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Clinacanthus nutans-based mucoadhesive films for oral ulcers

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Abstract

Current pharmaceutical products for oral ulcers are topical creams and pastes containing corticosteroids, when the excessive use increases various complications. Thailand's National List of Essential Herbal Medicines (NLEM), the recommended only dosages of Clinacanthus nutans (Burm. f.) Lindau (C. nutans) in a solution for treatment of oral ulcer. This experimental research aims to develop the C. nutans mucoadhesive films. The weights of polymethacrylates L-100 or E-100; polyvinyl alcohol (PVA); and sodium alginate (ALG-Na) or Carbopol 934P, were varied, given glycerine or PEG-400 as the plasticizer, giving rise to 72 initial formulations. The physicochemical characteristics and analysis were subsequently carried out and the results compared. Given the poor performance of PEG-400, the PEG-400 film formulations were excluded from further analysis. The findings showed that only the A3, B3 and A9 glycerine-based film formulations yielded the functional oral mucoadhesive films, where A and B denote polymethacrylates L-100 and E-100. To enhance the film performance, further experiments were carried out with the A3, B3 and A9 films by incorporating both ALG-Na and Carbopol 934P in the film formulations in the ratios of 1:1 and 2:1. The experimental results revealed that the A3.1 is the best physicochemical characteristics, with the dissolution time of 300 minutes, the in-vitro mucoadhesive time in excess of 6 hours and the lupeol bioactive content as high as 142.01 µg/ml. The A3.1 formulation, consisting of 22.5g polymethacrylates E-100, 11.25g ALG-Na, 11.25g Carbopol 934P and 45g PVA, is functionally ideal for pilot scale of the C. nutans oral mucoadhesive films.

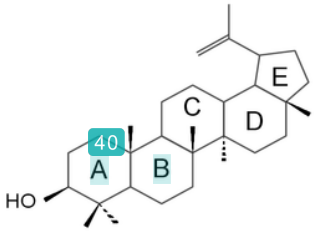
Key words: *Clinacanthus nutans* (Burm. f.) Lindau, Mucoadhesive film, Film former, Oral ulcer, Aphthous.

Introduction

Oral ulcers are characterized by a loss of the mucosal layer within the mouth and they afflict individuals of all genders and ages. In fact, oral ulcers can arise as a result of a number of disorders and are common in populations, particularly cancer patients undergoing chemotherapy and/or radiation treatment[1]. According to Naidu *et al.*[2], an estimated 40% of cancer patients undergoing chemotherapy and/or radiation had a 76% likelihood of developing oral ulcers. Moreover, deficiencies in vitamin B12, folic acid and iron, local trauma and several other factors could contribute to the development of oral ulcers. The oral complications associated with chronic oral ulcers ranged from oral discomfort, odynophagia, dysgeusia, dehydration, swallowing difficulty to the increased risk of malnutrition and morbidity[2]. Current pharmaceutical products for mouth ulcers are topical creams and pastes containing corticosteroids or tetracyclines. In Thailand, the oral pastes containing 0.1% triamcinolone acetonide are predominant in the market; however, the excessive use increases the likelihood of oral yeast infections and possible systemic infections[3].

According to Thailand's National List of Essential Herbal Medicines (NLEM) (2016), the recommended dosages of *Clinacanthus nutans* (Burm. f.) Lindau (*C. nutans*) in a glycerine solution for treatment of aphthous ulcers and chemotherapy- or radiation-induced oral mucositis are 2.5-4%[4]. This is consistent with Vetcho *et al.*[5], who documented that chemotherapy-treated cancer patients (7-12 years) who were administered with drops of glycerine *C. nutans* solution daily exhibited a significantly lower incidence of oral mucositis ($p<0.001$) than the control group who received no *C. nutans* solution after 21 days. In addition, the oral toxicity study of the methanolic extract of *C. nutans* dried leaves administered on male Sprague Dawley (SD) rats at 0.3 g/kg, 0.6 g/kg and 0.9 g/kg for 14 days found no harmful effects and organ damage in the rodents[6]. According to Indis[7], *lupeol* is the bioactive ingredient in the *C. nutans* leaves which is effective in oral ulcer treatment. Figure 1 (a), (b) respectively illustrate the leaves of *C. nutans* and the chemical structure of its bioactive ingredient *lupeol*.

