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Candidiasis management: current status of allopathic drugs and utility of coriander-based oil-less emulsions

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ABSTRACT

Candidiasis (also known as thrush and moniliasis) is the most common, multifactorial, and opportunistic yeast infection which causes severe damage to the mucosal tissues of tongue and mouth. Candida albicans is the notable fungus causing the candidiasis in both animal and human. Moreover, this fungus is capable of forming a difficult-to-treat biofilm structure over the mucosal tissues of tongue and mouth. Allopathic drugs in solid, liquid, parenteral and topical gels are prescribed in the oral candidiasis conditions. The plant material-based formulations did not explore much especially to disturb the biofilm structure formed by this fungus. The present review accentuates firstly the causes together with various types of candidiasis, secondly the use of different allopathic drugs in conjunction with their side effects and thirdly the performance demonstration of oil-less emulsion prepared based on hydroxyethyl cellulose, eutectic forming excipients, coriander seed/ extract and non-ionic surfactant to manage the oral candidiasis condition.

Keywords: *Candida albicans, allopathic, coriander, quercetin, oil-less emulsion, eutectic liquid.*

1. INTRODUCTION

Having infection-free oral cavity and thus the oral hygiene maintenance are every human's desire. However, the oral cavity and its associated mucus membranes are place of abode for microbial colonization. The microorganisms which positioned over the mucosal membrane of oral cavity are likely to be a major causative agent for diminished oral hygiene of individuals. In addition, the microorganisms sit on- and under- tooth cavity for causing/making the periodontal infections. Irrespective of sites, whether teeth routes, tongue or mucosal membrane, the symptom of inflammation and hence the pain arised are the most common symptoms for all oral infections. Among the available well known infections diminishing the oral hygienic conditions, the infections caused by fungus attracts much attention in recent years. One such fungal infection is oral candidiasis or candidosis.

Candidiasis (also known as thrush and moniliasis) is the most common, multifactorial, and opportunistic yeast infection which causes severe damage to the mucosal tissues of the tongue and mouth. Although the candida infection generally covers 300 to 400 species of various microorganisms, the 20 different species of candida fungi including *Candida albicans*, *C. tropicalis*, *C. krusei*, *C. lusitaniae*, *C. stellatoidea* and *C. glabrata* are found to create the oral infection in both animal and human beings [1,2]. Due to poor nutrition and having prolonged recovery, the treatment of oral candidiasis becomes a challenge to medical professionals. The tongue of the affected individuals contains several white patches as well as the red one [3,4]. Furthermore, an abnormal overgrowth of the candida series of fungi is routinely being observed in gastrointestinal, respiratory and urinary tracts of the immune-compromised patients [5]. Moreover, this fungus is also related to the development of nosocomial infections particularly by forming a difficult-to-treat biofilm structure over the surfaces of surgically put in or placed medical devices like catheters, heart valves, implant, etc., inside the animal or human bodies.

The present review accentuates firstly the causes together with various types of candidiasis, secondly the use of different allopathic drugs in conjunction with their side effects and thirdly the performance demonstration of oil-less emulsion prepared based on hydroxyethyl cellulose (HEC), eutectic forming excipients, coriander seed/ extract and non-ionic surfactant to manage the oral candidiasis condition.

2. EXPERIMENTAL SECTION

Oral candidiasis causes, types, diagnosis and management by allopathic drugs.

Based on the literature review, the causes and various types of candidiasis are shown in Table 1. There are several clinical methods which can helpful to differentiate the candidiasis severity, ie., whether it is the red ones, white lesions or the both red-white mucosal changes [6]. Pityingly, the severity level of lesions formed by candidiasis results in the possible development of the oral malignancy [7,8]. When looking the diagnosis part of oral candidiasis, the culture method is the standard approach in which the saliva, swap, cytology smear or biopsy of the lesion are taken from the oral cavity of patient for Gram-and periodic acid-Schiff (PAS)-stainings followed by the microscopic examination [9]. After that, the candida lesions can easily be differentiated by the

category of the white lesion and also with the oral hairy leukoplakia, chronic lesion of immunobullous diseases, chemical burns and nutritional deficiencies [10]. The list of presently used allopathic drugs along with their formulations, dose and side effects are narrated in Table 2.

