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Formulation and Evaluation of Nanoemulsion using Tazarotene and Curcumin

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Authors' contributions

This work was carried out in collaboration among all authors. All authors read and approved the final manuscript.

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Short Research Article

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ABSTRACT

Aims: To formulate and evaluate nanoemulsion of Tazarotene and Curcumin
Study Design: Ultrsonication Methods.
Place and Duration of Study, Sample: Swami Dayanand Postgraduate Institute of Pharmaceuticals Sciences, University of Health Sciences, Rohtak; 2020-2021
Methodology: Oleic acid, tween 80, and propylene glycol were selected as oil, surfactant, and co-surfactant, respectively. The ratio of oil: surfactant: co-surfactant was selected based on a ternary phase diagram using the aqueous titration method. The selected ratio was employed to develop eight formulations of Tazarotene-curcumin by ultra-sonication. The formulations (F1-F8) were characterized using several physicochemical methods like pH, viscosity, particle size distribution, zeta potential, drug content, and in vitro release. The optimized formulation was selected based on the results of characterization.
Results: The formulations (F1-F8) were formulated by using the ultrasonication (high energy) method. The optimized formulation possessed particle size 121, 0.382 PDI, and -20.1 zeta potential. The in vitro release of F6 was found to be 90.9 ± 3.1 at 24 hours. It also passed the thermodynamic stability tests.

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Conclusion: The current investigations conclude that Tazarotene-curcumin nanoemulsion can be used as an alternative to the oral route of tazarotene and is also useful in reducing the adverse effects associated with oral. The physicochemical evaluation of the formulation showed that the nanoemulsion had the necessary properties for a topical formulation.

Keywords: Tazatorene; curcumun; nanoemulsion; ultrasonication; topical.

1. INTRODUCTION

Nanoemulsions (NEs) are emulsions with particle sizes on the nanometric range, generally 20–200 nm, produced solely by shear or high-energy techniques [1]. Low-energy emulsification methods like inversion of phase composition and phase inversion technique involve transitionally inversion caused by factors changing that affect the system's HLB, such as temperature, or catastrophic inversion caused by increasing the dispersed phase volume fraction, i.e. composition. In this work, NEs were created and tested using high-energy ultrasonication [2-4].

Tazarotene(TAZA) is a retinoid prodrug rapidly de-esterified in animals and humans to its active form, the homologous carboxylic acid of TAZA. TAZA, 0.1 percent, was authorized by the US Food and Drug Administration (USFDA) in 2012 to treat acne vulgaris. Because of its poor systemic absorption and fast metabolism, TAZA has an extremely low systematic bioavailability (about 1%). It has serious adverse effects, including skin irritation, sensitization, and phototoxicity. TAZA NE will reduce adverse effects while allowing for controlled release distribution as the decrease in particle size reduces the skin irritation effect of TAZA [5-9]. Curcumin (CUR) is lipophilic and water-insoluble, while the O/W NE is hydrophilic; the formulation's hydrophilic-lipophilic balance is highly advantageous. A sound transdermal system must be biocompatible, preferably biodegradable, and non-irritant to the skin, in addition to enabling a suitable quantity of medication to pass the skin barrier. CUR has been extensively researched for its wide range of pharmacological properties. However, the most significant restriction observed is limited bio-distribution and bioavailability, limiting the potential efficacy against complicated illnesses such as inflammation, acne, and cancer [10-13]. As a result, the current study was carried out in order to create TAZA-CUR NE for topical medication delivery.