(a)



(b)

Fig-1 : (a-b): The *C. nutans* plant: (a) its leaves (b) the chemical structure of the active ingredient *lupeol*

Meanwhile, the concept of mucoadhesion has gained considerable interest in pharmaceutical technology over the past few decades due to its multiple advantages, including the ease of use, targeted delivery of active ingredients to the site, prolonged residence time, enhanced clinical efficacy, reduced dose frequency and increased patient compliance[8, 9, 10]. Nevertheless, the mucoadhesive drug delivery systems for treatment of oral ulcers are non-existent. Furthermore, in light of the oral ulcer healing property of *lupeol* in the *C. nutans* leaves and the increased incidence of oral yeast infections due to the excessive use of the chemical-based oral pastes, this experimental research thus aims to develop the *C. nutans* mucoadhesive films for oral ulcer treatment using the solvent casting method. In the study, the weights of the base matrix, co-polymer, natural and synthetic polymers were varied, given 4g *C. nutans* ethanolic extract; and the physicochemical characteristics subsequently assessed and compared.

Material and Methods

The dried leaves of *C. nutans* were acquired from V.P. Pharmacy, polymethacrylates L-100 and E-100 were from Jebsen & Jessen Ingredients (Thailand), and the reference standard *lupeol* (>98% purity) was from Sigma-Aldrich, USA. Meanwhile, sodium alginate (ALG-Na), Carbopol 934P, polyvinyl alcohol (PVA), glycerine and PEG-400 were supplied by TTK Sciences.

C. nutans ethanolic extracts preparation: Prior to the experiment, the dried *C. nutans* leaves were first ground into powder and submerged in 95% ethanol (1 kg of leaf powder per 4 liters of ethanol) for 7 days. The ethanol was then evaporated using a vacuum rotary evaporator (Heidolph-VAP precision rotary evaporator) for 50 g of *C. nutans* crude extract and retained at -20 °C until use.

C. nutans mucoadhesive films preparation: The experimental mucoadhesive films are made up of two layers: the drug-free and drug-containing layers. The drug-free backing membrane was prepared by dissolving 5% ethyl cellulose in 95% ethanol before transferring to a petri dish and oven-dried at 40 °C for 6 hours[11]. Meanwhile, the drug-containing (i.e. *C. nutans* ethanolic extract) layer was fabricated from variable polymers combinations of 10% w/v polymethacrylates L-100 or E-100, 6% w/v sodium alginate (ALG-Na), 1% w/v Carbopol 934P, 2% w/v polyvinyl

alcohol (PVA) and a plasiticizer using the solvent casting technique.

The drug-containing layer was realized by mixing either polymethacrylates L-100 or E-100 (18-30g) with 4 g *C. nutans* ethanolic extract (the active pharmaceutical ingredient or API)[4] and 10 drops of tween 80 as the emulsifier using a magnetic stirrer. Once mixed, PVA (22.5-45g), ALG-Na or Carbopol 934P (22.5-45g) and glycerine or PEG-400 as the plasticizer (10g) were introduced and homogenously mixed at 80 rpm for 30 min. Then, 1g of menthol and 0.05g of sodium benzoate (food preservative) were added and thoroughly mixed. The viscous mixtures were subsequently transferred to a petri dish lined with a drug-free backing membrane and oven-dried at 50 °C for 18 hour. The dried films were removed and cut into smaller circular films of 1.3 cm in diameter using an eyelet. The circular films were then arranged on a plastic sheet and packed in an aluminum zipper bag prior to storage in a vacuum dissector container at room temperature[12].

In this research, the weights of the polymers (e.g. 18-30g for the base matrix, 22.5-45g for PVA) were varied in accordance with Vasantha *et al.*[12], who fashioned the oral mucoadhesive films for other applications using polymethacrylates L-100 as the base matrix, PVA and the natural and synthetic polymers similar to this current research. Specifically, the combined weight of the drug-containing layer, excluding the API (4g), plasticizer (10g), menthol (1g) and preservative (0.05g), remained unchanged at 90g, consisting of the base matrix, PVA, natural and/or synthetic polymer of varying combinations. Given the variable weight combinations of the polymers (i.e. polymethacrylates L-100 or E-100, ALG-Na or Carbopol 934P and PVA) and two types of plasticizers (glycerine or PEG-400), there were thus 72 initial formulations. Table 1 tabulates the film formulations (36) with glycerine as the plasticizer and Table 2 presents another 36 film formulations with PEG-400 as the plasticizer.

