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FORMULATION, OPTIMIZATION AND CHARACTERIZATION OF FAST-DISSOLVING SUBLINGUAL FILM CONTAINING CLOVE OIL

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ABSTRACT: Clove oil is an essential oil made from the plant, Szygium aromaticum. It is commonly used to help ease digestive issues, relieve pain, and support respiratory conditions. This work aims to determine at what temperature sublingual films are formed most effectively during process. The given temperature batches were manufactured at 75 °C, 80 °C, 85 °C, 90 °C. The sublingual films were prepared by using the solvent casting method, and the materials used, such as Hydroxypropyl methylcellulose E5, and different grades of polyox were previously optimized. The various batches at different temperatures went through characterization regarding the viscosity of the solution before casting as well as film weight and thickness after casting. All other samples used were of 21 mm x 25 mm film. With these given film samples from each batch, surface pH, swelling index, folding endurance, tensile strength, disintegration time, and percent moisture were all tested. Thus, this study showed the optimum temperature for fast-dissolving sublingual films of clove oil to improve bioavailability and ease of administration.

INTRODUCTION: Sublingual films are rising as an innovative advancement in pharmaceutical and nutraceutical products. As a recent drug delivery technology advancement, sublingual films dominate the global market due to their effectiveness and convenience. Sublingual films are thin oral films containing an active pharmaceutical ingredient (API). These specific films are placed under the tongue and intended to dissolve the API without drinking water or chewing rapidly.

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Sublingual films are becoming more beneficial over traditional tablets due to their high bioavailability and patient compliance [1]. Sublingual films are much easier to intake for geriatric, pediatric, or ill patients who have trouble with swallowing. This also eliminates the danger of choking on large tablets. The ease of swallowing the sublingual films also makes it attractive to patients as the most oral environment of the mouth, and the thinness of the oral film allows the API to disintegrate within a patient's mouth easily.

Many drugs are absorbed well through the mouth and esophagus as saliva passes through them to reach the stomach. Compared to tablets, sublingual oral films will dissolve faster within the mouth, increasing its bioavailability. Many tablets are very fragile due to their softness or brittleness.

This requires more advanced and expensive packaging, making the tablets much more expensive on the consumer and producer side. However, sublingual films are more flexible and elastic, requiring simpler and cheaper packaging. Sublingual films have added sweeteners and taste maskers to make them much more palatable for younger patients. Sublingual films are very stable and contain a consistent dosage. The producers premade the films for dosage accuracy rather than relying on the consumer to measure it themselves.

The sublingual films are formulated using the main API and many other excipients affecting the product's performance and aesthetics. These include hydrophobic polymers, plasticizers, penetration enhancers, saliva stimulating, sweetening, flavoring, and coloring agents. The active pharmaceutical ingredients (API) make less than 25% of the polymer weight. The APIs that work best with sublingual films are usually potent and have high first-pass metabolism [1]. Due to the thinness of the oral films, it can easily break, so polymers are generally used to strengthen the film.[1] Pullulan is a popular polymer due to its low cost and efficiency [1]. Polymer films are usually paired with the best plasticizer to obtain the most desired characteristics. While polymers are used to strengthen the film, plasticizers are used to elongate and make the film more flexible [1].

It also reduces the glass transition temperature of the polymer. The weight of the plasticizers is generally less than 20% of the weight of the polymer. However, these values depend on the specific polymer and plasticizer being used. Penetration enhancers are used to increase the bioavailability of the API as they help penetrate intercellular lipid packing using fatty acids [1]. These penetration enhancers should be non-irritant and must reform the barrier of epithelium. Saliva stimulating agents are used to increase the saliva production rate to help dissolve the oral films faster. Usually, acids, such as citric and lactic acids, are used to stimulate saliva within the mouth. This is an important piece of sublingual oral films as it is marketed to not require water to dissolve. Sweetening agents improve the aesthetic characteristics of the film to help combat the bitter taste of the film. These artificial sugars, such as fructose and sucralose, easily dissolve within the oral cavity [1]. Polyhydric alcohols are significantly attractive due to their pleasant taste and cooling properties. Depending on consumer preference, flavoring agents can range from strong mints to sweet fruits. The flavor agents are derived from essential synthetic oils derived from plants. Coloring agents are another aesthetic enhancement to make the film more pleasing to consume. These natural colors are usually pigmenting of natural juice concentrates.

