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DEVELOPMENT AND EVALUATION OF MICRO-EMULSION FORMULATIONS OF TERBINAFINE HYDROCHLORIDE

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ABSTRACT

Microemulsions (ME) basically are the mixture of oil, surfactant (SA) and water, with a co surfactant (Co-SA) in different ratio. This mixture is clear and stable. The final prepared fluid possesses low viscosity. ME are isotropic, stable transparent systems of with a droplets diameter>500 nm. Due to small droplets size, they may serve an excellent carrier for drugs having poor water solubility. Terbinafine hydrochloride is derivative of allylamine, and is used orally in the treatment of hepatic failure, neutropenia. Whenever given topically, it is used for the skin infections like jock itch, and for ringworm and Candida species. In the present study an attempt was made to increase solubility of Terbinafine hydrochloride by the means of ME formulations. Prepared formulations were evaluated on different parameters. Study concluded that the means of microemulsions formulations solubility of Terbinafine hydrochloride can be enhanced.

KEYWORDS: Microemulsions, Terbinafine hydrochloride, Thermodynamics, Co-solvents, Transparent, Coarse.

INTRODUCTION

A microemulsion is considered to be a thermodynamically or kinetically stable liquid dispersion of an oil phase and a water phase, in combination with a surfactant. The dispersed phase typically comprises small particles or droplets, with a size range of 5 nm-200 nm, and has very low oil/water interfacial tension.[1,2] Because the droplet size is less than 25% of the wavelength of visible light, microemulsions are transparent.

ME are clear systems of with a droplets diameter>500 nm.[3] Due to small droplets size, they may serve an excellent carrier for drugs having poor water solubility. Aqueous phase consists of salt(s), and/or other ingredients, while oil consists of hydrocarbons and olefins. There is need of high shear in the preparation of emulsions, but for ME, there is no need of high shear, they simply formulated by the mixing of different ingredients[4].O/W microemulsion tends to increase solubility by changing in its dispersed phase and improve oral bioavailability by the means of increase in rate of absorption and its wettability.[5-8]

Terbinafine hydrochloride is derivative of allylamine, and is used orally in the treatment of hepatic failure, neutropenia. Whenever given topically, it is used for the skin infections like jock itch, and for ringworm and Candida species.[9,10]

In the present study an attempt was made to increase solubility of Terbinafine hydrochloride by the means of ME formulations.

MATERIALS AND METHODS

Terbinafine hydrochloride was obtained from Global Calcium PVT Ltd, Karnataka as a gift sample. Octanol, Castor Oil, Soyabean Oil, Linseed oil, Span 80, Tween 80 were obtained from Sweta Scientific, Lucknow, India. Other ingredients used were of analytical grade.

Selection of the oil phase

Selection of the oil phase was based upon the maximum solubility of the drug. Different oils including castor oil, Capmul Pg-12, soyabean oil, Kollisolv GTA, MCT were taken for solubility studies. Based on the solubility Capmul Pg-12 was selected as the oil phase.[10]

Selection of surfactants and co surfactant

Solubility of Terbinafine hydrochloride was checked in different surfactants and co surfactants. Emulsification efficiency of surfactants and co-surfactants to check their ability to emulsify selected oil.

To determine the emulsification ability, equal amount of surfactant was mixed with drug and after proper dilution, it was monitored for transmittance at 638 nm using UV-Vis spectrophotometer. The ease of formation of emulsion was monitored by the number inversions of volumetric flask required to produce uniform emulsion.

Similarly co surfactant were selected based on their ability to form stable and clear micro emulsion at a minimum concentration.[11]

Solubility analysis

About 10 gm of oil was accurately weighed in 25 ml glass beaker and 100 mg of Terbinafine hydrochloride was added into it, followed by stirring on magnetic stirrer at moderate speed to dissolve the drug. When drug was dissolved completely another 10 mg Terbinafine hydrochloride of was added and stirring was continued. Addition of drug was continued until the saturated solution is obtained. Finally, the total amount of drug consumed was determined by using UV-spectrophotometer at 250 nm. In the similar way solubility of Terbinafine hydrochloride was checked in different surfactants and co-surfactants.[12]

Construction of Pseudo-Ternary Phase Diagrams

The pseudo-ternary phase diagrams were constructed using water titration method to determine the microemulsion area and to detect the possibility of making microemulsions with different possible compositions of oil, surfactant/co-surfactant and water respectively. The ratios of surfactant to co-surfactants were selected to be 1:1, 2:1 and 3:1 with fixed 5 % oil amount. These mixtures (S/CoS) were mixed with the oil phase to give the weight ratios of 9:1, 8:2, 7:3, 6:4, 5:5, 4:6, 3:7, 2:8 and 1:9. Water was added drop by drop and stirred using a magnetic stirrer at constant temperature until a homogeneous dispersion or solution was obtained. After each addition, the system was examined for the physical appearance. The end point of the titration was the point where the solution becomes transparent or translucent. The amount of the aqueous phase required to make the mixture turbid was noted.[25-26] The percentages of the various incorporated pseudo phases were estimated, and the same procedure was followed for the other S/CoS ratios. All the ratios of S/Co gives dotted area in pseudo ternary phase diagram.[13-16]

Preparation of drug loaded microemulsion

Formulations were developed using water titration method. Predetermined amounts of Terbinafine hydrochloride (100) mg was dissolved in the required quantity of Capmul Pg-12 (oil). Tween-80**:** (surfactant) and Propylene glycol (co-surfactant) were added to the above mixture in different ratio. Distilled water was added gradually with continuous stirring, which resulted in the formulation of a transparent and homogenous microemulsion.[17]