2. MATERIALS AND METHODS

2.1 Materials

TAZA and CUR procured from Stallion Laboratory Limited Ahmedabad, India and Cure Tech Skin Care, Himachal Pradesh, India**)**,oleic acid, ethanol, castor oil, methanol, span 60, tween 80, propylene glycol, disodium hydrogen phosphate, potassium di**-**hydrogen orthophosphate were purchased from Loba chemicals, Mumbai**.**

2.2 Methods

Solubility analysis of TAZA and CUR was done using different surfactant, oil, and co**-**surfactant phases**.** Purified water was employed as aqueous phase and based on the solubility oleic acid, tween 80, and propylene glycol was used as oil, surfactant, and co**-**surfactant respectively**.** A pseudo**-**ternary phase diagram was then produced**.**

2.3 Pseudo Ternary Phase Diagram Constructions

To investigate the range of concentration components for the current boundary of NEs, the water titration method was utilized to generate pseudo**-**ternary phase diagrams**.** Two**-**phase diagrams were created by combining tween 80 with propylene glycol in the ratio of 1**:**2 **(**Smix**).** The oil **(**oleic acid**)** and Smix were combined in various ratios such as 1**:**1, 1**:**2, 1**:**3, 1**:**4, and 1**:**5**.** All of the combinations were then diluted with distilled water, which was added dropwise while shaking moderately**.** The optimal oil**:** Smix ratio was chosen based on the development of the zone of NEs in the phase diagram**[**14, 15**].**

2.4 Preparation of TAZA-CUR NE

To create the NEs, the chosen oil**:** Smix ratio was utilised to make NE through ultrasonication**.** Drugs were dispersed in oil phase and blended to aqueous phase using an ultrasonicator for the preparation of TAZA**-**CUR NE**.** To choose the

optimal formulation, a total of eight formulations were created and characterized **[**16**].**

2.5 Characterization of TFB-NEs

2.5.1 pH examination

The pH examination of the formulations was determined at room temperature using a digital pH meter (Thermo Scientific) that had previously been calibrated with standard buffers. To avoid contamination, the electrode was fully cleansed before measurement. pH measurement is necessary for topical applications to guarantee that the formulation does not irritate the skin.

2.5.2 Viscosity

The viscosity was tested at 25 °C using a Viscometer IQ Air (HAAKE RheoWin Viscometer) with a C35 2° spindle arrangement at 0.5 to 100 rpm speed [17, 18].

2.5.3 Particle size and PDI analysis

The droplet size of TAZA**-**CUR NEs was defined in triplicate using dynamic light scattering by zeta sizer at a temperature of 25 °C and an angle of 90°**. (**Malvern, UK**).** All samples were diluted 1**:**30 with distilled water prior to analysis**.** The software generated the graph illustrating the peak of droplet size with PDI **(**Polydispersity Index**).**

2.5.4 Determination of zeta potential

The goal of this research was to determine the amount of zeta potential existing in the NE**.** The NE sample was diluted with distilled water in the same way as dilutions were performed during particle size and PDI analyses**[**3, 19**].**

2.5.5 Entrapment efficiency (% EE) and loading efficiency (% LE)

The **%** EE and LE of all formulations were determined by computing the quantity of unentrapped medication in the aqueous solution, centrifuging at 5000 rpm for 25 minutes, and filtering the supernatant**.** Dilutions were also made and tested with a UV spectrophotometer calibrated to 351 and 421 nm**.** The following equations were used to calculate **%** EE and LE**:**

$$\%\mathrm{EE} = \frac{W_{(\text{total drug})} - W_{(\text{free Drug})}}{W_{(\text{total drug})}} \quad (1)$$

$$\%\mathrm{LE} = \frac{W_{(\text{total drug})} - W_{(\text{free Drug})}}{W_{(\text{total drug})} + W_{(\text{lipid content})}} \quad (2)$$

2.5.6 Drug content uniformity

Samples weighing 500 mg were taken and extracted using methanol, then centrifugation method for 15 minutes at 3000 rpm. The filtrate was examined using UV spectrophotometer at λ_{max} 351 nm and 421 nm for TAZA and CUR after the filtration of supernatant by using 0.45 µm filter paper. The process is performed in triplicate to avoid error and obtain the precise values[20, 21].