Table 1: The film formulations given glycerine as the plasticizer, where A and B respectively denote polymethacrylates L-100 and E-100

Formulations		polymethacrylates L-100 /polymethacrylates E-100 (10% w/v) (g)*	ALG-Na (6% w/v) (g)	PVA (2% w/v) (g)	carbopol 934P (1% w/v) (g)
		Base matrix	Natural polymer	Co-polymer	Synthetic polymer
A1	B1	30	30	30	-
A2	B2	25.5	25.5	39	-
A3	B3	22.5	22.5	45	-
A4	B4	25.5	39	25.5	-
A5	B5	22.5	33.75	33.75	-
A6	B6	20	30	40	-
A7	B7	22.5	45	22.5	-
A8	B8	20	40	30	-
A9	B9	18	36	36	-
A10	B10	30	-	30	30
A11	B11	25.5	-	39	25.5
A12	B12	22.5	-	45	22.5
A13	B13	25.5	-	25.5	39
A14	B14	22.5	-	33.75	33.75
A15	B15	20	-	40	30
A16	B16	22.5	-	22.5	45
A17	B17	20	-	30	40
A18	B18	18	-	36	36

Table 2: The film formulations given PEG-400 as the plasticizer, where A and B respectively denote polymethacrylates L-100 and E-100

Formulations		polymethacrylates L-100 /polymethacrylates E-100 (10% w/v) (g)*	ALG-Na (6% w/v) (g)	PVA (2% w/v) (g)	carbopol 934P (1% w/v) (g)
		Base matrix	Natural polymer	Co-polymer	Synthetic polymer
A1	B1	30	30	30	-
A2	B2	25.5	25.5	39	-
A3	B3	22.5	22.5	45	-
A4	B4	25.5	39	25.5	-
A5	B5	22.5	33.75	33.75	-
A6	B6	20	30	40	-
A7	B7	22.5	45	22.5	-
A8	B8	20	40	30	-
A9	B9	18	36	36	-
A10	B10	30	-	30	30
A11	B11	25.5	-	39	25.5
A12	B12	22.5	-	45	22.5
A13	B13	25.5	-	25.5	39
A14	B14	22.5	-	33.75	33.75
A15	B15	20	-	40	30
A16	B16	22.5	-	22.5	45
A17	B17	20	-	30	40
A18	B18	18	-	36	36

The 1.3-cm circular films associated with variable film formulations were subsequently assessed for their physicochemical properties, including the weight, thickness, and surface pH, percentage of water uptake, in-vitro mucoadhesive time, in-vitro dissolution, elongation and tensile strength. In addition, the film surface morphology, the film stability and the *lupeol* content were determined.

Weight and Thickness variation (g): The weights of the circular films were determined by weighing five film specimens on an analytical balance 200g/0.0001g. The measurements were averaged and the results expressed as the mean ± standard deviation (SD). Meanwhile, the thickness was determined by measuring five film specimens at the left edge, center and right edge of the films using a vernier micrometer 0.1-0.0001 inch. The measurements were averaged and the results expressed as the mean ± standard deviation (SD)[13].

Surface texture: The surface pH of the circular films of the various formulations were determined by first placing five film specimens on a plate containing 2% w/v agar and incubated at 37 °C for 2 h. The surface pH was then measured using a pH meter. The measurements were averaged and the results expressed as the mean ± standard deviation (SD).

The percentages of water uptake: The water uptake (%) of the formulated films were calculated using equation (1), whereby the film initial weight was first determined prior to placing it on a watch glass with the drug-containing layer facing up. Water droplets were released at 0.1 ml/min onto the film in an indiscriminate fashion and terminated once the film showed signs of deformation[14]. The film final weight was subsequently measured.

% water uptake = (Final weight – Initial weight) x 100 (1)

In-vitro mucoadhesive time: The in-vitro mucoadhesive time associated with each of the film formulations was determined using the porcine esophageal of a newly slaughtered swine (< 2 hours)[15], submersed in a beaker containing a Krebs buffer solution and placed in an ice bath. The porcine esophageal was next transferred and affixed on a Styrofoam before the mucoadhesive film was attached and then transferred to a beaker placed in a 37±0.5 °C water bath, a temperature range similar to the human oral temperatures. Then, droplets of simulated saliva[16] were released from a soluset at 0.5 ml/min, given the normal saliva secretion rate of 0.374-1.042 ml/min. The in-vitro mucoadhesive time is the length of time from the release of the simulated saliva droplet until the detachment of the film from the porcine esophageal[17].

