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Original article

QUANTIFICATION OF LINALOOL IN 3D PRINTED FAST-DISSOLVING ORAL FILMS BY A HIGH-PRESSURE LIQUID CHROMATOGRAPHY METHOD

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Abstract

Introduction: Linalool has shown inhibitory effects against *Candida albicans*. Microbial resistance is developing towards the current antifungal drugs. Therefore, an oral formulation of linalool oil may be used to effectively treat oral thrush. A wide range of patients can use fast-dissolving oral films (FDFs). Three-dimensional printing (3DP) may be utilised for the manufacture of FDFs.

Aims: to formulate linalool in FDFs and quantify it using high-pressure liquid chromatography (HPLC).

Methods: A powder formulation containing linalool (5%w/w) was prepared and filaments were produced at 75°C and printed at 185°C. The films were dissolved either in methanol or deionised water, and linalool was quantified in the aqueous solutions. The mobile phase of a previously reported HPLC method was modified to quantify linalool in the aqueous solutions. The HPLC method was validated by measuring linalool in standard methanol and aqueous solutions.

Results: Preparing aqueous solutions of filaments and films provided less variability in the analyses. 3D-printed FDFs had an average weight of 78.44 ± 6.84 mg. Applying the HPLC method revealed that the amounts of linalool changed from a theoretical 25 mg (per 0.5 g of filament) to the range of 23.98 ± 1.22 to 33.79 ± 2.43 mg. In contrast, the amounts of linalool were changed in films from theoretical 25 mg (per 0.5 g of film) to 13.82 ± 3.24 mg to 21.04 ± 0.92 mg. These observations indicated the evaporation of linalool considerably during printing at 185 °C.

Conclusion: This work found that linalool FDFs should be printed at temperatures lower than 185 °C and dissolved in deionised water for better HPLC analytical consistency.

INTRODUCTION

Candida albicans forms a part of the standard components of a healthy microbiota and is often cultivated within mucosal cavities such as the oral cavity, respiratory tract, and vaginal cavity (Patel, 2022). Biofilm-associated fungal cells have high levels of resistance to established antifungal drugs and are shielded from host immune responses. Candidiasis is a common occurrence from these defences amongst immunocompromised people, with a high incidence of 95% of patients with human immunodeficiency virus(HIV) and 90% of patients with acute leukaemia. In all those cases, *C. albicans* was isolated from the oral cavity while undergoing chemotherapy in the UK (Akpan & Morgan, 2002). A few antifungal drugs are used for the treatment of *C. albicans* infections. However, the infection is difficult to treat due to high recurrence rates (Patel, 2022). As a result, essential oils have been vastly studied for their antimicrobial activity.

Linalool is a monoterpene alcohol which occurs in over 200 plants, notably from Lamiaceae, Lauraceae and Rutaceae (Kamatou and Viljoen, 2008). It is most recognised as the main fragrance component in lavender and coriander plants and is used in cosmetics, perfumery, and food industries(Howe, 2020). Linalool is often used as an antimicrobial agent. Previous studies have applied linalool as an antifungal agent. It has been proven an effective inhibitor of *C. albicans* biofilm formation by interfering with adherence and affecting the stability of pre-formed biofilms (de Oliveira Lima et al, 2017; Patel, 2022). Linalool also affects germ tube formation, which is an integral part of biofilm formation; in dose-dependent response, linalool significantly reduces the percentage of cells that form germ tubes (de Oliveira Lima et al, 2017). Therefore, it has potential for clinical application in biofilm-associated with *C. albicans* infections. Linalool has previously been applied in vivo against isolates of oral *C. albicans*. It is an essential agent against *Trichophyton rubrum*, *Caenorhabditis elegans* and *Candida tropicalis* (de Oliveira Lima et al, 2017).