MATERIALS AND METHODS:

Materials: Polyethylene Oxide, NF/USP (Sentry Polyox WSR N10-Leo) and Polyethylene Oxide, NF (Sentry Polyox WSR 1105-Leo) were kindly supplied by Colorcon (Indiana, USA). Polyethylene Glycol 8000 Powder is supplied from The Dow Chemical Company (Illinois, USA). Polyethylene Oxide, NF/USP (Sentry Polyox WSR N80-Leo), Hydroxyl Propyl Methyl Cellulose and Hydroxypropyl Methylcellulose are kindly supplied from Nutrition & Biosciences (Illinois, USA). For the HPMC base Povidone (ISP Technologies, Texas, USA) and Edetate Disodium (Merck KGaA, Barcelona) were also purchased. Citric Acid Anhydrous (Avantor Performance Materials, Pennsylvania, USA) and Sodium Citrate Dihydrate (AMIJAC Chemicals, Mumbai, India) were purchased for drug suspension. Maltitol was kindly supplied by Roquette America Inc. (Iowa, USA) and Acesulfame Potassium was supplied by Anhui Jinhue Industrial (Anhui, China). For aesthetic consumption purposes, Yellow No.10 Powder (Sensient Colors LLC, Missouri, USA) and Clove Oil were purchased. All the solutions were prepared using purified water. Other reagents and chemicals were of analytical grade.

Preparation of Sublingual Fast Dissolving Oral Film Solution: Place the purified water (1733.3 g) under the stirrer and add PEG 8000 (40 g) plasticizer to the water. Sift and add Polyethylene Oxide National Formulary (90 g), Polyethylene Oxide National Formulary (200 g), Polyethylene Oxide National Formulary/USP (90 g) through 20# sieve to create a homogenous solution. 250 grams of purified water are heated to 55 degrees Celsius and Edetate sodium (10 g) is added in. Hydroxyl propel methylcellulose E5 (3 g) and HPMC E15 (11.6g) is stirred in to create cloudy homogenous mixture. 138.7 grams of purified water is mixed

with saliva stimulating agents, Citric acid anhydrous (40 g) and sodium citrate (20 g), which is manually stirred to create a homogenous viscous solution. Within 156.7 grams of purified water, Povidone (10 g) is stirred under a mixer to create a homogenous viscous solution. Finally, all solutions are mixed together and aesthetic characteristics such as FD & C Yellow No.6 Powder (0.3g) and Mint Flavoring (2g) were directly added to the final solution. The solutions then went through the casting system where they were thinly laid out and then dried. The solutions dried at 4 different temperatures: 75°C, 80°C, 85°C, and 90°C which were labeled MRF-001, MRF-002, MRF-003 and MRF-004, respectively. Each batch was carried out to be 2 feet in length.

Rheological Properties and Viscosity of Casting Solutions: The Viscometeris used to determine the viscosity of solution. Given that the solution is more viscous than the example solution, the L4 measuring system is used and at a low RPM (2-8) to keep torque less than 100%. All measurements were carried out at 25 degrees Celsius [4].

Film Weight and Thickness: The weight is determined by weighing the 1 foot of film on a digital analytic scale (Mettler Toledo Pre-590, Ohio, and USA). The film thickness is determined by using a caliper (Mitutoyo Absolution Digmatic 500, USA) on a random position on the film.

Surface pH: Two sublingual films are placed in 6 mm diameter petri dishes with 1 mL of purified water for 8 min at room temperature. The pH is then measured using a calibrated pH probe (Fisher Scientific QCL #150, USA) which makes close contact with the wet top part of the surface of the film [4].

Swelling Index: Each dry film from the batches are weighed before to obtain the initial weight of the film using a balance (Mettler Toledo Pre-590, Ohio and USA). This is done by placing the dry film on a Petri dish with 4 mL phosphate buffer at room temperature. Then, the excess liquid surrounding the film is removed by using a pipette and clean cloth. The weight of the film, in the petri dish, is measured again. The Petri dish is pre-weighed and subtracted from the preliminary and concluding weight found.

Swelling Index Equation: $(W_2 - W_1) / W_1 \times 100\%$

W_2 being the weight of the film and W1 being the weight of the film after swelling. This is all multiplied by 100 to see the swelling index percent [4].

Folding Endurance: Folding endurance correlates to the brittleness of the film. The films are repeatedly hand folded in the same position until any visible cracks are demonstrated or the film breaks.[3]

Tensile Strength: Testing the tensile strength shows the force, in Newtons, needed to break the film completely. A clamp (Chatillon Ametek C5 225 Series, Florida, and USA) pulls the film apart at 250mm/min. This test is performed to 3 different films from each batch.

Disintegration Test: The disintegration test is performed by placing each film in small tubes and repeatedly dipping and rising them into solvent using DISEK (Disintegration System 300). This is used to simulate conditions of the mouth where the film will be dissolved. The solvent temperature is kept at 37 degrees Celsius. This is performed on 3 different films from each batch [5].