In-vitro dissolution: The in-vitro dissolution was carried out using the dissolution apparatus 2 paddle type where the film specimens of the various formulations were independently submerged in 800 ml of simulated saliva (pH 6.8) maintained at 37±2 °C and a 50 rpm stirring. The dissolution time is the length of time from the submersion to a complete dissolution[16, 18].

Percentage of elongation and tensile strength: Mechanical properties of mucoadhesive films were determined using a universal testing machine equipped with a 50 kg load cell. Nonetheless, due to the small size of the 1.3cm circular films, the percentage elongation and tensile strength were thus investigated using the 2x5cm (WxL) bubble-free formulated films. In the measurement, the film was drawn by the top clamp at 0.3 mm/sec and terminated at break. The measurements were carried out in triplicate for each film formulation and the results expressed as the mean ± SD[19, 20].

Surface morphology and Stability tests at accelerated: The surface morphology of the drug-containing layer of the circular mucoadhesive films was investigated using scanning electron microscopy (SEM). The accelerated stability testing was carried out with five film specimens from each film formulation under five 24-hour heating-cooling thermal cycles (4 - 45 °C) and the physical properties of the films (i.e. weight and thickness) measured[14,21].

Quantitative determination of *lupeol*: The *lupeol* content in the circular mucoadhesive films was determined using the high performance liquid chromatography (HPLC) method[22], whereby the bioactive ingredient (*lupeol*) was quantified using the reference standard *lupeol* and the 1260 Infinity Binary LC System equipped with a UV detector. Prior to the analysis, the *lupeol* stock solution (10 mg/ml) and the film specimens were independently prepared in methanol. The *lupeol* separation was performed in triplicate in a 5µm, 100x4.6 mm C18 column. The mobile phase was methanol:acetonitrile in a ratio of 30:70%v/v, filtered through a 0.45 µm membrane filter and degassed by a sonicator. The injection volume and flow rate were 20 µl and 1.0 ml/min, with a UV wavelength of 210 nm.

Results and Discussion

The experimental results revealed that PEG-400 contributed to the dry, rigid and brittle films and thus a poor plasticizer. The film formulations with PEG-400 as the plasticizer were thus excluded from further analysis. Meanwhile, the formulations with glycerine as the plasticizer exhibited unequal film-forming performance, with only formulations A3, B3 and A9 yielding the functional oral mucoadhesive films. The findings were attributable to the low molecular weight (LMW) of glycerine (92.02), readily incorporating into the film structure and thereby the film plasticity, whereas PEG-400 has a high molecular weight of 380-420[23].

Table 3 tabulates the physicochemical characteristics of the formulations that produced the glycerine-based functional oral mucoadhesive films. The in-vitro mucoadhesive durations associated with the A3, B3 and A9 formulations were in excess of 6 hours (> 6 h), with the corresponding dissolution time of 105, 75 and 150 minutes and very porous surface, as illustrated in Figure 2. Interestingly, despite the elongated dissolution time (> 180 minutes) and very high water uptake (1159.54%), the A12 film exhibited a very short in-vitro mucoadhesive time of only 1 hour and very dry surface (Fig-2), rendering it less ideal due to the increased application frequency and lower patient compliance. In fact, the high percentage of water uptake could be attributed to the greater hydrophilicity of Carbopol 934P relative to ALG-Na[24]. This results was related to Chanda et al., 2008 that Carbopol 934 show the maximum of swelling property[25].

Table 3: The physiochemical characteristics of the functional oral mucoadhesive films with glycerine as the plasticizer

	Weight (mg.)	Thickness (mm.)	Surface pH	% Water uptake	%elongation	Tensile strength (MPa)	Dissolution time (mins.)	in-vitro mucoadhesive time (h)
A3	0.064±0.005	0.403±0.003	5.233±0.119	247.26	29.467±0.611	0.384±0.101	105	>6
A9	0.083±0.006	0.484±0.020	5.100±0.154	417.28	35.200±8.773	0.462±0.081	150	>6
A12	0.045±0.001	0.263±0.027	5.517±0.032	1,159.54	NA	NA	>180	1
B3	0.11±0.006	0.61±0.008	6.74-7.06	37.93	82.79±10.97	0.28±0.04	75	>6

Note: N/A denotes "not available" as the film failed to break once arriving at the maximum distance limit of 10 cm.