Traditional treatment for oral thrush is a topical oral cream gel, or even a capsule containing antifungal ingredients. Fast dissolving oral films (FDFs) provide an alternative approach that could be more widely accepted due to easier administration than conventional treatments. FDFs may be considered an advancement from traditional methods, as the cream typically tastes unpleasant. FDFs can be produced by hot melt extrusion, a more widespread process than solvent casting. This is because the hot melt extrusion is solvent-free and has less chance of drug instability(Jani & Patel, 2015). FDFs may also be produced by 3D printing (3DP) (Ehtezazi et al, 2018), which allows precision dosing. FDFs can be used for both oral and buccal drug delivery without water (Ehtezazi et al, 2020). The development of 3D printing has produced complex oral dosage forms, (Prasad & Smyth, 2016; Serrano et al, 2019; Melocchi et al, 2020; Kimbell & Azad, 2021) even including commercial-scale production of Spritam, a fast-dissolving tablet (Norman et al, 2017).

The combination of active drug excipients and natural products constituents such as linalool could increase the efficacy of standard medications or even replicate and be as effective as standard treatments. Prior to any antimicrobial evaluations of FDFs, it is essential to quantify the amounts of linalool in these products. In this work, a previously developed High-Performance Liquid Chromatography method (Xia et al, 2010) was optimised to measure the amounts of linalool in the powder mixture, filaments and 3DP films. The fused deposition modelling (FDM) was employed to produce FDFs. This study also evaluated the loss of linalool during the preparation of FDFs by FDM 3DP.

MATERIALS AND METHODS

Materials

Polyethylene oxide (PEO) Mw100,000 Da, Linalool (97%), Kolliphor® P188 were purchased from Sigma Aldrich (UK). Kollidon VA 64 and Kolliphor P188 were gifts from BASF (Darmstadt, Germany). All solvents used were analytical grade.

METHODS

Powder Formulation

Each 10 g of powder contained 5% linalool (active ingredient), 20% Kollidon VA 64, 70% Poly(ethylene oxide), and 5% Kolliphor P188. The powder was weighed inside a beaker, and then linalool was added. All the ingredients were mixed manually.

High-Performance Liquid Chromatography (HPLC)

An Agilent 1200 series HPLC (Stockport, Cheshire, UK) was used to analyse the linalool content of the powders, filaments and films. The linalool (97%) was analysed using a modified previously developed high-performance liquid chromatography (HPLC) method (Xia et al, 2010) with a Reverse Phase C-18 column (4.6 x 150mm, 5 µm; Waters®, USA), using acetonitrile and water (35/65 v/v) as mobile phase with a flow rate of 1.0 mL/min. The column temperature was set to 25°C, and the detection spectrophotometer was set at 210 nm, with an injection volume of 5 µL.

A 10-point calibration curve for linalool in methanol was prepared with solutions in the range of 0-200 µg/mL. As linalool has a water solubility of 1590 mg/L (Rodríguez-López et al, 2020), then aqueous solutions of linalool in distilled water were prepared. The stock solution was created by weighing 50 mg of linalool into 100 mL. Serial dilutions were made from this stock solution using deionised water.

Validating the Powder Mixture Extraction Method

The powder mixture was aliquoted into ten parts of 1g each and introduced into sample bottles. Methanol (10 mL) was added to each part to extract linalool from the powder. The suspension was mixed by inversion for 5 min, and then 1 mL was filtered using 0.45 µm filter to remove sediment. To create a serial dilution with each sample ideally containing 100µg/mL, 0.2mL of filtrate was diluted with 9.8 mL of methanol. Each sample was transferred into an HPLC vial, and the amounts of linalool were measured as explained above. This method was replicated three times.

To ascertain whether the filter retains linalool, a serial dilution containing only linalool was used in place of the powder. First, 0.5 g linalool was diluted with 10 mL methanol as a stock solution and mixed by inversion for 5 min. To replicate the dilution of the 1 g of powder, 1 mL of the 10 mL of stock was separated into 10 samples; each was diluted with 9 mL of methanol. From each sample, 1 mL was filtered using 0.45 µm filters, and 0.2 mL of filtrate from each sample was diluted with 9.8 mL of methanol. The second set of samples was done with the same method but without a filter. This was. Each sample was transferred into an HPLC vial, and the amounts of linalool were measure. This method was replicated 3three times.

