

Salivary stimulation by prolonged release of pilocarpine in Sjögren's syndrome.

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Abstract: Introduction: Prolonged drug delivery in the oral cavity offers many advantages, such as reducing adverse effects. Pilocarpine is an FDA-approved parasympathomimetic drug for the treatment of glandular hypofunction; however, its adverse effects limit its use. Objective: To evaluate the stimulation of salivary flow by the use of pilocarpine-releasing films, as well as their effects on the symptoms of xerostomia and adverse effects in patients with Sjögren's syndrome (SS). Materials and methods: Hydroxypropylmethylcellulose (Methocel K4MCR) films were prepared in 1% acetic acid and pilocarpine was added under magnetic stirring. The pH and thickness, as well as diffusion uniformity and kinetics of drug release per cm² were evaluated by spectrophotometry. The films were tested sublingually in 40 patients with Sjögren's syndrome for a period of two weeks. Changes in their salivary flow were evaluated by analyzing samples of total saliva. Additionally, patients were screened for symptoms of xerostomia and adverse effects. Results: The films had a pH of 2.91±0.035, a thickness of 0.06866±0.00152µm, and a diffusion uniformity of 91% per cm². Use of the films resulted in an increase in salivary flow in both primary and secondary Sjögren's syndrome, but this increase was only significant in primary SS. Conclusion: Films showed optimal physicochemical properties for their administration, and proved effective in stimulating salivary flow without causing adverse effects during their administration.

Keywords: *Hyposalivation; Sjögren's syndrome; pilocarpine; hydroxypropylmethylcellulose, xerostomia.*

INTRODUCTION.

Sjögren's syndrome is a slow progressive chronic autoimmune disease of unknown etiology,¹ with a prevalence of 0.1-3.0% at global scale.²

SS may occur as primary³ or secondary SS in conjunction with other autoimmune diseases such as rheumatoid arthritis⁴ and systemic lupus erythematosus.⁵ Prevalence of SS has been estimated at 300 to 600 per 100,000 people,⁶ being more frequent in adults in their fourth or fifth decade of life, with a female/male ratio of 9:1.⁷

Sialogogue drugs, such as pilocarpine, have a wide range of adverse effects.⁸ Alternative ways to administer these type of medicines have been sought in order to reduce their adverse effects, such as mouthwashes, spray,¹⁰ gel,¹¹ tablets/pills¹² and polymeric inserts.¹³

Local use of prolonged drug administration or delivery provides multiple advantages, such as increased pharmacological action at the desired site, reduction of drug dose and mitigation of adverse effects.¹⁴ In previous research it has been demonstrated that the local use of bioadhesive films

containing pilocarpine is effective for increasing the salivary flow *in vivo*.¹⁵ They have also proved to be biocompatible and possess the best physicochemical properties for this type their administration.¹⁶

The objective of this study was to evaluate the stimulation of salivary flow by the use of pilocarpine-releasing films, as well as their effects on the symptoms of xerostomia and adverse effects in patients with Sjögren's syndrome.

MATERIALS AND METHODS.

Design and population.

A cohort study, involving a 2-week follow-up period, was carried out. Evaluation was performed by a single examiner. Study subjects included patients with SS previously diagnosed by the Rheumatology Unit at Hospital Universitario at Universidad Autónoma de Nuevo León, Mexico.

Male and female patients with primary and secondary SS, aged 40 to 80 years old, were included in the study. Patients were excluded from the study who presented with another factor inducing hyposalivation that may have affected the outcome, such as: head and neck radiation therapy, history of Hepatitis C, Human Immunodeficiency Virus (HIV), pre-existing lymphoma, sarcoidosis, subjects with graft-versus-host disease, diabetes mellitus, and patients with a history of anticholinergic and parasympathomimetics drug use in the previous 4 months.

Patients who did not attend the follow-up appointments, who did not follow the treatment rigorously, those who stopped treatment during the time of experimentation and patients who developed any disease during the course of the study or ingested drugs that may have produced any changes in salivation were excluded from the study.