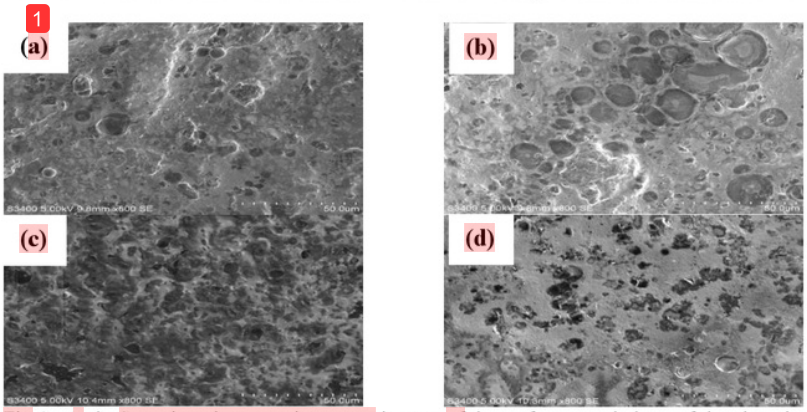


Fig-2 : (a-d): Scanning electron microscope images of the surface morphology of the glycerine-based (a) A3 (b) A9 (c) A12 (d) B3 formulations

The research findings also indicated that the film formulations with only ALG-Na achieved long in-vitro mucoadhesion durations but poor mechanical performance. The mucoadhesive duration significantly increased as the concentration of ALG-Na increased due to its glucuronic acid content and the subsequent improved gelling properties[26]. On the other hand, the formulations without ALG-Na (i.e. only Carbopol) exhibited outstanding mechanical characteristics but poor in-vitro mucoadhesive time.

According to Chaudhary *et al.*[27], mixing 0.8% w/v ALG-Na with 0.2% w/v Carbopol 934P in a ratio of 4:1 ratio with glycerine as the plasticizer significantly improved the mucoadhesive strength (i.e. the tensile strength and elongation) and the mucoadhesive time (i.e. the dissolution time and in-vitro mucoadhesive time). Thus, this current research further experimented with the functional glycerine-based oral mucoadhesive films (i.e. formulations A3, B3 and A9) by incorporating both natural (ALG-Na) and synthetic polymers (Carbopol 934P) in the film formulations. The experimental ratios of ALG-Na to Carbopol 934P were 1:1 and 2:1. The lower polymer ratios relative to that in Chaudhary *et al.*[27] (i.e. 4:1) were attributable to this current research's considerably higher ALG-Na and Carbopol 934P concentrations of 6% w/v and 2% w/v, vis-à-vis the previous work's 0.8% w/v and 0.2% w/v. Specifically, the mixture became excessively viscous for any polymer ratio beyond 2:1. Table 4 presents the glycerine-based functional oral mucoadhesive film formulations, given the combined weight of 90g and the ALG-Na to Carbopol 934P ratios of 1:1 and 2:1. Combined natural and synthetic polymer recommended for combined properties in one hydrogel including the strong point of mucoadhesive , biodegradable natural polymers when combined with synthetic polymers to represent strong points both type of polymers[28-29].

Table 4: The formulations of the functional oral mucoadhesive films given the combined weight of 90g and glycerine as the plasticizer

Formulations	polymethacrylates L-100 (A)	polymethacrylates E-100 (B)	ALG-Na (6% w/v) (g)	carbopol 934P (1% w/v) (g)	PVA (2% w/v) (g)
A3.1 (1:1)	22.5	-	11.25	11.25	45
B3.1 (1:1)	-	22.5	11.25	11.25	45
A9.1 (1:1)	18	-	18	18	36
A3.2 (2:1)	22.5	-	15	7.5	45
B3.2 (2:1)	-	22.5	15	7.5	45
A9.2 (2:1)	18	-	12	24	36

Note: A and B respectively denote polymethacrylates L-100 and E-100. The ratios of the natural to synthetic polymers (ALG-Na : Carbopol 934P) are 1:1 and 2:1, as respectively represented by 1 and 2 at the end of the formulation nomenclature.

Table 5 compares the physicochemical characteristics of the *C. mutans* mucoadhesive films associated with formulations A3, B3 and A9, given the ALG-Na to Carbopol 934P ratios of 1:1 and 2:1 and glycerine as the plasticizer. There are six experimental formulations: A3.1, A3.2, B3.1, B3.2, A9.1 and A9.2, where A and B denote polymethacrylates L-100 and E-100 and the numbers 1 and 2 at the end of the formulation nomenclature denote the 1:1 and 2:1 ratios.