Finally, powder mixture was prepared as the above, and 0.5 g of the powder was transferred into a small beaker and diluted with 50 mL of deionised water. The solution was stirred with stirring bar at 700 rpm until powder was fully dissolved. These sample are predicted to contain 25 mg concentration of linalool. The samples were filtered using 0.45 µm syringe filters and then transferred into HPLC. Ten samples were run in total.

Preparation of Filaments

The active ingredient and powder polymers were weighed into a beaker using an analytical balance, and linalool was dripped into the centre of the beaker according to the weight needed. Immediately after linalool was added, the powder was hand mixed for precisely 5 min until the linalool is wholly combined and was not sticking to the base of the beaker. The contents were transferred into a single screw Noztek Pro Filament Extruder (Noztek, Shoreham, UK) and the temperatures were set at 80°C and 75°C. The nozzle diameter was 1.75 mm. The extruder was placed at a height, which provided constant gravity pull on the extrudate to achieve straight filaments with uniform diameter. As the filament was extruded, the diameter was checked every 10-15 cm employing a digital vernier calliper (RS Pro, Corby, UK) to ensure uniformity of the filament. Achieving the ideal diameter of between 1.70 – 1.80 mm was vital for using in the 3D printer. If the digital calliper measurements indicated that the filament diameter was greater than the ideal range, then one-gram object was added to the beginning section of the extruded filament to increase the gravitational pull on the fresh filament and adjust the diameter.

3D Printing of FDFs

The films were printed using a fused deposition modelling (FDM) Original Prusa i3 MK3S+ 3D printer (Prague, Czech Republic). SolidWorks 3DCAD (Dassault Systems SolidWorks Corp, Waltham, Massachusetts, USA) was used to design the film. The films were designed to be square with a length and width of 20 mm, and height of 0.2 mm. The extruder nozzle of the printer was 0.4 mm, and the extruder temperature was set to 185°C as it resulted in most uniform results. Extruder speed was set at 70 mm/s for PEO films and with a traveling speed of 45 mm/s and 100% infill with a monotonic aligned rectilinear infill pattern. The monotonic infill provided a homogenous shine throughout the film with no ridges within the texture. Blue masking tape was used to facilitate adhesion of printed film on to printer bed and printer bed temperature was heated to 45°C. Printing time was 2 min for a single plain film.

Powder, Filament, and Films Samples

Samples of 0.5 g were obtained from powder, filaments, and films. Filaments or films were cut into smaller sections and dissolved into 50 mL of deionised water by using bars on magnetic plates at 700 rpm until samples were fully dissolved. After filtering with 0.45 µm filters, each set of samples was transferred into HPLC vials. All measurements were performed in triplicates. In preliminary studies heating (50°C) was used to accelerate the dissolution of the filaments and films, however, it was found that linalool was evaporated from the samples. Powders and films were stored in lidded containers at room temp, while filaments were stored in a vacuum sealed Pyrex vacuum desiccator at room temperature.

RESULTS

Figure 1A presents the calibration curve for methanol solution of linalool. A best fit line was obtained with R^2 of 0.9986. Methanol could not be used for quantification of linalool in powder mixtures, as the filters got blocked due to undissolved powder particles in methanol. Therefore, aqueous solutions of powder mixtures were prepared, which was also useful for measuring the amounts of linalool in filaments and films. Figure 1B shows an excellent calibration curve for linalool aqueous solution with R^2 of .0.9984.