Sample size estimation considered a prevalence of 35%, an error of 14% and a confidence level of 95%. Ten patients were estimated for each group, resulting in a total of 40 patients.

Preparation of films

Hydroxypropylmethylcellulose (HPMC, Methocel K4M CR), donated by the company Colorcon from Mexico (Cuajimalpa, Mexico) and pilocarpine obtained

from Sigma-Aldrich Chemical Company (USA) were used to carry out the experimental studies.

In an aqueous solution containing 1% acetic acid, a formulation of HPMC (1.5g/100ml), 0.5mL/100mL of glycerin, was prepared adding a dose of pilocarpine (2.5mg/mL). The formulation was homogenized under magnetic stirring at 70°C for one hour. Afterwards, it was aliquoted into 15ml Petri dishes and air-dried for 24 hours, at which stage it was ready to use.

Evaluation of physicochemical properties of films

During the preparation of films, once the homogenization process was finished and the formulation cooled to room temperature, pH was recorded using a pH meter (UltraBASIC, Denver Instrument, USA).

After the films were dried and removed from the Petri dishes, their thickness was determined by means of a micrometer in five different zones, as described previously.¹⁶

To determine the uniformity of pilocarpine in the films, 2.5mg of pilocarpine were dissolved in 25mL of distilled water under magnetic stirring at 37°C for one hour, and absorbance was measured using a spectrophotometer (Genesys 10uv Scanning, ThermoFisher, USA) in a range of different wave lengths (200nm-500nm) at intervals of 10nm, in order to obtain a reference value that could be used as control, and the wave length at which the highest absorbance value was recorded was chosen as reference.

Once the reference value for the control with pilocarpine was obtained, 1cm² of the HPMC/pilocarpine film was taken and dissolved in 25mL of distilled water at 37°C under magnetic stirring for one hour, the absorbance of the solution was measured in order to determine the quantity of pilocarpine contained in the films.

To determine the drug release time of the HPMC/Pilocarpine film, 1cm² of the film was placed in 25mL of distilled water at 37°C under magnetic stirring. Additionally, in order to assess release kinetics, the optical density of the solution was measured every 15 minutes, over a period of 12 hours at 280nm, which was determined during the drug diffusion uniformity test as optimal.

Evaluation of salivary flow

In order to evaluate changes in the salivary flow produced by the films, the salivary flow rate was obtained by collecting a sample of total saliva from the

patients. During this procedure patients were instructed to remain seated and completely at rest, without moving facial muscles, the tongue or swallowing saliva for 5 minutes. Subsequently, the collected saliva was emptied into pre-weighed plastic microtubes.

After obtaining the samples, microtubes were weighed again. The total weight obtained minus the initial weight of the tube was calculated in order to obtain the rate of salivary volume in a period of 5 minutes. Then, this value was divided by 5 with the aim of finding the volume of saliva produced per minute. This procedure was performed before and after the placement of the films.

Application of films

Patients were given a brochure with information about the study and its benefits. In addition, a kit was provided for each patient. The kit included two boxes containing the films (previously sterilized with UV light), sterile tweezers and an instruction manual explaining how to place the films. The manual included a section for considerations and frequently asked questions.

The films were placed sublingually every 12 hours (9 am and 9 pm) for two weeks. For this, patients had to use the included sterile tweezers. Once the film was adhered to the mucosa, the patient was able to perform any subsequent activity, except smoking and drinking alcohol.

Evaluation of xerostomia and adverse effects

The evaluation of xerostomia consisted of a symptomatology survey and a clinical evaluation. The questionnaire was applied before and after the treatment, and included questions regarding difficulty speaking, difficulty swallowing solid or dry foods, dysgeusia, dry lips and throat, a burning sensation on the tongue, mouth breathing, dry eyes and the frequent need for drinking fluids. To answer these questions, the patient had three options: “No”, “Often” or “A few times”.