Table 1. Comprehensive list of candidiasis types and their possible causes.

Type	Site	Symptoms	Causes/associated factors
Chronic hyperplastic	Tongue	White lesions	Due to smoking, Dysplasia (*Candida leukoplakia*)
Chronic atrophic candidiasis	Upper jaw and palate	Occurrence of lesions	Denture stomatitis
Acute pseudomembranous candidiasis	Labial, hard and soft palate, tongue, oropharynx	White patches	Due to smoking
Acute atrophic	Tongue become red in color (in some cases)	Burning of the mouth or on the tongue	Dry mouth
Angular cheilitis (erythematous fissuring)	End or on the corners of the mouth	One or both corners may be: bleeding, blistered, cracked, crusty, itchy, painful, red, scaly, swollen	Dry mouth
Median rhomboid glossitis	Anterior of the tongue to the circumvallate papillae	Lesions on hard palate and angles of mouth	Due to smoking and continuous use of steroids

Table 2. Non-exhaustive list of allopathic drugs used in oral candidiasis [11].

Drug	Formulation	Dose	Side effect
Amphotericin-B	50 mg for infusion	100-200 mg	Hypoxia, anxiety, confusion and insomnia
Clotrimazole	Gel 1%	10 mg 4-5 times	Unpleasant mouth sensation, pruritus and stomach upset
Nystatin	Suspension 60 ml, ointment 30 g and tablet	4-6 ml/ 6 hr	Nausea, vomiting and other gastrointestinal side effect
Fluconazole	Tablet suspension	50-100 mg/day	Diarrhea and abdominal pain
Itraconazole	Capsule	100-200 mg/day	Nausea, vomiting and cardiovascular side effects
Ketoconazole	Tablet	200 mg	Hepatotoxicity and hypersensitivity

Development and performance demonstration of coriander (leaves extract and seed powder)-based oil-less emulsions for topical use.

Coriandrum sativum L. is a glabrous aromatic, herbaceous annual plant, which has a long history as a culinary herb is the source of aroma compounds with biologically active components possessing antibacterial, antifungal and antioxidant activities. Thus *C. sativum* is useful in food preparation (as a flavoring agent or adjuvant) and preservation as well in preventing food borne diseases and food spoilage [12,13]. The active constituents of coriander are depicted in Table 3. Most of these constituents possess the inhibitory effect on the candidiasis-causing fungi by binding to their ergosterol layers of fungus membrane which generally helps in the permeation of the fungi into the oral mucosal tissues.

Table 3. Active constituents present in coriander.

Constituents of coriander
Linalool
Camphor
Limonene
Geranyl acetate
p-cymene
Terpinene
Rutin
α-pinene
Quercetin
Cholorgenic acid
Caffeic acid

Traditionally, the emulsions are developed based on oil, water and emulsifier molecules. The plant-derived active constituents also possess an adequate amount of solubility in oils and oil-based formulations such as emulsions [14]. However, the presence of oil or oil combination in the emulsions always show a tendency of oxidation reaction and thus initiating the degradation of the emulsion-incorporated active constituent of plants. The propensity of oxidation-induced degradation of plant-derived active constituents may be diminished by the inclusion of additional antioxidant excipients in the emulsions. On the other hand, the hydrotropic mixture system such as eutectic liquid made from eutectic forming excipients may be of use to dissolve plant derived active constituents. Since the eutectic liquid itself consists of counter irritation and rubefacient activities following its topical application into the oral mucosal tissues, the further exacerbation of the already affected mucosal tissues in oral candidiasis condition and thus the chances of patient compliance problems are likely to occur [15,16]. In order to eliminate the oil or oil combination and antioxidant molecule from the emulsions, a very attractive but less expensive alternative/replacement is the utilization of eutectic liquid made from eutectic forming excipients as the oil phase to prepare oil-in-water emulsion. Since the developed emulsions do contain water and emulsifier molecules but they do not have the oil or oil combination, it can conveniently be termed as oil-less emulsions. The peculiar property of eutectic liquid is the hydrophobic nature and thus able to dissolve the sufficient amount of plant derived active constituents like the traditional oil or oil combination do. At the same time, the chances of so-called irritation effect produced by

