Contents lists available at UGC-CARE

International Journal of Pharmaceutical Sciences and Drug Research

[ISSN: 0975-248X; CODEN (USA): IJPSPP]

journal home page : http://ijpsdr.com/index.php/ijpsdr

Research Article

Development and Characterization of Topical Microemulsion of Tranexamic Acid

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ARTICLE INFO

Article history:

Received: 19 May, 2021

Revised: 14 February, 2022

Accepted: 22 February, 2022

Published: 30 March, 2022

Keywords:

Hyperpigmentation, Microemulsion, Topical drug delivery, Tranexamic acid.

DOI:

10.25004/IJPSDR.2022.140205

ABSTRACT

The present study was performed to develop a topical microemulsion of the drug tranexamic acid (TXA) to help patients with hyperpigmentation. Microemulsion was made using dropwise addition method with the help of several surfactants and co-surfactants. The formulation was then evaluated for several parameters like clarity, particle size, drug diffusion etc. Drug Diffusion study was done using goat epidermal skin and at the end of the study it was found that the drug release was of 93.83%. Clarity of microemulsion was 98% and particle size and zeta potential of the formulation suggested it was a clear and stable system. To conclude, a promising drug delivery system for treatment of hyperpigmentation was developed and that it would help cosmetic market.

Introduction

Tranexamic acid (TXA) is known as synthetic derivative of lysine. It is an anti-fibrinolytic agent used to treat and prevent major bleeding in the human body. Despite of having similar mechanism of action that of aminocaproic acid this drug is 10x more potent than those traditional aminocaproic acid. TXA was first patented in 1957 and that was registered for approval in 1986. The oral formulation of TXA is used to treat hypermenorrhea – a condition of excessive bleeding during menstruation in women. Injections of TXA are also available to stop bleeding in patients of major accident. In the recent studies, researchers found that the drug exhibited anti-hyper pigmentary effect in the women who used TXA for their menstruation condition.[1] Later, more studies revealed its mechanism in treatment of hyperpigmentation is promising. If a healthy individual consumes the drug only for the sole purpose of getting flawless skin, it could cause severe side effects like alteration of blood clotting time, high risk of myocardial infraction, varicose vein etc. To overcome these side effects, it was call of time to formulate a topical system for drug delivery of TXA.[2] The topical drug transfer has become a technology under the spotlight that offers a diversity of noteworthy quantifiable profits over other delivery systems.[3] Since topical drug delivery bids precise release of the drug into the subject, it helps maintain stable blood-level profile, resultant in condensed systemic undesirable effects and, occasionally, enhanced effectiveness over other dosage forms offered to patients. In addition, because topical dose forms are user-friendly, suitable, trouble-free, and offer multi-day dosing, it is usually acknowledged that they offer enhanced patient compliance.[4] As we target skin in the topical route of administration the desirable results are observed has the only disadvantage that it cannot be taken orally for the sole purpose of treating hyperpigmentation. It is necessary to

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Relevant conflicts of interest/financial disclosures: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

come up with a safer route of administration to overcome those side effects. This topical system would help TXA act where it is meant to be i.e., in skin.[5]

The sole purpose of this experiment is to develop a topical drug delivery mode for the drug which helps overcome the systemic side effects and yet give us the desirable effect and treat the condition of hyperpigmentation.

Microemulsion has gained its place in spotlight in pharmaceutical industries and exertions are under progress to outspread its claims in various paths of pharmaceutical formulations.[6] Microemulsions have energetically influenced drug distribution research over several eras and several micro/nanoscale skills/carriers have been and are in verge of being sightsaw for refining healing efficacy of drugs.[7] The numerous customs by which microscale technologies can advance therapeutic efficiency of drugs are:

- Enhancing solubility capacity of lipophilic medications.
- Enhancing permeation or transportation of drugs that cannot cross skin barrier easily. (class III and class IV drugs as per the Biopharmaceutical Classification System [BCS])
- Altering biodistribution and drug character of drugs in plasma.
- Averting dilapidation of drugs in biological environment.
- Permitting beleaguered transport of active to the site of action.