2.5.7 *In vitro* release study

The *in vitro* concentrations of TAZA and CUR in TAZA**-**CUR NEs were determined using a Franz diffusion cell with a glass cylinder open at both ends**.** NE equal to 2 mg of TAZA**-**CUR was evenly distributed over the surface of cellophane membrane **(**which had already been soaked in 7**.**4 pH PBS for 24 hours**)**, and the donor compartment was filled with 7**.**4 pH PBS**.** The entire assembly was placed on a magnetic stirrer set at 37 2 °C and 100 rpm**.** For 24 hours, aliquots of 1 ml sample were extracted at predetermined intervals**.** After collecting the samples, a UV spectrophotometer with maximum settings of 351 nm and 421 nm was used to analyse the release [21, 22].

2.5.8 Thermodynamic stability studies

Thermodynamic stability studies are important for establishing the physical stability of TAZA-CUR NEs. The following study was performed to examine the formulations' thermodynamic stability.

2.5.8.1 Freeze–thaw cycle (6 cycles at -25° and 25°C)

The formulations were maintained at a temperature of 25 °C for 24 hours. After 24 hours, the formulation was withdrawn and kept at room temperature (25 °C). TAZA-CUR NEs returned to their original temperature in around 2-3 minutes. Such cycles were repeated three times.

2.5.8.2 Centrifugation

The NEs were then centrifuged for 30 minutes at 5000 rpm to check for creaming, cracking, and phase separation.

2.5.8.3 Statistical analysis

The mean SD value was used to express all of the data, and the n value is three**.**

3. RESULTS

The aqueous phase titration research determined that the oil: surfactant: co-surfactant ratio should be 1:1:2. Utilizing this ratio, 8 nanoemulsion formulations were created using a high energy technique such as ultrasonication. The formulas and different characterization characteristics of the nanoemulsion are described in Table 1.

3.1 pH, Viscosity, Drug Content Analysis

Table 2 describes the pH and viscosity of all formulations. The pH range for oleic acid containing topical preparations has been shown to be stable in the range of 5.9 ± 0.7 to 6.33 ± 0.5. The observed pH range is within the safe range for topical treatments as well as the pH of skin. The viscosity range was determined to be 15.8± 3.8 to 19.5± 3.9 Pas. The viscosity study indicated that the TAZA-CUR NEs had finely dispersed particles, indicating a satisfactory flow. Table 2 shows that the drug content ranged from 71.2±1.3 to 90.9 ± 3.1 for TAZA and 70.9 ± 0.9 to 89.9 ± 2.5 for CUR.

3.2 Particle Size, PDI, and Zeta Potential

The formulations' particle sizes and PDIs varied from 121 ± 2.4 to 256.4 ± 3.7 nm and 0.246 to 0.481, respectively. The PDI value is less than 0.7, indicating homogeneous and tapered particle dispersion. The size range also revealed the effective particle size of the formulation for topical nanoemulsion administration. Furthermore, the zeta potential ranges from -14.1 ± 5.1 to -20.1 ± 1.8, suggesting that the surface charge potential is stable and the formulation has a lower inclination to assemble (Fig. 2 and 3). Table 1 shows the droplet size and zeta potential values.

3.3 In-vitro Release Studies

The *in vitro* release behavior of all formulations in phosphate buffer (PBS) pH 7.4 and indicated the percent cumulative release of formulations F1 to F8. In comparison to other formulations, the F8 formulation was shown to have the highest in vitro release at 24 hours, i.e. 89.15 ±3.8 (Fig. 3). This demonstrated the importance of tween 80 and propylene glycol as surfactants and cosurfactants in increasing drug release. Tween 80 has the capacity to change the physicochemical properties of skin when it interacts with the phospholipid bilayer, allowing the medication to enter deeply.

3.4 Thermodynamic Stability Testing

After physical stability testing, no substantial changes in the formulation were found, and no evidence of phase separation were seen during centrifugation. Table 3 summarizes the findings of thermodynamic stability investigations.