Percent Moisture: Film is cut into small pieces and 1 gram of the small pieces are placed in LOD (OHAUS). LOD dries the piece of film for over 2 minutes and takes up the percent moisture value.[5]

Percent Moisture content = (Initial Weight-Final Weight) / (Final Weight) × 100%

RESULTS AND DISCUSSION:

Rheological Properties and Viscosity of Casting Solutions: Fig. 1 demonstrates the viscosity curves of the formulation used to prepare the sublingual films. Due to the content of the films, a highly viscous solution is required to produce the sublingual films. The viscosity ranged from 9000 cP to 7400 cP through various rpm (revolutions per minute values which ranged from 2 to 8), proving that the solution is very viscous. Having a viscous solution for sublingual film is beneficial to strengthening the film and protecting it from the casting engine's high temperature. It is also important to have a viscous solution to prevent leaking through the side of the plate and in casting.

However, as the rpm gradually increases by 1, the viscosity decreases, showing lower resistance to flow. Such a decrease in viscosity demonstrates that the material is of pseudo-plastic flow and flows as a plastic at high shear rates. Pseudo-plastic solutions with high viscosities are optimal in making sublingual films.

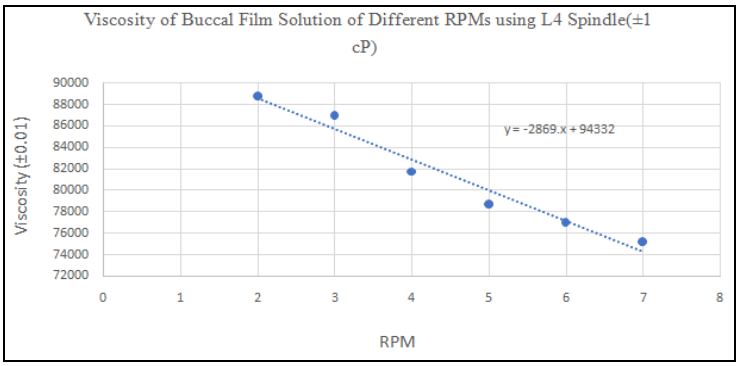

FIG. 1: VISCOSITY OF CASTING SOLUTION AT VARIOUS RPM (2-8) USING L4 SPINDLE. CALCULATIONS AND GRAPHS WERE FORMATTED USING EXCEL

Film Weight, Thickness: The film weight of one foot for MRF-001 (6.28 ± 0.659 g), MRF-003 (6.54 ± 0.659 g) and MRF-004 (6.41 ± 0.659 g) are of similar weight; however,, MRF-002 (4.91 ± 0.659 g) is much lower. The thickness of each batch if film was also very similar. MRF-001 was 0.14mm thick, MRF-002 was 0.11mm, MRF-003 and MRF-004 were 0.12 mm thick. Although the temperature was altered for the various batches, this rarely seems to affect the weight or thickness of the films.

Surface pH: Surface pH tended to increase as the temperature increased. The pH found from the two films that were tested were averaged to get the average pH of the films. For MRF-001, it was 4.53 pH, MRF-002 was 5.66 pH, MRF-003 was 5.70 pH and MRF-004 was 6.35pH. The pH showed that the film is acidic when simulated to feel like it is in the mouth. However, the higher the temperature, the more basic it becomes.

Swelling Index: The swelling index shows that every 2 minutes after 1 min, the sublingual film logarithmically swelled until slowing down by 9 minutes time. The values shown in **Table 1** indicate the percent increase after the given number of seconds. For MRF-001, the swelling index increased greatly from 60 seconds to 180 seconds; however, began to slow down and eventually remained the same at 410 seconds and 630 seconds at 44.9%. MRF-002's swelling index quickly increases from 47.7% to 95.4% between 180 seconds and 300 seconds. The index remained the same at a high number of 95.4%. MRF-003's swelling index quickly increased from 38.6% to 62.5% between 60 seconds and 180 seconds. It then gradually increased for the following about of time until 630 seconds. Similarly, for MRF-004, the swelling index quickly increased from 33.2 % to 50% between 60 seconds and 180 seconds but slowed down for the remaining amount of time up to 630 seconds. The highest swelling index ended up being for MRF-002. MRF-002's swelling index also quickly increased as it reached its maximum swelling by 300 seconds. MRF-001 had the lowest swelling index at 44.9% at 630 seconds. This was its maximum swelling as it had the same index as 420 seconds.