Microemulsion system is referred to as thermodynamically stable, isotropic and very clear liquid mixture of oily phase and aqueous phase stabilized by a surfactant usually accompanied by co-surfactant.[8]

The microemulsion is likely to be a very appropriate system as a drug delivery system for the drug agents. Topical systems formulated with the microemulsion technology possess excellent stability and very small particle size which gives it a very special position in the pharma market.[9]

This particular research work will create a new possibility in treatment of hyperpigmentation. Unlike the conventional drugs which exhibit the side effects like skin erythema, hypopigmentation and redness this research provides a chance of better and safer treatment for the condition. Also, TXA can be used as over the counter because of its safety profile.[10] We forecast this study to be breakthrough in the skincare and topical industry.

Components of Micro Emulsion

A basic microemulsion consists of three phases namely, oil phase or non-aqueous phase, surfactant-co surfactant system and aqueous phase. Oil phase helps the lipophilic drug to penetrate the skin better while aqueous phase helps hydrophilic part to penetrate better. While surfactant systems help oil to get miscible properly.[11]

Materials and Methods

TXA was gifted by Evonik, Co-enzyme Q 10 was gifted by diagnostic and statistical manual (DSM), Tween 20 and Tween 80 were sampled by Croda, the sample of PEG 40 hydrogenated castor oil was given by Seppic, propylene glycol and PEG 400 was given by Rankem, jojoba oil and coconut oil were given by AG Organics. All the samples were arranged by Brillare Science Pvt ltd and we offer our sincere thanks to them.

Formulation of Microemulsion

Several numbers of microemulsions were prepared by opting for drop wise addition method. Firstly, the drug was dissolved into the aqua with help of stirring. Then, the oil and surfactant system were added to aqua drop wise under the stirring condition until the clear microemulsion system was formed.[12] Preliminary batches were taken as per the above mentioned procedure and is shown in Table 1

Calibration Curve of TXA

Accurately weighed drug (10 mg) of drug was transferred to 100 mL volumetric flask. Drug was dissolved in 25 mL distilled water and volume was completed up-to 100 with distilled water. Standard solution of 100 µg/mL was thus made in distilled water.

Aliquot part of 0.2 to 2.0 mL shares of standard solution was transferred to a succession of 10 mL volumetric flask and volume was made up-to the mark of 10 mL with distilled aqua & succession of 2 to 20 µg/mL concentration solutions were obtained. All these samples were then taken for absorbance readings at 440 nm as wavelength maxima keeping distilled water as blank solution in Shimadzu UV-visible spectrophotometer.[13]

Table 1: Preliminary trial batches of Microemulsion

Batches	*METR1 (%)*	*METR2 (%)*	*METR3 (%)*	*METR4 (%)*	*METR5 (%)*	*METR6 (%)*
Drug	5	5	5	5	5	5
Jojoba Oil	5	3	-	-	-	-
Coconut Oil	-	-	3	5	-	-
All Q Plus	-	-	-		5	5
Simulsol 1293	30	20	25	25	10	12
PEG 400	15	10	12.5	12.5	10	12
Distilled water	45	62	54.5	52.5	70	66

Evaluation of Topical Microemulsion

Particle Size

A Nanotrack Wave II armed with and argon optical maser was employed for assessing the size of particle and particle size dispersal. Light scattering was scrutinized at 90° angle and 25°C. The mean drops dimensions and polydispersity index be situated considered from intensity, volume, and bimodal distribution presumptuous spherical particles.[14]

Measurement of Zeta Potential

Zeta potential was determined with Zetasizer HSA 3000. Trials were positioned in clear one-use zeta cells and outcomes were documented. Earlier tapping the renewed sample, cuvettes were cleaned with the methanol and bathed by means of the sample to be measured before all experiments.[14]

Drug Analysis

% Drug content of TXA was determined spectrophotometrically at 440nm in UV-Visible Spectrophotometer.[13]

