the salivary flow rate	1,603
2010	Aframian *et al.*[43]	Evaluation of a mucoadhesive lipid-based bioerodable tablet as a novel device to decrease signs and symptoms associated with mouth dryness	0,643
2011	Mattioli *et al.*[67]	Evaluation of the effects of antidepressants and pilocarpine on the quantity of myoepithelial cells and on the proliferation index of the epithelial cells of rat parotid glands	1,422

In this study the patent databases used included all the patents issued in the world which guarantee the wideness of the study. Analyzing the patents related to the use of pilocarpine for xerostomia treatment, it was possible to find several pharmaceutical forms and presentations chronologically developed. Furstenberg had described in 1944 that the oral administration of pilocarpine hydrochloride or nitrate in 10 milligram dosages repeated 3 times a day results in restoration of temporary salivation in patients suffering from dry mouth. The administration of pilocarpine had a transient effect, but the preparation of the patient with a diet to induce specific acidosis enabled the prolongation of salivatory effect due to the increase in absorption, although to result in sustained side effects. Adverse effects are dose-dependent and include sudoresis, facial blushing and increased urinary frequency. These possible disadvantages and undesirable systemic side effects were caused by the oral route.

The systemic administration of pilocarpine hydrochloride has given rise to the tablets which is the only pharmaceutical form in the market approved by the FDA for treatment of xerostomia in 1994.[1] MGI Pharma Inc.[36], currently Eisai Co. Ltd. is assignee of the French patent 2737661, which claimed the pilocarpine tablet for use in xerostomia.[37] The recommended doses of this tablets was 5 mg repeated 3-4 times a day, an attempt to reduce the side effects.[29] Although the maximum dosage of 20 mg daily is well-tolerated by most patients who use pilocarpine tablets, repeated dose and high serum concentration can in some cases lead to the discomfort caused by the unpleasant taste and susceptibility to side effects during treatment, such as flushing, hypotension, bradycardia, sweating, increased urination and diarrhea.[25] To solve the problem surged the US patent 4209505 for a mouthwash formulation. It contained a diluted pilocarpine hydrochloride that was aimed to produce the relief of dry mouth for a prolonged period without the inconvenience of systemic side effects. This invention also innovated by using dosages ranging from 0.025 % to 1 % by weight of the topical formulation. It was described like a solution for gargling, kept in contact with the oral mucosa for at least 30 seconds. The dosage given was dependent on the needs of each patient and the solution was especially effective in patients suffering from xerostomia induced by drugs such as antidepressants, antipsychotics, antihypertensives and allergy. However, the local and transient application was not enough to permit a good absorption rate of the drug, making this formulation not sufficiently effective.[23]

On the other hand, in the study of Bernadi *et al.*[24], pilocarpine containing solutions prepared at concentrations of 1 to 2 % were evaluated for stimulating salivary flow in healthy patients which revealed the efficacy of pilocarpine mouthwash solutions in increasing salivary flow in healthy volunteers, with no adverse effects. Mouth rinsing with these solutions induced a significant objective and subjective dose-dependent increase in salivary flow, similar to the results reported by others studying the effect of oral 5 mg pilocarpine. Although additional studies on patients with xerostomia are needed to substantiate this theory[24,25]. After, a prodrug for pilocarpine was developed to raising the solution stability, the European patent 106541. Without use for dry mouth, it is a pilocarpic acid derivative that can be converted to pilocarpine to the eye tissue, developing the cholinergic agonist action in the treatment of glaucoma.[26] If the mechanism could be described and if the effect was adapted for salivary glands maybe the side effects could be avoided with oral pilocarpine used in xerostomia. A big contribution for the knowledge of pilocarpine bioavailability was described for the world patent 9401108. For extended release tablet has established that the serum concentration of pilocarpine should be maintained between 4 and 40 ng / mL for a period of 6 hours for effective action against xerostomia, xerophthalmia and excessive intraocular pressure, with reduced side effects.[28] In this patent, eight patients were monitored while using the controlled release formulation and they showed no adverse effects.[29] However, the assignee companies Theratechnologies Inc.[30] and Oramed Inc.[31], the responsible for that patent, have no product on the market. An interesting innovation which could provide a reduction on side effects is a transdermal system that would enable to improve bioavailability and to maintain a constant and prolonged drug level with reduced frequency of dosing.[34] The adhesive for percutaneous absorption was prepared in Japanese patent 7 330 602. It consists of a film support with pilocarpine in free form and substances which absorb moisture.[32] The Pfizer Inc. holds the patent as an acquisition of Lederle Japan Ltd.[33], assignee of such patent. However, despite its potential therapeutic, there is no product on the market or research involving this pharmaceutical form of pilocarpine.