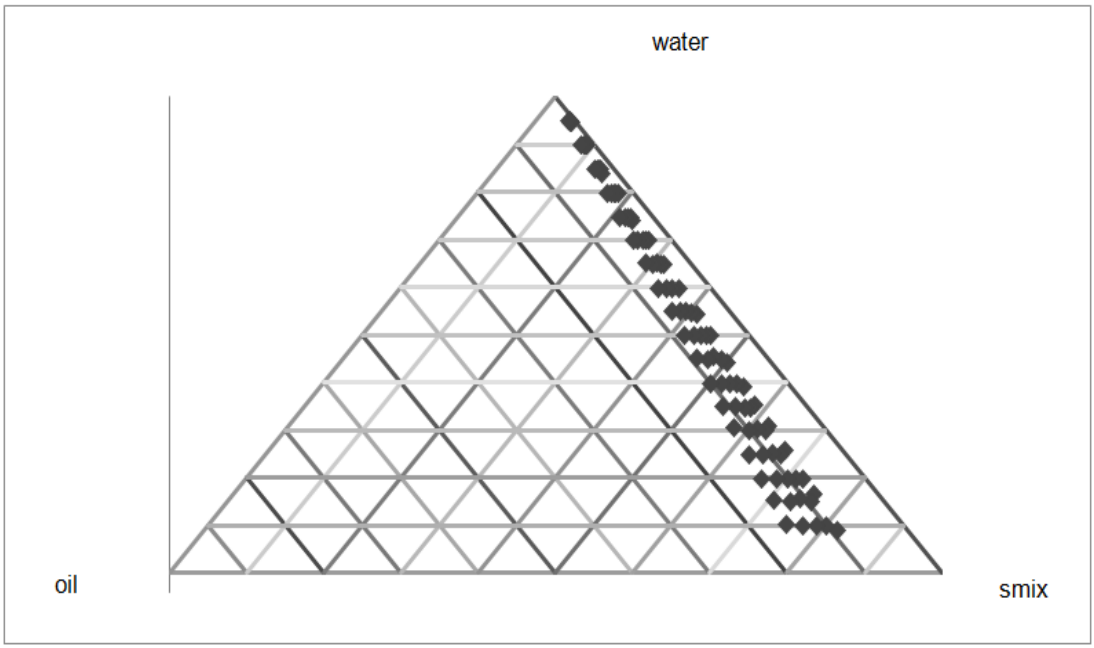

Fig. 1. Description of pseudo ternary phase diagram construction

Table 1. Description of the formulation and characterization parameters of TFB-NE

Formulations	Oil	Surfactant	Co-surfactant	Particle Size (nm)	Zeta potential	Entrapment Efficiency of TAZA	Loading Efficiency of TAZA
F1	12.5	12.5	25	165 ± 2.6	-17.1 ± 1.8	79.8 ± 4.2	10.5 ± 0.9
F2	10	10	20	201 ± 1.1	-14.9 ± 2.1	72.9 ± 1.8	9.3 ± 2.4
F3	12.5	12.5	25	171.2 ± 2.6	-19.8 ± 1.2	80..5 ± 3.6	11.1 ± 1.3
F4	10	10	20	188.5 ± 1.1	-15.5 ± 3.6	70.1 ± 2.9	9.1 ± 1.8
F5	15	15	30	127.6 ± 1.9	-17.9 ± 2.5	80.5 ± 4.3	15.1 ± 0.8
F6	15	15	30	121 ± 2.4	-20.1 ± 1.8	79.2 ± 3.5	16.01 ± 2.1
F7	8	8	16	252.2 ± 2.1	-18.5 ± 1.2	71.8 ± 4.2	6.8 ± 3.2
F8	8	8	16	256.4 ± 3.7	-15.5 ± 3.3	70.4 ± 4.1	5.6 ± 1.3