Viscosity Measurement

The viscosity of the final optimized batches was determined using Brookfield LV viscometer. Samples were examined with spindle #61 at 3 rpm. Spindle #61 are usually employed for samples which have watery consistency. Samples were evaluated at room temperature and were analysed thrice.[15]

pH Measurement

The pH of the microemulsions was determined Lab India pH meter at room temperature.[14]

Physical Stability of Microemulsion

A stability study was done by exposing them to temperature stability. The temperature steadiness study was passed out according to ICH Q1(C) guideline. So, constructed on the guideline keeping preparations trial at dissimilar temperatures (2-8°C, 25^{0}C) for one month and pictorial examination was done by withdrawing samples at month & assessed parameters were phase parting, formation of floccules & settlement of precipitates.[16]

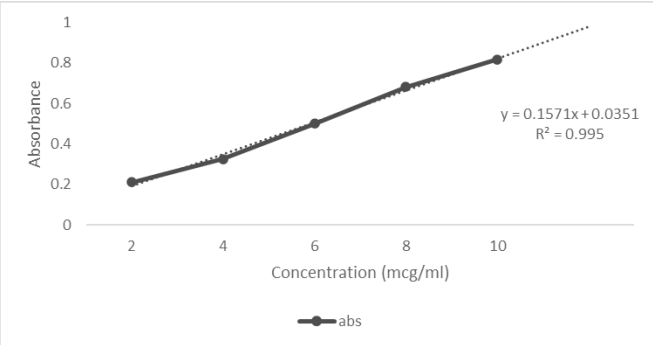

Fig. 1: Calibration Curve of Tranexamic Acid at 440 nm

In vitro Diffusion studies

The diffusion studies of the developed microemulsion serum were carried out in Franz diffusion cell for examining the release of drug from the serum through goat skin. Sample of formulated serum (2 g) was taken on goat skin[17] and it was made sure that the hairs were removed to make sure there is no alteration in release pattern and the diffusion studies were done at room temperature using 21 ml of phosphate buffer (pH 5.5) [17] as the diffusion medium. 2 ml of respective sample was withdrawn occasionally at time difference of 1, 2, 3, 4, 5, 6, 7 and 8 hrs. and each sample were swapped with equivalent capacity of fresh phosphate buffer. Then the 1ml samples were diluted with suitable diluent and analyzed for the drug component by using phosphate buffer as blank. Samples were then taken forward for recording the corresponding absorbance.[18]

Results and Discussion

Results

Calibration curve of TXA

This particular method opted for calibration plot of TXA showed good linear regression of absorbance for the sample of several concentration range. This gave the equation of y = 0.1571x + 0.0351 with a correlation co-efficient of 0.995.[13] The linear calibration graph is shown in Figure 1.

Determination of Particle Size

Samples were analyzed for particle size and the results suggest that METR1 which had lowest concentration of surfactant-co-surfactant in ratio 1:1 had lowest particle size. Graphs of particle size determination are given below. The peak suggests maximum particles within that size range. The particle size graph is as shown in Fig. 2.

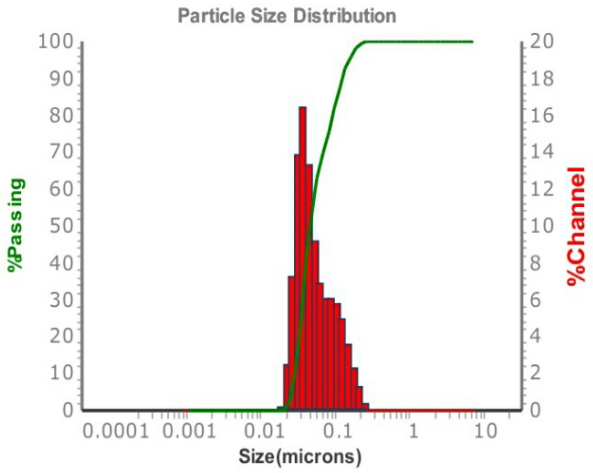

Fig. 2: Particle size graph of formulation METR1

Clarity of Microemulsion

As per the definition of Microemulsion it should be a clear system, because of the micro size of the globules the system can easily transmit light through it and hence optical clarity of the system is of utmost importance. Transmittance was studied against of water and it was found that the system has 98% of transmittance.[19] Fig. 3 displays the clarity of optimized batch of microemulsion