the eutectic liquid are also likely to be less because the eutectic liquid is simply dispersed in the continuous aqueous medium with the coverage of mono-or multi-molecular emulsifier film. In addition, the question of droplet-droplet coalescence and subsequent breakage of dispersed eutectic liquid droplets of the oil-less emulsions is not likely to occur due to the emulsifier film coverage around the dispersed eutectic liquid droplets of the oil-less emulsions. Keeping this point in mind, the coriander seed powder is initially mixed with the eutectic liquid. The water phase is constituted by mixing the aqueous extract of coriander leaves (prepared after boiling the leaves in water over 2-3 hours) with non-ionic emulsifier molecules. The emulsification is done by mixing of the coriander containing eutectic liquid (oil-less) and water phases together using the mechanical stirrer, electric stirrer and finally with ultrasonicator. To impart viscosity to the formulation, the oil-less emulsion is deliberately mixed with a fixed amount of hydroxyethylcellulose (HEC) during the emulsification step. The viscosity of the formulation is enhanced intentionally by keeping the point in mind that the final product should consist of required resistance against the eroding effect produced by the salivary fluid after the formulation application over the oral cavity. Table 4 shows the composition of the oil-less emulsion containing coriander seed powder. By changing the amount of each ingredient, the various oil-less emulsions (designated as F1, F2, F3, F4, F5, F6 and F7) were produced and evaluated for their physical stability. Taking the instability problems of dispersed eutectic liquid droplets of the oil-less emulsions into consideration, the formulations F1, F2 and F3 were left out and only other formulations (from F4 to F7) underwent for further evaluations.

Table 4. Composition of oil-less emulsion containing coriander seed powder.

Oil-less phase	Water phase
Camphor	Tween 80
Menthol	Aqueous extract of coriander leaves
Coriander seed powder	
Hydroxyethylcellulose (HEC)	
Acetone	

3. RESULTS SECTION

As mentioned previously, the oil-less emulsion was manufactured by mixing the coriander constituents containing oil-less phase with the water phase using the mechanical stirrer followed by electric stirrer at 800 rpm for over the period of 30 minutes and then, keeping the crude emulsion formed in ultrasonicator for another 10 minutes. The final emulsion formed looks like milky white with minimum or no amount of suspended coriander seed powder as it was completely dispersed or dissolved in the eutectic liquid (oil-less phase) before emulsification with water phase. Figure 1 depicts the photomicrograph of emulsion droplets taken after keeping the emulsion droplets in a glass slide to view under optical microscope.

Coming to the characterization of developed coriander-loaded oil-less emulsions, the determination of mean particle diameter of the dispersed eutectic liquid droplets was determined using Malvern mastersizer (Figure 2). The observed $d_{(0.5)}$ value is 71.227 µm. Other characterization works performed are the drug content, *in vitro* quantitative and qualitative anti-fungal activities and *in vitro* drug diffusion/permeation.

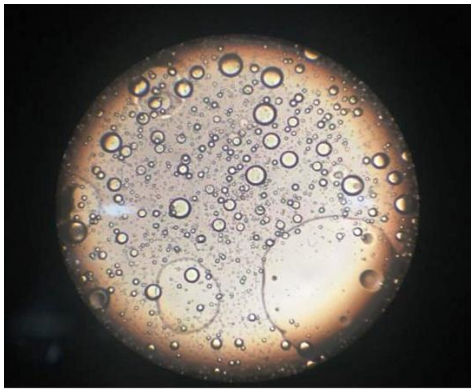


Figure 1. Photomicrograph of oil-less emulsion particles taken using optical microscope.

Since the coriander consists of multiple active ingredients (Table 3), it was decided to run a high performance thin layer chromatography (HPTLC) of coriander-loaded oil-less emulsion for finding out a marker constituent suitable to indicate the drug content of the emulsion developed. The HPTLC method developed was simply followed in the present study [17,18]. The HPTLC chromatogram obtained for coriander-based oil-less emulsion is shown in Figure 3.