More interesting yet was the Korean patent 9606319 that describes a formulation of pilocarpine base flavored and sweetened chewing gum with a concentration ranging from 0.13 to 0.20 % of active pilocarpine. The mechanism of salivation is a result of sensory and mechanical stimulation. The first is represented mainly by smell or sight which leads to nerve stimulation of sympathetic and parasympathetic systems, resulting in the production, storage and release of saliva into the mouth. The second is represented mainly by chewing and leads to the release of pre-stored saliva in the salivary glands. Joining the two mechanisms was created the chewing gum that provides better mouth odor besides improve the speech due to salivary stimulation.[35] Unfortunately do not exist a commercial products of the patented form. Following the same reasoning Hamlar *et al.*[21] conducted a study using candy like pastilles of pilocarpine to promote the increase of salivary flow. There was subjective improvement in salivary flux although the mechanism has not been well understood if influenced by the drug or the simple mechanical stimulation of the pastilles. As expected there were significant complaints as to side effects.[25]

Other presentations which are based on topical application principles to the oral mucosa have arisen over the years (see Table 1) which may be commercialized in a short period of time. Another example is the Pilobuc™ Buccal Insert, a hydro gel polymer that releases pilocarpine in the oral mucosa, whose rights were purchased by Marillion Pharmaceuticals, to be marketed in the near future, but not yet determined.[41] Despite the competition from the market for to discover new promising drugs, new drug delivery technologies can benefit patients who did not had successful in the treatment of xerostomia. Advances in permeability modulation and formulations with appropriate enhancers can increase effectiveness in the oral drug delivery. A example is the mucoadhesive systems that provide for the drug an intimate

contact with oral mucosa which may result in appropriate concentration of the active in a local area with high efficacy and reduction of side effects.[42,43] The oral mucoadhesive gel, patent 200805520 from Brazil, has defined a composition based on pilocarpine, carboxymethylcellulose, pectin, mineral oil, mint, nipagim and water. This is a formulation with lasting local application where the drug will kept adhered on the oral mucosa, fastened onto the matrix polymeric of carboxymethylcellulose, being released slowly and continuously. In studies with rats good spread ability was obtained in its oral tissues besides good results in drug activity over the parotid glands. Furthermore was showed that oral gel applied only twice a day had effectiveness with no side effects.[44,45] Among the many patented products, the pilocarpine hydrochloride tablet (Salagen, MGI Pharma Inc., Minnesota, US) is definitely the only commercially available formulation. Despite the predisposition to side effects and the inconvenience of multiple daily doses, in general, the recommended dosage not exceeding 20 mg daily is well-tolerated by most patients.[25] Thus, pilocarpine hydrochloride is still the best way to prevent the undesirable effects of xerostomia.

Conclusion

The tablets form of pilocarpine hydrochloride is the only currently available on the market for the treatment of xerostomia and its use is indicated in addition to the treatment of diseases that causes dry mouth for a long time leading to serious damage to the mouth. However the systemic use of pilocarpine hydrochloride tablet is destined only for patients who tolerate the side effects of cholinergic drug. In this way the use of pilocarpine in patients with xerostomia have generated several patents focused on the administration forms. Although interesting and promising no other forms of application patented are available on market yet.

Conflict of interest statement

The authors report no conflicts of interest. The authors alone are responsible for the content and writing of this paper.

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