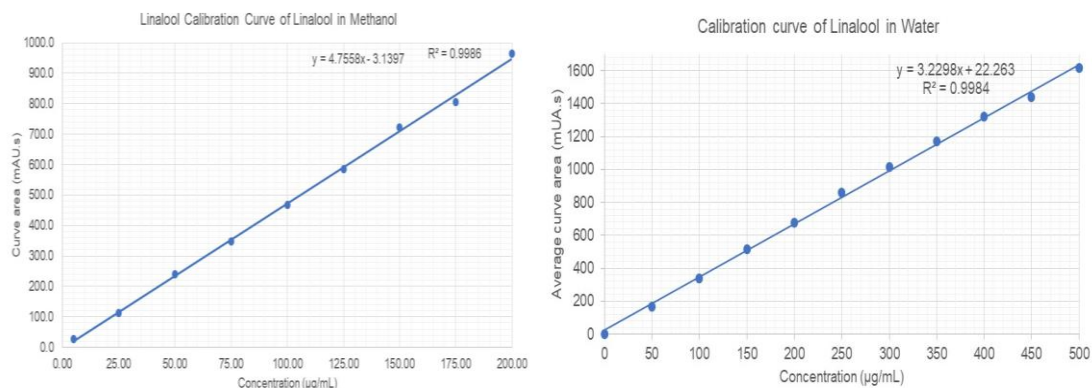


Figure 1: Calibration curve of linalool in A) methanol B) deionised water obtained by the HPLC method.

Figure 2 shows the amounts of linalool measured in each 1 mL of 10 mL stock solution containing 50 mg/mL linalool in methanol. The amounts of linalool were greater than 90% of target value (the red line in the graph shows ideal amounts). The slight decrease may be contributed to the evaporation of linalool during measurements, or adsorption of linalool to the consumables such as filter.

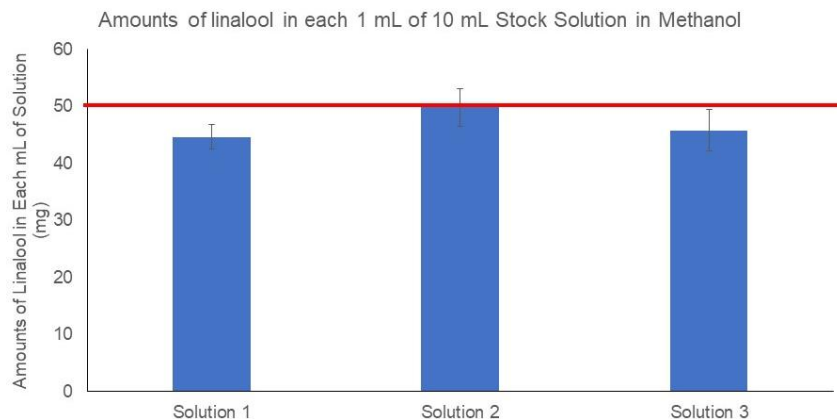


Figure 2: Validating quantifications of linalool by HPLC using methanol as the solvent. The red line presents the expected amounts. Error bars indicate average \pm SD (n=3).

Figure 3 presents the distribution of linalool within the powder mixture measured by using methanol as solvent. The linalool was relatively uniformly distributed in the powder mixture. However, the data suggested slight loss of linalool during preparation of powder (the red line in the graph shows ideal amounts). As explained in the above this could be due to the evaporation of linalool during preparation of the powder mixture or adsorption of linalool to analytical consumables.

