Original Article

Characterization and Formulation of Miswak Film for the Treatment of Chronic Periodontitis: An In Vitro Study

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INTRODUCTION

Periodontitis is a pathologic condition that affects the supporting structures of the teeth. It causes destruction of periodontal ligament, loss of alveolar bone, and apical migration of periodontal ligament. It is an inflammatory response to the plaque accumulation in periodontal pocket.[1] Bacteria in plaque are the primary cause but they cannot explain rapid periodontal breakdown in patients with minimal plaque accumulation. The role of herpesviruses are suspected in such cases. Herpesviruses are isolated from gingival crevicular fluid and periodontal tissues.[2] Periodontitis is treated by mechanical debridement and systemic antibiotics. Mechanical debridement cannot be done effectively in teeth with complex anatomic root structure.[3] They also fail to totally eliminate bacteria such as Porphyromonas gingivalis and Aggregatibacter actinomycetemcomitans due to their invasive nature into gingiva and the surrounding tissues. This leads to the use of antimicrobials to overcome the shortcomings of mechanical debridement.[4] Systemic antibiotics, such as penicillins, tetracycline, and metronidazole, have the drawback of developing gastrointestinal disturbances and drug resistance, and they also fail to achieve adequate concentration at the site of action.[3] To overcome these shortcomings, local drug delivery (LDD) system has been developed.[4]

People are turning back to nature for solutions to various ailments. Various herbal products are used nowadays. The use of chewing sticks to brush our teeth is a well-known...
practice in rural India. Miswak is a lesser known chewing stick [Figure 1] in India, but it is commonly used in Arabic countries. Its botanical name is *Salvadora persica*. It is basically a small tree, approximately 3 m in height. The leaves, flowers, berries, and sticks have medicinal properties. They are traditionally used to treat cough, asthma, scurvy, piles, and rheumatism. They have mustard smell and pungent taste.

Miswak sticks have various constituents with beneficial effects, listed as the following:

- Silica: Abrasive material to remove plaque
- Tanins: Reduces gingivitis and the level of *Candida albicans*
- Resins: Forms a layer over enamel and prevents dental caries
- Alkaloids: Antifungal and antibacterial activity
- Sulfur: Antibacterial activity
- Vitamin C: Tissue repair
- Sodium bicarbonate: Dentifrice
- Calcium: Enamel remineralization
- Fluoride: Anticariogenic activity
- Chloride: Inhibit calculus formation
- Benzyl isothiocyanate: Anticarcinogenic and antibacterial activity
- Trimethylamine: Antibacterial activity

LDD can provide sustained release of drug at the site of periodontal pocket. They can provide effective treatment at a much smaller dose. Various forms of LDD that can be used at the site of periodontal pocket are films, gels, fibers, strips, nanoparticles, and microparticles. Hydroxypropyl methylcellulose (HPMC) is a creamy white granular or fibrous powder used in pharmaceutical preparations. It is most widely used because of its various advantages such as chemical inertness, safety, stability, regulation of viscosity, metabolically inert, and solubility in water. Eudragit is a polymer that usually has the capacity to combine with active agents or drugs to release drugs at a specific rate. Miswak possesses many properties, which can used to treat periodontitis. So miswak can be added with HPMC and Eudragit to prepare an LDD agent in the form of film to be placed in periodontal pockets.

The aim of this study was to formulate and characterize an LDD agent in the form of film to deliver miswak at the site of action for the treatment of chronic periodontitis.

**Materials and Methods**

The study was conducted in the department of pharmaceutical biotechnology, JSS College of Pharmacy, Ooty, Tamil Nadu, India. Certified miswak powder [Figure 2] was procured commercially from Vilumin Herbals through IndiaMART traders. Miswak extract was obtained from this powder.

The minimum inhibitory concentration (MIC) against *P. gingivalis* and MTT (3-[4,5-dimethylthiazol-2-yl]-2,5-diphenyltetrazolium bromide) antiviral assay against herpes simplex virus-1 (HSV-1) of this miswak extract was calculated. The specified bacteria and virus are important pathogens involved in chronic periodontitis. They were collected from the stock preserved in college. The MIC against *P. gingivalis* was calculated to be 62.5 µg/mL. The therapeutic index against HSV-1 was calculated to be 11.03 µg/mL. The half minimal inhibitory concentration (IC₅₀) was calculated to be 18.6 µg/mL. The cytotoxicity concentration against 50% cells (CC₅₀) was 210 µg/mL. The cell line Vero (African green monkey, kidney) was used. This cell line is comparable to human cells.

The raw materials used for preparing miswak film are as follows:

1. Miswak raw extract (Vilumin Herbals, Indore, India)
2. HPMC K 100: HPMC (Colorcon Asia, Goa, India)
3. Eudragit L 100 (Evonik Roehm Pharma, Mumbai, India) is a pharmacologically inert, extended-release matrix-forming agent. HPMC K 100[7] is a pharmacologically inert, extended-release matrix-forming agent. Eudragit L 100 is also a pharmacologically inert material. It adds stability[8] to HPMC K 100. Both HPMC K 100 and Eudragit L 100 are used to prepare film coat tablets and oral capsule.