Evaluation of Microemulsion Formulations

The pH of all 3 formulations was detected in the series of 6.2 to 6.6 which is shown in Table 2, which was close to the skin pH and may not have any irritation to the skin. From the results METR1 (6.2 ± 0.06), METR2 (6.4 ± 1.23), METR3 (6.6 ± 0.86) preparations were neutral in the nature, METR1 formulation has pH near to the skin pH.[20] From the results, it was found that all 3 formulations have differences in viscosity. As surfactant concentration increases formulation viscosity increases. METR1 had shown less viscosity (2.30 ± 0.14) than the METR2 (3.60 ± 0.46), METR3 (4.13 ± 0.37) preparation which is shown in viscosity Table 2. % Drug content was determined by the UV spectroscopy analysis to discover out the stability of the microemulsion. From the results obtained, it was found that formulation METR1 (98.65 ± 0.01) showed highest % drug content in comparison to METR2 (95.18 ± 0.14) & METR3 (93.76 ± 0.07) which is displayed in Table 2.

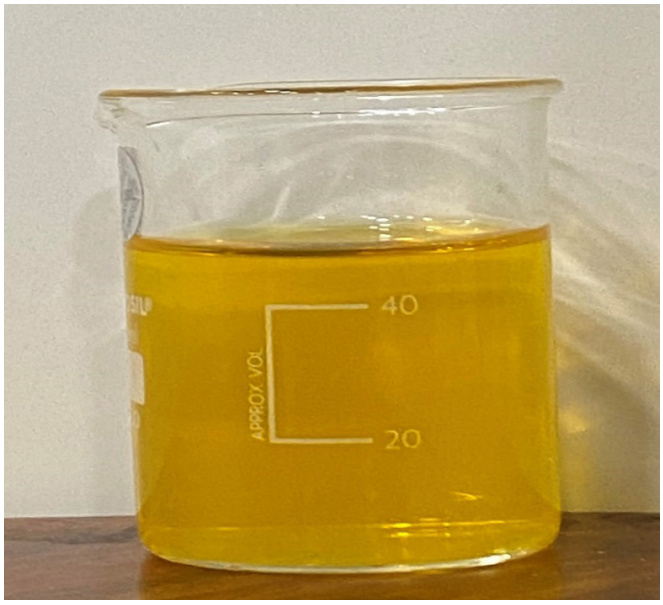

Fig. 3: Clarity of Microemulsion METR1

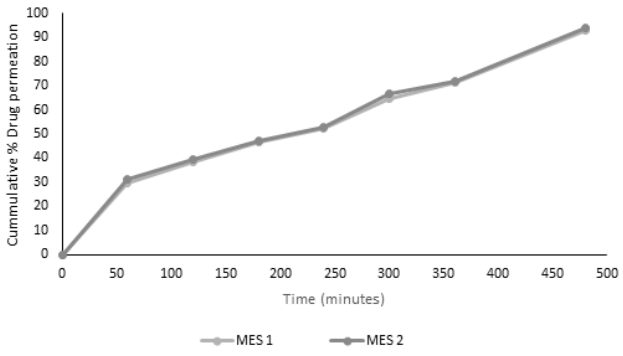

Figure 4: Cumulative % Drug permeation profile of Tranexamic Acid microemulsion based serum formulation through the goat abdominal skin

Table 2: Assessment of Microemulsion Formulations

Formulation	*pH*	*Viscosity (cps)*	*% Drug Content*
METR1	6.2±0.06 *	2.30±0.14*	98.65 ± 0.01*
METR2	6.4 ±1.23*	3.60±0.46*	95.18 ± 0.14*
METR3	6.6 ±0.86*	4.13±0.37*	93.76 ± 0.07*

**- Data expressed as mean±SD (n=3)*

Physical Stability Study of Microemulsion

Stability studies of METR1 were done by exposing them to temperature stability. Temperature conditions were applied according to the ICH Q1(C) guideline.[21]

METR1 microemulsion presented that no any type of layer separation, formation of floccules & occurrence of precipitates at all three diverse temperature conditions after 30 days.