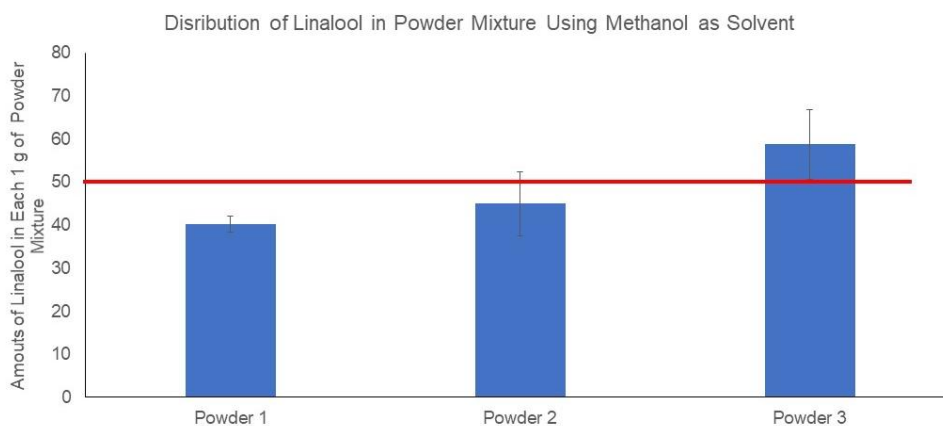


Figure 3: HPLC Quantifications of linalool distribution in the powder mixture by using methanol as solvent. The red line presents the expected amounts. Error bars indicate average \pm SD (n=3).

Figure 4 presents the distribution of linalool in powder mixture by dissolving the samples in deionised water. The amounts of linalool varied around $(40.1 \pm 1.9$ $58.7 \pm 7.9)$ the target value (the red line in the graph shows 50.0 mg ideal amounts).

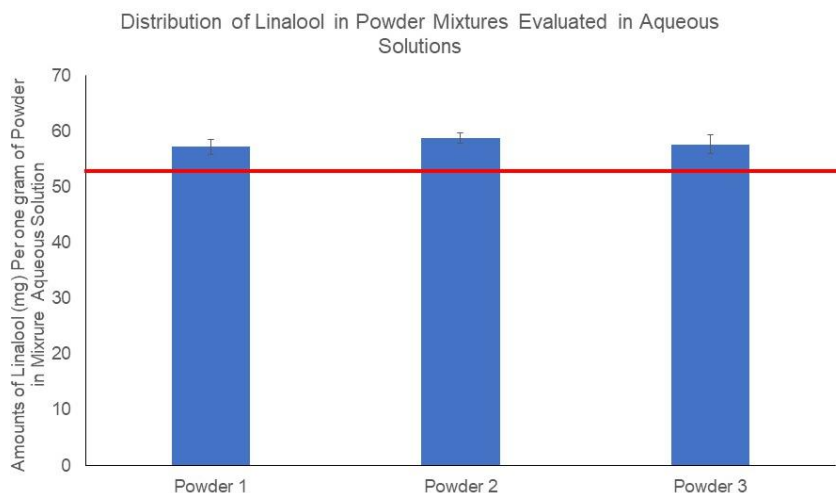


Figure 4: HPLC Quantifications of linalool distribution in the powder mixture by using deionised water as solvent. The red line presents the expected amounts. Error bars indicate average \pm SD (n=3).

Figure 5 compares between the measured and theoretical amounts of linalool in 0.5 g of filament samples. The measured values were in the range of 23.9 ± 1.2 mg to 33.7 ± 2.4 . These were around the typical theoretical values (25 mg), apart from filament 2, which showed slightly higher linalool amounts. These observations suggests that linalool did not evaporate or degrade during the manufacturing of filaments. Preliminary studies found that increasing the aqueous solution temperature to 75°C to accelerate the dissolution of the filament would lead to reduced amounts of linalool in the linalool. This observation suggested evaporation of the linalool during dissolving the filament at high temperatures. Therefore, filament solutions were heated maximum to 30°C .