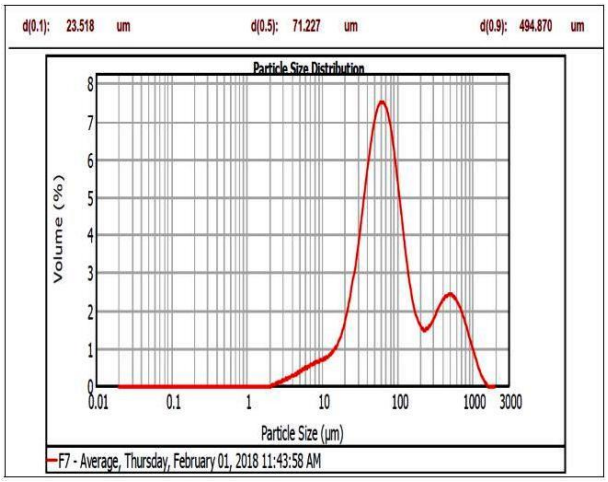
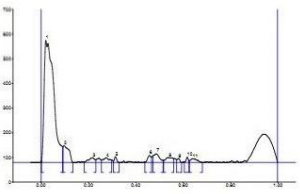


Figure 2. Particle size distribution of coriander-loaded oil-less emulsion.



Peak	Start Rf	Start Height	Max Rf	Max Height	Max %	End Rf	End Height	Area	Area %	Assigned substance
1	0.00	7.0	0.02	495.6	64.44	0.09	64.2	15590.8	77.41	unknown *
2	0.09	64.5	0.10	68.3	8.88	0.13	0.1	1329.4	6.60	unknown *
3	0.18	1.8	0.22	20.2	2.62	0.23	11.7	408.3	2.03	unknown *
4	0.26	10.2	0.28	20.4	2.65	0.30	10.4	413.7	2.05	unknown *
5	0.31	6.0	0.31	24.3	3.16	0.33	0.1	186.4	0.93	unknown *
6	0.44	1.8	0.46	28.8	3.74	0.47	21.0	336.9	1.67	unknown *
7	0.47	27.9	0.49	36.2	4.71	0.52	9.0	707.4	3.51	unknown *
8	0.52	9.0	0.54	20.3	2.63	0.56	15.7	503.8	2.50	unknown *
9	0.57	11.9	0.58	17.0	2.21	0.59	0.2	152.4	0.76	unknown *
10	0.61	2.6	0.62	22.2	2.88	0.63	6.4	157.2	0.78	unknown *
11	0.63	6.7	0.64	16.0	2.08	0.68	0.2	353.3	1.75	unknown *

Figure. 3 HPTLC chromatogram obtained for coriander-loaded oil-less emulsion.

From Figure 3, it is clear that the coriander-loaded oil-less emulsion exhibited one prominent and sharp chromatogram at position number 1 having the peak area and the end retention factor (R_f) values of 15590.8 and 0.09, respectively. As per the R_f value [19,20,21], the corresponding active constituents identified at this R_f value is "Quercetin". Therefore, this compound was selected as marker compound to indicate the drug content, anti-fungal activity and interpreting the drug permeation *in-vitro* data. Furthermore, the calibration curve was also established for quercetin with concentrations ranging from 2-30 µg against the peak area obtained in HPTLC analyses. Figure 4 shows the quercetin calibration curve obtained with the validated HPTLC method. The quercetin present in the formulations F4 to F7 was determined via HPTLC analysts and the amount was calculated using the calibration curve Figure 4. The quercetin amount present in coriander-loaded oil-less emulsions is shown in Table 5. The quercetin amount ranging from 299.64 ± 0.52 to 300.02 ± 0.78 µg was found to be present in the oil-less emulsions. Furthermore, the presence of quercetin in the oil-less emulsion was substantiated via TLC analysis (Figure 5). The quercetin showed a R_f value of 0.54 ± 0.02 whereas the coriander-loaded oil-less emulsion exhibited the R_f value of 0.56 ± 0.01.

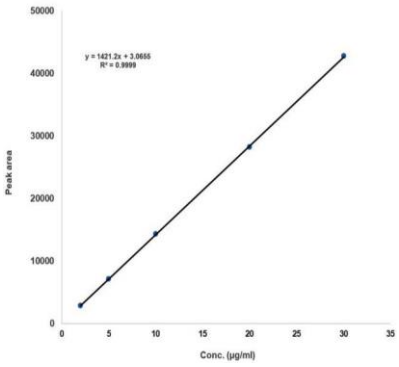


Figure 4. Calibration curve of quercetin obtained by HPTLC method.