Clinical evaluation consisted of three aspects; each

of them was given a value to determine the degree of dryness. The first aspect was lip dryness where: 0=Normal, 1=Dryness of the vermilion zone and 2=Presence of angular cheilitis. The second aspect was the dryness of the mucous membranes where: 0=Normal, 1=Dry without causing the tongue depressor to stick, 2=Very dry causing the tongue depressor to stick; and 3=Very dry causing the tongue depressor to stick and without detecting parotid ducts.

At the end of treatment, a survey was conducted on the presence of adverse effects, questioning patients about anxiety symptoms, excessive sweating, nausea or vomiting, gastritis or heartburn, palpitations, difficulty breathing, increased urinary frequency, spontaneous tearing eyes, as well as their experience with the films.

Ethical Considerations

This study was approved by the Bioethics Committee of Universidad Autónoma de Nuevo León (SPSI - 010613. Folio: 0094). Before enrollment and reviewing of medical history, each patient signed an informed consent form.

Data analysis

Results were analyzed by means of ANOVA and Tukey HSD tests to identify specific groups that showed significant results among them, both with 95% reliability (IBM SPSS Statistics, Version 20, USA and Microsoft Excel 2010).

RESULTS.

Results showed that the formulation of the films had a mean pH of 2.91 ± 0.035 . The thickness of the films was measured in five different zones to obtain a uniform mean thickness of $0.06866 \pm 0.00152 \mu\text{m}$.

The mean optical density of pilocarpine dissolved in 25mL of distilled water at 280nm was 0.034 ± 0.00057 . Subsequently, absorbance of film was performed under the same conditions, obtaining 0.031 ± 0.00058 , resulting in a uniformity of 91% per cm^2 .

During release kinetics relative to the uniformity of

Table 1. Initial and final sialometry.

	Primary Sjögren		Control		Secondary Sjögren		Control	
	Mean	SD	Mean	SD	Mean	SD	Mean	SD
Initial	0.170*	0.246	0.359	0.416	0.153	0.255	0.161	0.167
Week 2	0.298*	0.333	0.376	0.436	0.224	0.320	0.154	0.163
p-value	0.047		0.053		0.135		0.057	

*SD: Standard Deviation.

Table 2. Evaluation of symptomatology of initial and final xerostomia.

Item	Primary Sjögren			Control			Secondary Sjögren			Control		
	No	Often	Few time	No	Often	Few time	No	Often	Few time	No	Often	Few time
Initial												
Do you experience difficulty speaking due to dry mouth?	50%	20%	30%	33%	50%	17%	25%	50%	25%	38%	13%	50%
Do you have difficulty swallowing solid or dry food?	20%	40%	40%	17%	33%	50%	38%	50%	13%	38%	0%	63%
Do you think your meals have no taste?	60%	0%	40%	33%	17%	50%	38%	38%	25%	50%	50%	0%
Do you feel a burning sensation on your tongue?	60%	20%	20%	33%	50%	17%	38%	25%	38%	50%	13%	38%
Do you feel your lips dry?	40%	30%	30%	0%	83%	17%	13%	75%	13%	50%	13%	38%
Have you had swollen salivary glands in adulthood?	70%	20%	10%	67%	17%	17%	63%	25%	13%	100%	0%	0%
Do you need to get up during the night to drink fluids	70%	10%	20%	17%	0%	83%	63%	0%	38%	50%	0%	50%
Do you usually breathe through your mouth?	60%	10%	30%	67%	0%	33%	38%	25%	38%	13%	38%	50%
Do you feel your eyes dry?	0%	80%	20%	0%	83%	17%	13%	63%	25%	0%	13%	88%
Do you feel dryness in your throat?	30%	50%	20%	0%	83%	17%	38%	63%	0%	0%	88%	13%
week 2												
Do you experience difficulty speaking due to dry mouth?	80%	0.0%	20%	83.3%	0.0%	16.7%	50%	0%	50%	100%	0%	0%
Do you have difficulty swallowing solid or dry food?	60%	0%	40%	83.3%	16.7%	0%	25%	25%	50%	62.5%	37.5%	0.0%
Do you think your meals have no taste?	80.0%	0%	20.0%	83.3%	0%	16.7%	75%	12.5%	12.5%	50%	12.5%	37.5%
Do you feel a burning sensation on your tongue?	100%	0%	0.0%	66.7%	0%	33.3%	100%	0.0%	0.0%	87.5%	0.0%	12.5%
Do you feel your lips dry?	40.0%	20.0%	40.0%	33.3%	33.3%	33.3%	62.5%	12.5%	25.0%	12.5%	0.0%	87.5%
Have you had swollen salivary glands in adulthood?	90.0%	0.0%	10.0%	100%	0.0%	0.0%	87.5%	12.5%	0.0%	50.0%	37.5%	12.5%
Do you need to get up during the night to drink fluids	80.0%	0.0%	20.0%	100%	0.0%	0.0%	87.5%	0.0%	12.5%	75.0%	0.0%	25.0%
Do you usually breathe through your mouth?	80.0%	0.0%	20.0%	50.0%	0.0%	50.0%	62.5%	25.0%	12.5%	50.0%	25.0%	25.0%
Do you feel your eyes dry?	10.0%	30.0%	60.0%	50.0%	33.3%	16.7%	37.5%	37.5%	25.0%	25.0%	62.5%	12.5%
Do you feel dryness in your throat?	50.0%	10.0%	40.0%	83.3%	16.7%	0.0%	37.5%	37.5%	25.0%	25.0%	62.5%	12.5%