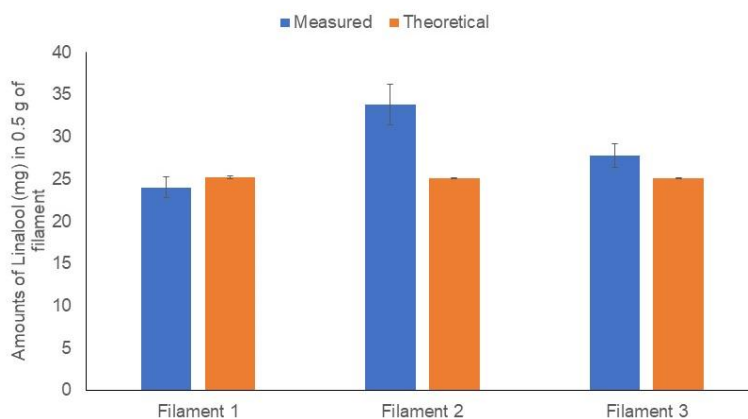


Figure 5: Quantification of linalool in filaments by HPLC and using deionised water as solvent. The theoretical amounts in filaments are also included in the plot. Error bars indicate average \pm SD (n=3).

Figure 6 presents the photographs of printed films. The films had average weight of 78.44 ± 6.84 mg. Generally, the films had a consistent structure, apparat from cases when there were defects in the structure of the film. Figure 7 compares the amounts of linalool in 0.5 g of films between the measured and theoretical values. The amounts of linalool in films were considerably less than theoretical values, 16-45% of theoretical value. This suggests the evaporation/degradation of linalool during printing.

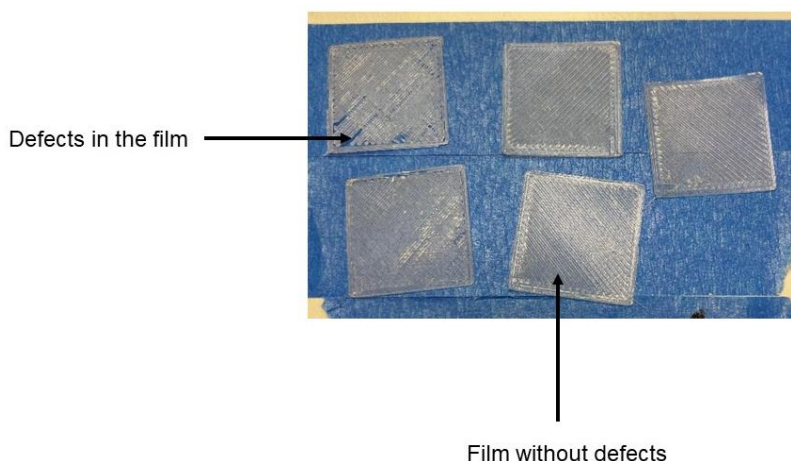


Figure 6: Photographs of 3D printed films.

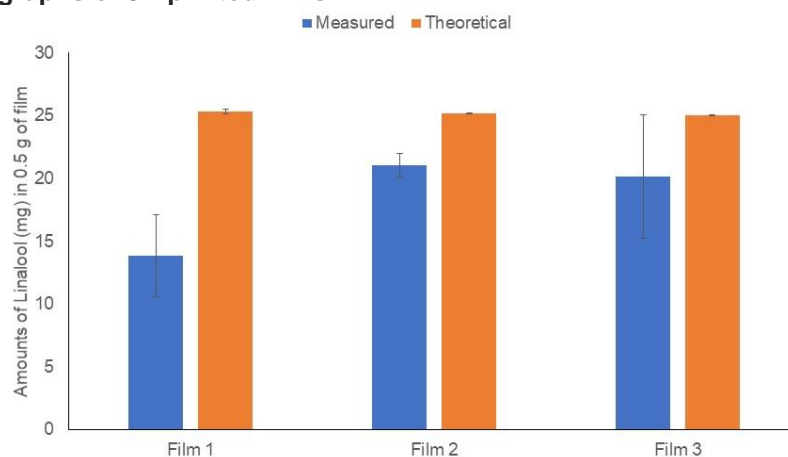


Figure 7: Quantification of linalool in films by HPLC and using deionised water as solvent. The theoretical amounts in films are also included in the plot. Error bars indicate average \pm SD (n=3).