In Vitro Skin Permeability Studies of Microemulsion

The diffusion studies of the developed microemulsion serum were carried out in Franz diffusion cell for examining the release of drug from the serum through goat skin. Sample of formulated serum (2 g) was taken on goat skin and it was made sure that the hairs were removed to make sure there is no alteration in release pattern and the diffusion studies were done at room temperature using 21 ml of phosphate buffer (pH 5.5) as the diffusion medium. 2 ml of respective sample was withdrawn occasionally at time difference of 1, 2, 3, 4, 5, 6, 7 and 8 hrs. And each sample were swapped with equivalent capacity of fresh phosphate buffer. Then the 1ml samples were diluted with suitable diluent and analyzed for the drug component by using phosphate buffer as blank. Samples were then taken forward for recording the corresponding absorbance.

The formulations showed very good diffusion data. As shown in Figure 4 the formulations showed very good diffusion data. MES1 and MES2 had 92.73% and 93.83% drug release after 480 minutes respectively. This recommends that the formulation is skilled of releasing the drug into skin effectively.

Discussion

Topical drug delivery system of the drug TXA was a need of the hour to utilize its amazing anti-hyper pigmentary effect. It cannot be consumed orally because of the serious side effects associated with it. Microemulsion based serum is one of its kind formulations, which will help

drug permeate through outer layer of skin. As the first step of experiment the solubility of the drug was checked in various oils, surfactants and co-surfactants. From the result it was found that co-enzyme q10 when used as oil showed maximum solubilizing capacity of drug. For surfactant PEG 40 hydrogenated castor oil showed great results in solubilizing the drug and for co-surfactant PEG 400 proved itself best choice for the drug. It is vital to check solubility in all the components to ensure maximum encapsulation of drug and hence enhancing the performance of drug.[22,23]

After the optimization and all the stability data, 24% smix formulation was formulated into serum. Serum is nothing but a slightly viscous microemulsion. Hence two concentrations were used to see which formulation has capacity to form a proper drop. These serums were also evaluated for pH, viscosity, %drug content and in-vitro drug dissolutions.

pH of both the formulations was set to 5.5 because that pH is similar to skin pH. Having it closer to skin is beneficial because it not only proves it self-non-irritant but also aids in penetration of the skin. Ideally for serums pH is set to 5-5.5 commercially.[24]

Viscosity increased than that of simple microemulsion. It was also noted that the batch MES2 showed slightly more viscosity aiding to the increased concentration of xanthan gum.

In-vitro drug release was performed in Franz diffusion cell using goat abdominal skin as permeation membrane. Studies were performed for 480 minutes using phosphate buffer as diffusion media. After the end of the studies, it was also found that MES2 formulation showed more drug release than MES1.[25]

Stability of the serum batch was also performed and end of the stability parameters like pH, viscosity and drug content. It was found that no significant change was observed in the parameters after 30 days.[26]

Conclusion

Topical microemulsion formulation of TXA was successfully developed for the treatment of hyperpigmentation. These formulations were optimized and characterized for various physicochemical parameters which indicated stable microemulsion with desired release profile of the TXA. The optimized formulation showed release of the TXA into skin effectively for 8 hrs. This microemulsion can be a novel breakthrough for skincare industry.

Acknowledgements

We would very much grateful to Brillare Science Pvt. Ltd for providing us with their guidance and all the materials which were required for the experimental studies.

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HOW TO CITE THIS ARTICLE: Shukla M, Patel RP, Patel N. Development and Characterization of Topical Microemulsion of Tranexamic Acid. Int. J. Pharm. Sci. Drug Res. 2022;14(2):189-194. **DOI:** 10.25004/IJPSDR.2022.140205