Table 3. Initial and final clinical evaluation.

Item	Primary Sjögren			Control			Secondary Sjögren			Control		
	0	1	2	0	1	2	0	1	2	0	1	2
Initial												
Dryness of lips	50.0%	50.0%	0.0%	0.0%	100%	0.0%	12.5%	75.0%	12.5%	12.5%	87.5%	0.0%
Dryness of the mucosa	10.0%	70.0%	20.0%	16.7%	66.7%	16.7%	0.0%	100%	0.0%	12.5%	87.5%	0.0%
Palpation of the major salivary glands	90.0%	10.0%	0.0%	83.3%	16.7%	0.0%	75.0%	25.0%	0.0%	100%	0.0%	0.0%
Week 2												
Dryness of lips	50.0%	50.0%	0.0%	0.0%	100%	0.0%	12.5%	87.5%	0.0%	12.5%	87.5%	0.0%
Dryness of the mucosa	70.0%	30.0%	0.0%	0.0%	100%	0.0%	12.5%	87.5%	0.0%	12.5%	87.5%	0.0%
Palpation of the major salivary glands	100%	0.0%	0.0%	100%	0.0%	0.0%	100%	0.0%	0.0%	100%	0.0%	0.0%

Table 4. Evaluation of treatment with pilocarpine.

Item	Primary Sjögren			Control			Secondary Sjögren			Control		
	No	Often	Few times	No	Often	Few times	No	Often	Few times	No	Often	Few times
Did experience anxiety and/or tremors?	100%	0.0%	0.0%	83.3%	0.0%	16.7%	87.5%	12.5%	0.0%	100%	0.0%	0.0%
Did you experience increased sweating?	90.0%	0.0%	10.0%	100%	0.0%	0.0%	75.0%	12.5%	12.5%	100%	0.0%	0.0%
Did you feel nauseous or vomited?	90.0%	10.0%	0.0%	100%	0.0%	0.0%	87.5%	0.0%	12.5%	100%	0.0%	0.0%
Did you experience gastritis or heartburn?	80.0%	0.0%	20.0%	100%	0.0%	0.0%	87.5%	0.0%	12.5%	100%	0.0%	0.0%
Did you experience palpitations or increased heart rate?	100%	0.0%	0.0%	100%	0.0%	0.0%	100%	0.0%	0.0%	100%	0.0%	0.0%
Have you had difficulty breathing?	100%	0.0%	0.0%	100%	0.0%	0.0%	100%	0.0%	0.0%	100%	0.0%	0.0%
Did you notice an increase in urinary frequency?	80.0%	10.0%	10.0%	83.3%	0.0%	16.7%	87.5%	0.0%	12.5%	100%	0.0%	0.0%
Did you have a tearing eye?	60.0%	0.0%	40.0%	100%	0.0%	0.0%	100%	0.0%	0.0%	75.0%	0.0%	25.0%
Do you think the administration of films alleviated the dryness in your mouth?	0.0%	40.0%	60.0%	33.3%	16.7%	50.0%	25.0%	37.5%	37.5%	0.0%	0.0%	100.0%
Did you suffer from irritation or feel any discomfort in the oral mucosa because of the films?	100%	0.0%	0.0%	100%	0.0%	0.0%	100%	0.0%	0.0%	100%	0.0%	0.0%