Table 5: The physiochemical characteristics of the *C. mutans* mucoadhesive films associated with formulations A3, B3 and A9 given glycerine as the plasticizer

	Weight (mg.)	Thickness (mm.)	Surface pH	% Water uptake	%elongation	Tensile strength (MPa)	Dissolution time (mins.)	in-vitro mucoadhesive time (h)
A3.1	0.058±0.002	0.332±0.003	5.383±0.118	602.82	17.057±2.084	0.197±0.018	125	>6
A3.2	0.056±0.009	0.295±0.004	5.187±0.012	642.76	9.787±7.285	0.186±0.049	160	>6
A9.1	0.058±0.001	0.392±0.004	5.293±0.006	213.08	26.013±9.547	0.163±0.017	106	>6
A9.2	0.079±0.003	0.430±0.000	5.303±0.015	354.56	81.013±16.093	0.277±0.131	84	>6
B3.1	0.09±0.007	0.53±0.008	7.33±0.083	173.63	82.79±10.97	0.280±0.040	300	>6
B3.2	0.11±0.006	0.32±0.011	7.46±0.024	182.10	NA	NA	80	>6

Note: A and B respectively denote polymethacrylates L-100 and E-100. The ratios of the natural to synthetic polymers (ALG-Na : Carbopol 934P) are 1:1 and 2:1, as respectively represented by 1 and 2 at the end of the formulation nomenclature.

The experimental results revealed that the weight and thickness of the films were in the ranges of 0.056±0.009 - 0.110±0.006 g and 0.295±0.004 - 0.534±0.008 mm, respectively. The surface pH were in the range of 5.187±0.012 - 7.46±0.024, closely resemble the normal salivary pH of 5.6-7[8]. In addition, the elongation and tensile strength were enhanced with glycerine due to the effective bond formation between the polymers and the plasticizer[14].

By comparison, the B3.1 mucoadhesive film, with the 1:1 ratio of ALG-Na to Carbopol 934P, exhibited the largest percentage of elongation (82.79±10.97%) and tensile strength (0.28±4.0 MPa). The findings are consistent with Renuka *et al.*[31], who documented that Carbopol 934P is a very stretchable material and thus high elongation, while ALG-Na is a brittle material and thus high tensile strength. In addition, the surface pH of the B3.1 oral film was in the range of 7.33±0.083, thereby inducing minimal irritation due to the neutral pH[32].

More importantly, the B3.1 formulation (with polymethacrylates E-100 as the base matrix) achieved the longest dissolution time (300 min), given the fact that polymethacrylates E-100 is soluble below pH 5, whereas polymethacrylates L-100 at pH>6[23]. Given the normal salivary pH of 5.6-7[8], the oral mucoadhesive film with polymethacrylates L-100 as the base matrix would be rapidly dissolved by saliva. Moreover, the *lupeol* content, the bioactive ingredient effective in oral ulcer treatment[7], in the B3.1 mucoadhesive film was as high as 142.01 µg/ml. In addition, the physical properties of the film (i.e. the weight and thickness) exhibited no significant change following the accelerated stability test. Figure 3 illustrates the surface morphology of the B3.1 film, alongside a sample of the oral mucoadhesive film. By comparison, the B3.1 formulation, consisting of 22.5g polymethacrylates E-100, 11.25g ALG-Na, 11.25g Carbopol 934P and 45g PVA, is functionally ideal for the *C. mutans* oral mucoadhesive films.

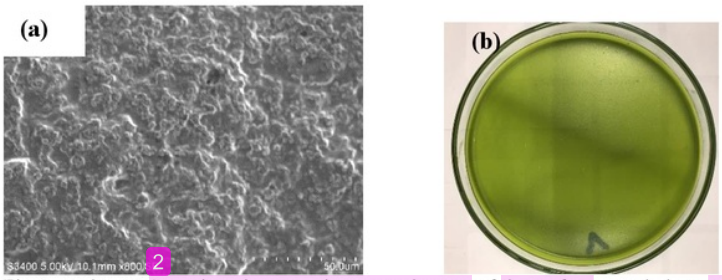


Fig-3 : (a-b): (a) Scanning electron microscope images of the surface morphology of the B3.1 film, (b) a sample of the oral mucoadhesive film

Conclusion

The experimental results revealed that the formulation consisting of 22.5g polymethacrylates E-100, 11.25g ALG-Na, 11.25g Carbopol 934P and 45g PVA, is functionally ideal for the *C. nutans* oral mucoadhesive films, with the suitable physicochemical characteristics. Furthermore, a clinical trial should be undertaken to assess the efficacy of the *C. nutans* mucoadhesive film in relation to the existing chemical-based oral ulcer medicines.

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No conflict of interest

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