**All the values are expressed in terms of mean±SD, where n=3*

Table 2. Showing the results of pH, viscosity, and drug content

Formulations	pH	Viscosity (Pas)	Drug Content of TAZA	Drug Content of CUR
F1	5.9 ± 0.7	18.9 ± 4.4	88.3 ± 1.8	85.3 ± 3.4
F2	6.2 ± 0.8	16.5 ± 5.2	85.3 ± 2.1	81.3 ±1.5
F3	5.7 ± 0.5	19.5 ± 3.9	87.3 ±0.8	85.6± 2.3
F4	6.2 ± 1.1	18.7 ± 3.6	78.4 ± 2.3	75.8 ± 1.3
F5	5.9 ± 0.6	16.1 ± 2.9	90.6± 2.3	88.6± 1.6
F6	6.0 ± 0.5	15.8 ± 3.8	90.9 ± 3.1	89.9 ± 2.5
F7	6.33 ± 0.5	14.1 ± 5.1	73.9 ± 1.8	79.2 ± 1.4
F8	6.1 ± 0.6	18.3 ± 3.4	71.2±1.3	70.9 ± 0.9

**All the values are expressed in terms of mean±SD, where n=3*

Table 3. Showing results of thermodynamic stability studies

Physical Stability Tests	Particle Size	pH	Drug Content OF TAZA	Drug Content of CUR	Phase Separation
Freeze–thaw cycle	122.6 ± 1.2nm	6.1± 0.3	90.76 ± 2.9	89.61 ± 1.6	Not observed
Centrifugation	No significant change observed				

Z-Average (d.nm):	121.0	**Peak 1:**	182.8	98.4	115.9
PdI:	0.382	**Peak 2:**	4861	1.6	696.2
Intercept:	0.980	**Peak 3:**	0.000	0.0	0.000
Result quality	Good				