**Calculation of dose**

From the microbial and viral studies, 100 µg of miswak was calculated to be the ideal dose. This 100 µg is dispersed in a film of size 2 cm². This film size is suitable for placement in periodontal pocket.

\[ >2 \text{ cm}^2 \]

Equivalent to 100 µg/mL

\[ 0.5 \times 0.4 \text{ cm} \]

The dose was selected because of the following reasons:

1. The film remained stable.
2. It can exhibit therapeutic activity against *P. gingivalis* and HSV-1.
3. It does not show cytotoxic effect.
4. It helps to obtain extended-release activity.

The dental film is prepared by using solvent casting method. Area of the casting plate is 100 cm² (10 × 10 cm). The amount of miswak raw extract for 100 cm² is calculated to be 5 mg (100 cm² / 2 cm²).

\[ >100 \text{ cm}^2 \]

Equivalent to 5 mg (100 / 2 cm² = 50 fold)

10 × 10 cm

**Solvent casting method**

Here the water-soluble materials are dissolved to form a viscous solution [Figure 3]. The steps involved in the miswak film preparation are:

- **Step 1:** 3% of HPMC K 100 and 1.5% of Eudragit L 100 are taken in a empty beaker.
- **Step 2:** 100 mL of 1:1 ratio of ethanol and water are added to the aforementioned mixture. Calculated quantity of miswak raw extract is added to the solution.
- **Step 3:** Thorough mixing with mechanical stirrer at 750 rpm for 30 min is carried out.
- **Step 4:** The solution is kept undisturbed for 12 h to remove air bubbles. Later, it is casted in casting plate of 100 cm².

This results in the formation of a film of uniform property and thickness [Figure 4]. Later, it is cut into pieces of desired size.[11]

**Disintegration test**

The film of 0.5 × 0.4 cm was subjected to disintegration in phosphate buffer at pH 6.8 in a plastic vial of 5 mL capacity [Figure 5]. The vial was agitated occasionally (approximately once every 1 h) and controlled at 37°C.[12]
The film was observed to completely disintegrate into solution at the end of 137 h (5 days 17 h).

**Discussion**

In our study, we had attempted to create an LDD agent containing miswak in the form of film for the treatment of periodontitis. No such formulation has been attempted so far. This is the first time such an attempt has been made.

Al Sadhan and Almas[13] in 1999, in his article has discussed about miswak, their composition and their properties. Shetti et al.[14] in 2016, had shown that miswak in the form of mouthwash reduced plaque score and gingival score effectively. A review by Sukkarwalla et al.[15] in 2013, showed that miswak shows antibacterial property against various gram-positive and gram-negative bacteria.

In our study, we studied the antibacterial effect against *P. gingivalis* and antiviral effect against HSV-1. *P. gingivalis* is a common periodontopathic bacteria.[16] Recent studies show that HSV-1 has been positively related to chronic periodontitis.[16] The therapeutic dose against *P. gingivalis* was calculated to be 62.5 µg/mL. The therapeutic index against HSV-1 was calculated to be 11.3 µg/mL. Cell cytotoxicity was calculated to be 210 µg/mL, which was done on Vero cells. These cell lines are the most commonly used mammalian cell line for the study of bacteria, virus, and various chemicals.[17] The antibacterial and antiviral activity could be due to benzy1 isothiocyanate in miswak raw extract.[13]

Keeping the aforementioned results in mind, a dose of 100 µg/mL was selected. This dose can act against *P. gingivalis* and HSV-1; also, it is not cytotoxic to cells. This dose was used to create the miswak film. Delivering antimicrobial in the form of LDD provides 100-fold greater concentration than a systemic regimen.[19]

The film is made of polymers HPMC K 100 and Eudragit L 100. They are basically a type of HPMC and Eudragit. HPMC is nontoxic and water soluble. Antimicrobials can be mixed with HPMC without affecting their nature. HPMC is also chemically inert and not absorbed or metabolized in human body.[7] Eudragit provides adhesive property and decreases the drug release rate. So it is mixed with HPMC to enhance its drug-release properties.[9]

The film, thus formed by the mixture of miswak raw extract, HPMC K 100, and Eudragit L 100, was subjected to disintegration test. The test showed that the film remained considerably stable and underwent complete disintegration only after 5 days 17 h. This showed that the film can release the miswak extract at the site of periodontal pocket for around 5 days.

**Conclusion**

In this study, we formulated the miswak raw extract–containing film. This film can act against *P. gingivalis* and HSV-1. It does not affect the mammalian cells and remains stable for around 5 days. So it can be used to treat chronic periodontitis by placing it in periodontal pockets.

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**Conflicts of interest**

There are no conflicts of interest.

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