the drug, it was observed that the release rate was 55% at 30min, 88% at 1hr, 91% at 1h 30min, 97% at 2hr and 2hr 30m and 100% from 3 to 4hr.

The results of the evaluation of the salivary flow before and after the treatment are shown in Table 1, symptomatology in Table 2, clinical xerostomia in Table 3 and adverse effects in Table 4.

DISCUSSION.

Due to the wide variety of adverse effects of sialogogue drugs, alternative ways to administer this type of medicines have been sought in order to mitigate their adverse effects. The local use of prolonged delivery of drugs through films provides multiple advantages, increasing the pharmacological action at the desired site, reducing the dose used and mitigating adverse effects, in addition to avoiding hepatic metabolism, gastric irritation and enzymatic degradation by the gastrointestinal environment.¹⁷ *In vivo* and *in vitro* oral administration methods based on chitosan and HPMC have been recently developed for the prolonged release of drugs such as pilocarpine, becoming a promising means for controlled delivery method in the oral cavity.¹⁵

Lockhart *et al.*,¹⁸ pioneered studies on the controlled release of pilocarpine. They proposed the administration of three doses of 15mg of pilocarpine hydrochloride at 12 hour intervals. The formulation was designed to release 5mg for the first 2 hours, 11mg for the next 8 hours and the remaining drug for the next 4 to 6 hours. The initial salivary flow rate of 0.6mL/min was increased to 1.25mL/min during the first hour of initial administration, and at 4 hours the salivary flow was double the initial measurement, then declining to 1.14mL/min at

10 hours. Likewise, the first dose of the second administration increased the salivary flow to 1.28mL/min and the third dose to 1.37mL/min during the first two hours, however, although this result was satisfactory, its application was not an intrabuccal local application.

Gibson *et al.*,¹³ evaluated the controlled release of pilocarpine by intrabuccal polymer inserts in patients with Sjögren's syndrome. They designed a polymer hydrogel buccal insert 17x5mm in size and 0.6mm thick, containing 5mg of pilocarpine hydrochloride, which should be placed 3 times a day and changed every 3 hours. Their results suggest that there is a marked improvement in salivary flow rate from day 8 of treatment, with an increase from 0 to 1.2mL, maintaining that high salivary flow rate for 4 days. However, although their study found excellent salivary flow rates, it was only conducted on seven patients; researchers did not describe the formulation used or the methods of verifying the uniformity of the drug in the polymer insert. Nevertheless their findings coincide with the present study in finding a stimulation of salivary flow in primary SS.

Previous studies have evaluated the physicochemical, antimicrobial, cytotoxic and sialogogue properties; the results showed that films have the best physicochemical properties for their mode of administration, a high cell viability, produce considerably increased salivary flow, but do not show antimicrobial activity.¹⁶

CONCLUSION.

Films showed optimal physicochemical properties for their manipulation and administration, with the total release of the drug after 3h in an aqueous medium. They also proved effective in stimulating salivary flow in primary and secondary SS, without causing adverse effects.

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