TABLE 1: SWELLING INDEX WEIGHTS EVERY AT 1 MINUTE, 3 MINUTES, 5 MINUTES, 7 MINUTES, AND 9 MINUTES FOR ALL FOUR BATCHES. ALL CALCULATIONS AND FORMATTING WERE DONE USING EXCEL

	Swelling index (±0.1%)			
Number of Seconds (±1 s)	**MRF-001**	**MRF-002**	**MRF-003**	**MRF-004**
60	1.20	34.6	38.6	33.2
180	25.1	47.7	62.5	50.0
300	37.1	95.4	87.5	57.4
420	44.9	95.4	89.8	64.7
630	44.9	95.4	92.0	66.2

Folding Endurance: The folding endurance decreased as the temperature increased through the batches as there was a slight gradual decrease from MRF-001, which had to 11 folds without visible crack, to MRF-002, 10 folds, to MRF-003, 8 folds, to finally MRF-004, which only after 7 folds was there visible breaks within the film. The higher the folding endurance, the more elastic or flexible it is therefore, the flexibility decreases as the temperature increase.

Tensile Strength: After averaging the data for the tensile strength of three different films for each batch, it was noticeable to see more force (Newtons) was required to break the film as the temperature of the film batches increased. MRF-001 required 28.0 N, MRF-002 required 29.7 N, MRF-003 required 33.7 N, and MRF-004 required 34 N to break the 21mm x 25mm film. As the force needed gradually increased per batch, the higher the temperature, the higher the tensile strength.

Disintegration Test: The average disintegration time for the four batches did not directly correlate with the temperatures the Batches were casted at. The values taken to find the average are shown in **Fig. 2**. The average disintegration time for MRF-001 was 126 ± 67 seconds. The average disintegration for MRF-002 was 329 ± 235 seconds. The average disintegration for MRF-003 was 166 ± 22 seconds. The average disintegration time for MRF-004 was 459 ± 244 seconds. The high standard deviation for MRF-002 and MRF-004 show many errors in the testing process. Due to the thinness of the film and the small size of the Disintegration System tubes, it will be difficult to properly place the film. However, MRF-001 has the shortest disintegration time making it best for developing the sublingual film. The faster the disintegration time, the faster it can dissolve in the patient's mouth and reach other body parts.

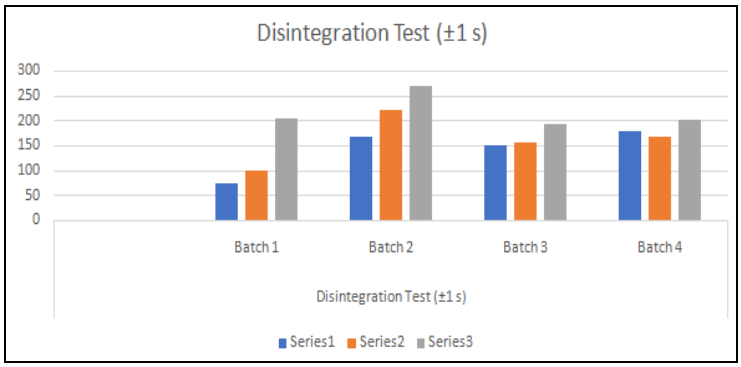

FIG. 2: THE AMOUNT OF TIME EACH FILM WITHIN THE FOUR BATCHES TAKES TO DISINTEGRATE OR DISSOLVE. TRIALS WERE DONE FOR EACH BATCH INDICATED BY SERIES 1, SERIES 2, SERIES 3. THE GRAPH AND DATA WERE FORMATTED USING EXCEL

Percent Moisture: The Percent Moisture of the various films remained constant in MRF-001 (1.40%) and MRF-002 (1.40%), but began to decrease to MRF-003 (0.87%). The percent moisture rose up in MRF-004 (1.30%). Moisture seems to degrade API, so having a lower AP (less than 2%) is better. It also should not be too low as the films but have a sustainable amount of water. The percent moisture in Batch MRF-001, MRF-002 and MRF-004 are best because they are between 1%-2%.

CONCLUSION: It can be concluded that sublingual films are a promising drug delivery system for getting local action of clove oil. From the present study, it can be concluded that the optimum temperature is required to meet the ideal film requirements. Optimized sublingual films of clove oil with the combination of polyox can meet the ideal requirements of fast-dissolving sublingual film, which can be a good way to bypass the extensive hepatic first-pass metabolism and provide local action orally.

Disclaimer: The products used for this research are commonly and predominantly use products in our area of research and country. There is no conflict of interest between the authors and producers of the products because we do not intend to use these products as an avenue for any litigation but for advancing knowledge. Also, the research was not

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