DISCUSSION

This study developed an HPLC method to quantify the amounts of linalool in powder mixtures, filaments, and FDFs. Dissolving the preparations in deionised water was required to obtain clear solutions, allowing filtration through 0.45 μ m films. The HPLC method allowed quantification of linalool in the range of 50-500 μ g/mL. Analysing linalool distribution in powder mixture revealed that when methanol was used as the solvent the average amounts of linalool not only was less than the theoretical values, but also with a large variation in the samples. This suggested promotion of linalool evaporation by the organic solvent. However, the variation of linalool within the powder samples was minimal when aqueous solutions were prepared. In addition, the average amounts of linalool were comparable to the theoretical values. This suggests a suitable distribution of linalool within the powder by hand mixing, at 5% w/w of linalool.

The developed HPLC method was applied to measure the amounts of linalool in filaments and films. It was found that amounts of linalool were as expected in filaments, i.e., there was minimal linalool evaporation. Linalool has a boiling point of 198°C. Therefore, the loss of linalool would not be expected during preparation of filaments as the operational temperature was 75°C. However, it was needed to increase the operational temperature to 185°C, during printing the film. This temperature was close to the boiling point of linalool. Expectedly, there was a significant linalool loss during printing the films. Printing at high temperature was required to allow a smooth flow of molten formulation from the 0.4 mm printer head nozzle. Even, defects were observed in the films during printing at this high temperature. These observations

suggest utilising lower temperatures for printing the films. This may be achieved by increasing the printer head nozzle diameter, which is under investigation.

Lavender oil has been formulated as 80 mg oral capsules (Kasper et al, 2018). These contain Silexan, which is a drug substance. This is a standardised essential oil of *L. angustifolia* flowers obtained by steam distillation.(Kasper et al, 2018) This is an approved drug in Germany and it is sold under brand name of LASEA® (Yap et al, 2019). The capsules are administered for the treatment of anxiety (Kasper, 2013). It was found that a 200 µL dose of lavender oil reduced the heart rate of healthy subjects when neutral video clips (eliciting mild anxiety) was presented to them (Bradley et al, 2009). The lavender essential oil was prepared in capsules containing sunflower oil. The pharmacokinetic studies revealed that blood levels of linalool appeared 10 min, reached maximum level at 30 minutes, and reached minimum level 45 min after dose administration (Bradley et al, 2009). The recommended dose is 80 mg/day for lavender essential oil (Silexan) (Kasper et al, 2018). Therefore, an 80 mg film will contain 4 mg linalool without linalool evaporation. Therefore, 20 films would be the maximum number of films per day and taking a couple of films for the treatment of oral thrush would be below the daily recommended dose of lavender oil (linalool). Consequently, the next step would be evaluating the antifungal activity of the FDFs and identify required number of films per day for the treatment of oral thrush (required total daily dose). As FDFs are easier to administer compared to oral capsules, then FDFs may be also evaluated for the treatment of anxiety. In this approach the films might be thicker to contain more lavender oil. In addition, lavender oil has been formulated as oral gel. Initially a nanoemulsion of lavender oil was formulated utilising Labrasol:Labrafil 1944 in the ratio 6:4 as surfactant mixture, and Lauroglycol-FCC as co-surfactant. Finally, the nano-emulsion was dispersed in chitosan gel (Hosny et al, 2021).

This study optimised previously developed method for quantification of linalool (Xia et al, 2010) in pharmaceutical dosage forms. The previous method measured the amounts of linalool in plant samples. Although filtration was employed using 0.45 µm filters, filter blockage was not reported. While our work clearly experienced filter blockage by powder mixtures. Furthermore, our method allows to measure linalool in filaments and films, which are insoluble in methanol. The dissolution of the filaments and films are needed in the solvent to allow accurately measurements of linalool amounts in the preparations.

CONCLUSIONS

This study developed an HPLC method for quantification of linalool in powder mixtures, filament, and 3D printed films. It was found that printing at high temperatures led to significant linalool loss in the range of 16-45% of initially added linalool into the formulation. Therefore, future work should optimise the printing process to reduce linalool loss.

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