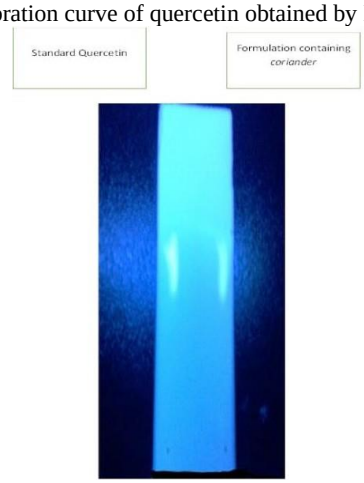


Figure 5. TLC spots of standard quercetin and oil-less emulsion containing coriander (F6).

Table 5. Quercetin amount present in coriander-loaded oil-less macroemulsions prepared using different formula.

Formulation	Quercetin content in whole emulsion, µg
F4	299.99 ± 0.52
F5	300.02 ± 0.78
F6	299.64 ± 0.67
F7	299.64 ± 0.98

Using the Frank diffusion cell with artificial cellophane membrane, the permeation of quercetin released from the coriander-loaded oil-less emulsions (F4-F7) was quantified by the validated HPTLC. Figure 6 depicts the *in vitro* permeation of quercetin via cellophane membrane over the time period of 30 minutes. No statistical difference between the permeated amounts of quercetin was seen among the oil-less emulsions tested. At 30 min post-permeation time period, the quercetin amount was found to be in the range of 8268.8 ± 457.68 - 24861.53 ± 17.08 µg/ml. This indicates that after the topical application of coriander-loaded oil-less emulsions over the oral cavity, the released quercetin is able to ferry the candidiasis infected tissues to contain the fungi.

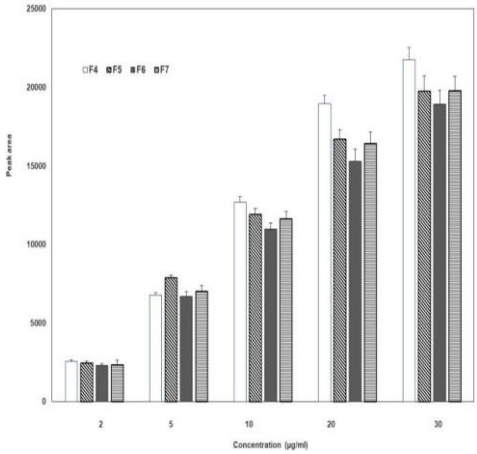


Figure 6. *In vitro* permeation (via cellophane membrane) of quercetin released from the coriander-loaded oil-less emulsions.

Figure 7. Petri plates having the colour change observed with fungi, fluconazole and coriander-loaded oil-less emulsion.

To see whether or not the coriander-loaded oil-less emulsions consist of biofilm disturbing ability, the antimicrobial activity of the emulsions against the *Candida albicans* was investigated by qualitative evaluation using the zone inhibition method. Although the zone inhibition values did not measure, the colour change observed in the portion where the fluconazole standard or coriander-loaded oil-less macroemulsions were applied. The candida only containing Petri plate showed the formation of dense fungal colonies with yellow colour. The disappearance or change of colour is the indication of antifungal activity of applied products. Based on this assumption, the fluconazole applied Petri plate consisted of a colour of pink (Figure 7) signifying its antifungal activity. Similarly, coriander-loaded oil-less macroemulsion applied Petri plate showed pink colour in less intensity (Figure 7).

4. CONCLUSIONS

To break the traditional way of dispersion system production either by mixing oil with water or water with oil in presence of surfactant molecule, the production of emulsion (like particles) was made by utilizing the mixture of eutectic components and

solution of slightly hydrophilic cellulosic polymer in acetone as an alternative or replacement to vegetable or semi-synthetic oils. By doing so, the solubility or dispensability of so-called hydrophobic and fibre characters of plant-derived drug such as coriander is improved. Although the results concerning the performance demonstration in real patient with candidiasis are not shown in this review, the potential of coriander-based oil-less emulsion in the topical therapeutic use is very certain.

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