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2021

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ABSTRACT

FORMULATION OF A TOPICAL ANTI-ACNE DRUG DELIVERY SYSTEM INCORPORATING ESSENTIAL OILS

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Acne, a skin disease arising from the pilosebaceous unit, affects approximately 80% of all adults at some point during their lifetime. In the age of emerging antibiotic resistance, researchers are continuously seeking natural alternatives to conventional antibiotics. Essential oils are potent, volatile plant essences which present as a possible alternative. Due to their volatility, water insolubility and thermal instability, the formulation of essential oils into commercial products remains a pharmaceutical challenge. This study aimed to develop a viable anti-acne topical treatment in the form of oil-in-water emulsified lotions as an avenue to overcome these challenges, and optimise the balance between antimicrobial efficacy and physical stability.

The broth microdilution method was used to determine the Minimum Inhibitory Concentration (MIC) of 19 essential oils. The mean MIC across four acne-inducing pathogens (*Cutibacterium acnes*, *Staphylococcus aureus*, *Staphylococcus epidermidis* and *Streptococcus pyogenes*) was calculated for each essential oil to rank them according to their effectiveness. *Vetiver zizanioides* (vetiver) was found to be the most noteworthy essential oil with a mean MIC of 0.14 mg/mL. The second ranked oil was *Santalum austrocaledonicum* (sandalwood), which displayed a mean MIC of 0.23 mg/mL and was the most effective essential oil against *S. aureus*, *S. epidermidis* and *S. pyogenes*. A mean MIC of 0.40 mg/mL for *Thymus vulgaris* (thyme), 0.49 mg/mL for *Syzigium aromaticum* (clove) and 0.50 mg/mL for *Origanum vulgare* (oregano) were obtained, respectively. These five top ranked essential oils were then selected for formulation development.

The Hydrophilic-Lipophilic Balance (HLB) method was used to prepare lotions of optimum physical stability. To determine the HLB of each essential oil, coarse emulsions at HLB values 7-11 were prepared and the emulsion displaying the lowest degree of separation (least creaming) was selected as the required HLB (rHLB) of the essential oil. An HLB value of 7

for *V. zizanioides,* 10 for both *O. vulgare* and *T. vulgaris,* and 11 for both *S. austrocaledonicum* and *S. aromaticum* were obtained. These individual HLB values were then used to calculate the overall rHLB of their respective formulations taking into consideration the HLB of each excipient. Emulsions at this calculated HLB value as well as emulsions extending one HLB unit above and below were prepared. Each emulsion was then assessed and the optimum HLB was determined by selecting the emulsion with the lowest creaming index (CI) over 28 days, the smallest change in mean droplet diameter (MDD) and polydispersity index (PDI) over 84 days and the lowest difference in turbidity ($\%D_T$) between the top and bottom ends of the emulsion over 28 days. The emulsified lotions of *O. vulgare, S. aromaticum* and *V. zizanioides* showed no creaming or phase separation and hence gave no indication of the optimum HLB. The remaining lotions both showed increasing CI with increasing HLB, with the minimum observed at HLB 11 for *S. austrocaledonicum* and HLB 10 for *T. vulgaris*. At tested HLB values of 8, 9 and 10, *V. zizanioides* emulsions displayed maximum stability at HLB 9 with a minimum change in MDD and PDI of 20.61% and 33.33%, and a $\%D_T$ of 0.349%. Emulsions of *T. vulgaris* were prepared at HLB values of 10, 11 and 12 and displayed a change in MDD and PDI of -50.65% and 63.75% respectively and the lowest $\%D_T$ (38.37%) at HLB 10. The *S. austrocaledonicum* emulsions were found to be the most stable at HLB 11 with a change in MDD and PDI of -63.54% and 377.92% respectively and a minimal $\%D_T$ of 8.39%. Similarly, *S. aromaticum* emulsion displayed maximum stability at HLB 11 with a % change in MDD and PDI of 206.06% and 29.57% respectively and a $\%D_T$ of 0.34%. Lastly, peak stability of *O. vulgare* emulsions was seen at HLB 11 with a minimum change in MDD and PDI of 4.57% and 7.65% and $\%D_T$ of 29.19%.

Emulsions of each essential oil at optimum HLB were then selected for further antibacterial studies. Time-kill assays of the formulations were conducted against *S. aureus, S. epidermidis* and *S. pyogenes.* Emulsified lotions of *O. vulgare, S. aromaticum* and *T. vulgaris* exhibited complete bactericidal activity after 3 hrs (faster than the positive control, ciprofloxacin) while those of *V. zizanioides* and *S. austrocaledonicum* eliminated the bacterial load after 24 hrs. The efficacy of time-kill was found to be dependent on the MDD of the formulations, rather than the individual MIC's of the essential oils themselves. All five formulations displayed bactericidal activity against the selected pathogens after three months of storage, signifying long-term antimicrobial stability.

This study has highlighted the potential of essential oils as viable options in the treatment of acne by producing formulations of optimal stability and long-term antimicrobial activity.

Furthermore, this study demonstrates the importance of evaluation of antimicrobial properties in combination with stability studies to develop effective topical preparations in order to deliver consistent and accurate dosing of essential oil containing acne preparation.