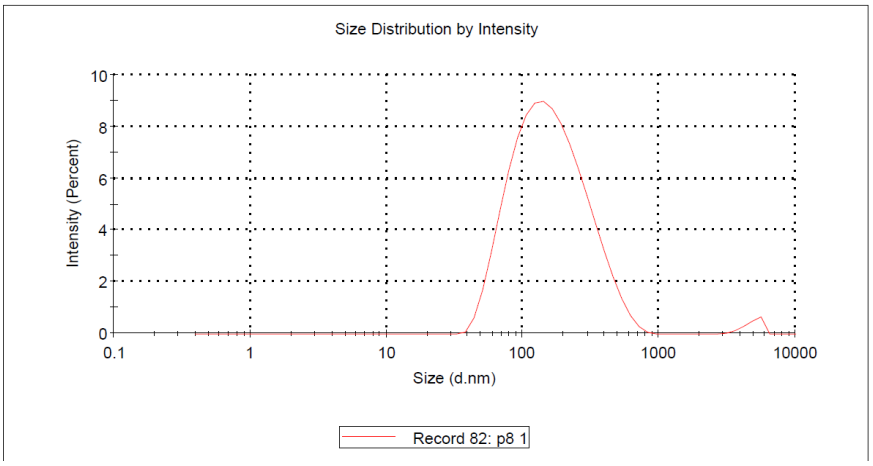

Fig. 2. Description of particle Size

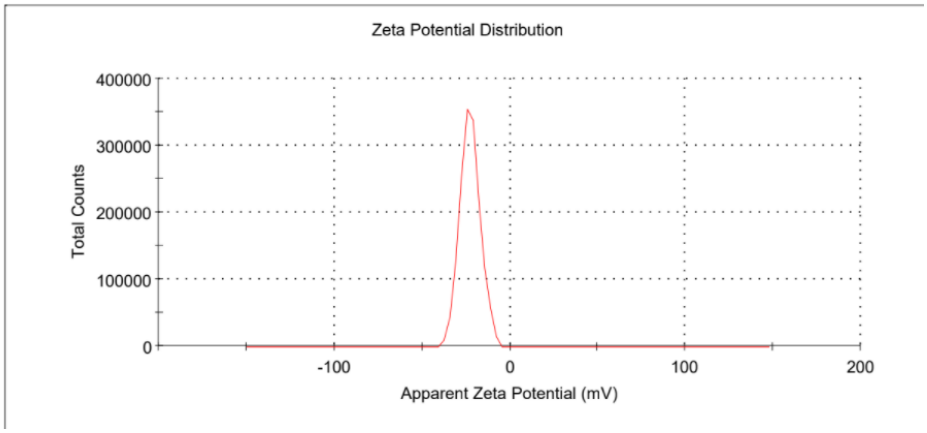

Fig. 3. Description of zeta potential

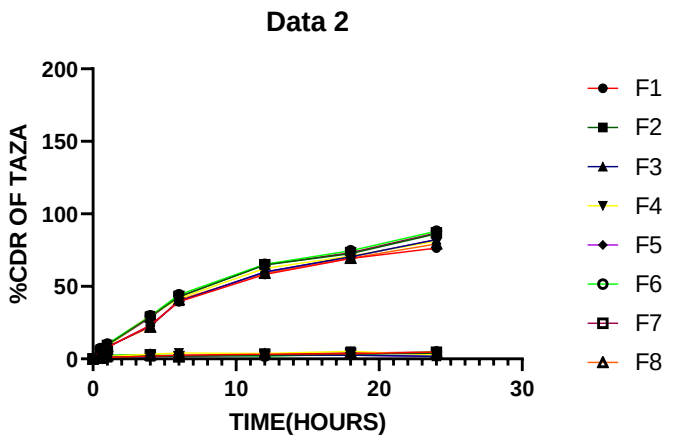

Fig. 4. Depicting % cumulative release of TAZA from formulations (F1- F8)

4. DISCUSSION

The present formulation makes extensive use of oleic acid, tween 80, and propylene glycol. Oleic acid can act as a percutaneous absorption enhancer for a number of medications by breaking the lipid structure of the stratum corneum and permitting drug penetration [23]. It is derived from natural sources and is biodegradable, making it suitable for use on human skin. Tween 80 is a non-ionic hydrophilic surfactant used in component emulsification and dispersion. It also helps to reduce particle size and improves the NE's medication loading efficiency. Propylene glycol aids in the trapping of drug molecules and their in vitro permeability [24-27].

The pH of the NE formulations F1-F8 ranged from 5.8±0.5 to 6.3±0.8, confirming their appropriateness for the skin, as extremely acidic or alkaline pH might induce skin irritation or erythema. The particle size with range from 121 ± 2.4 to 256.4 ± 3.7 nm all formulations. Permeability through the stratum corneum is aided by the small size. The zeta potential range of +25 mV to -25 mV shows the stability of the NE; the zeta potential of all formulations was determined to be in this range.F6 had a percent EE of 79.2 ± 3.5, a percent LE of 16.01 ± 2.1 of TAZA, and a drug content of 90.9 ± 3.1and 89.9 ± 2.5, respectively for TAZA and CUR. In comparison to other formulations, revealed the greatest amount. Furthermore, the in vitro release of F6 was determined to be 89.15 ±3.8, which is the highest in comparison to other formulations. The highest release from F6 indicated that the composition of F6 is extremely efficient in TAZA-CUR penetration from skin. The thermodynamic stability experiments further demonstrated the stability of F6 during the freeze-thaw cycle and centrifugation, with no significant change seen following the thermodynamic stability studies. As a result of the aforementioned results of the physicochemical properties of TAZA-CUR NE, it can be claimed that NE can serve as a superior dosage form option for topical delivery.

5. CONCLUSION

The current study found that a NE formulation comprising TAZA and CUR may be effectively formed utilizing a high energy technique, such as ultrasonication. As a result, the TAZA-CUR NE may be a successful method that may be administered topically for greater performance and fewer side effects. Furthermore, the co-additive formulation of TAZA CUR possesses all of the required features; nevertheless, there is a dearth of research that can determine the validity of this co-additive addition for diverse skin ailments. The NEG was discovered to have acoustic properties.

DISCLAIMER

The products used for this research are commonly and predominantly use products in our area of research and country. There is absolutely 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 the advancement of knowledge. Also, the research was not funded by the producing company rather it was funded by personal efforts of the authors.

CONSENT

It is not applicable.

ETHICAL APPROVAL

It is not applicable.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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