Characterization of micro emulsion

Percentage Transmittance

Transparency of micro emulsion formulation was determined by measuring percentage transmittance through U.V. Spectrophotometer at 638 nm with distilled water taken as blank and three replicates were performed for each sample.[18]

pH determination

The apparent pH of all micro emulsions was determined at 25°C by immersing the electrode directly into the micro emulsion using a digital pH meter.[19]

Refractive index

Refractive indices of the prepared micro emulsions were determined at 25°C by Abbe's refractometer by placing one drop of micro emulsion on the slide.[20]

Viscosity measurement

Micro emulsions are generally low viscosity systems. The viscosity of the prepared micro emulsion was measured at 25°C at 60 rpm by LV spindle no. 63 using a Brookfield viscometer.[21]

Determination of Drug Content in the Terbinafine hydrochloride micro emulsion formulations

The drug content of the micro emulsion formulation was determined by dissolving 1 ml (equivalent to 10 mg drug) of the formulation in 10 ml of methanol. After suitable dilutions with methanol, absorbance was determined using the UV spectrophotometer keeping blank micro emulsion as control at wavelength 250 nm and three replicates were performed for each sample.[22]

Drug solubility study: Terbinafine hydrochloride was added in excess to the optimized microemulsion formulation as well as each individual ingredient of the formulation. After continuous stirring for 4 hours at room temperature, samples were withdrawn and centrifuged for 10 minutes. The amount of drug soluble in optimized formulation as well as each individual ingredient of the formulation was calculated by subtracting the drug in the sediment from the total amount of drug added. The solubility of drug in microemulsion was compared with respect to its individual ingredients.[23]

***In-vitro* drug release:** The diffusion study was carried out on a modified Franz diffusion cell of volume 20ml. The receptor compartment was filled with 20 ml of Phosphate buffer (pH 7.4). The donor compartment was fixed with cellophane membrane (Cut Off weight = 1000 Da) contains Terbinafine hydrochloride microemulsion formulation (equivalent to 5 mg of drug) and plain drug solution separately. At predetermined time intervals samples were withdrawn from receptor compartment and analyzed for drug content by UV Spectrophotometer at 250 nm.[24]

Drug release kinetic data analysis

Release data was evaluated through PCP disso software for the kinetic models. First, and Peppas and Korsmeyer model were studied.[25-27]

Table 1: Solubility of Terbinafine hydrochloride.

Oils	Solubility	Surfactant	Solubility (mg/ml)	Cosurfactant	Solubility (mg/ml)
Castor Oil	1.24±0.20	Span 80	11.45±2.31	PEG 200	18.64±0.47
Soyabean Oil	0.45±0.01	Tween 80	13.43±0.77	PEG 400	7.65±0.51
Peanut oil	0.586±0.0091	Labrasol	12.63±0.31	Propylene glycol	25.77±0.85
Capmul Pg-12	15.2543±0.0182	Tween-60	11.55±2.31	Iso propyl alcohol	0.96±0.04
Linseed oil	1.3453±0.0121				
Cottonseed oil	.659±0.0048				

Table 2: Emulsification efficiency (selected oil and surfactant).

Surfactant	% Transmittance	HLB Value
Tween-80	87.127±0.0241	14
Labrasol	75.261±0.0218	13
Tween-60	84.157±0.0172	13.9

Table 3: Emulsification efficiency (selected surfactant and cosurfactant).

Co surfactant	% Transmittance	HLB Value
PEG 200	71.141±0.0138	5-6
PEG 400	72.132±0.0141	8-9
Propylene glycol	78.253±0.0231	11.6

Table 4: Compostion of ternary phase diagrams (quantity in ml).

Oil: SA/CoSA	Capmul Pg-12 (Oil)	Tween-80:Propylene glycol (Surfactant:Cosurfactant)					
		1:1		2:1		3:1	
1:9	1	4.5	4.5	6.0	3.0	6.7	2.3
2:8	2	4.0	4.0	5.3	2.7	6.0	2.0
3:7	3	3.5	3.5	4.6	2.3	5.3	1.7
4:6	4	3.0	3.0	4.0	2.0	4.5	1.5
5:5	5	2.5	2.5	3.3	1.7	3.8	1.2
6:4	6	2.0	2.0	2.6	1.3	3.0	1.0
7:3	7	1.5	1.5	2.0	1.0	2.3	0.7
8:2	8	1.0	1.0	1.3	0.7	1.5	0.5
9:1	9	0.5	0.5	0.7	0.3	0.7	0.3

(Terbinafine hydrochloride=100 mg)

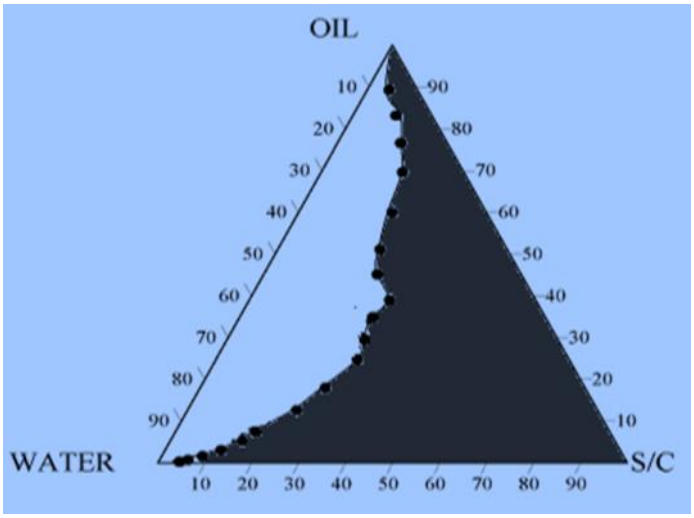

Figure 1: Pseudo ternary phase diagram for 1:1.

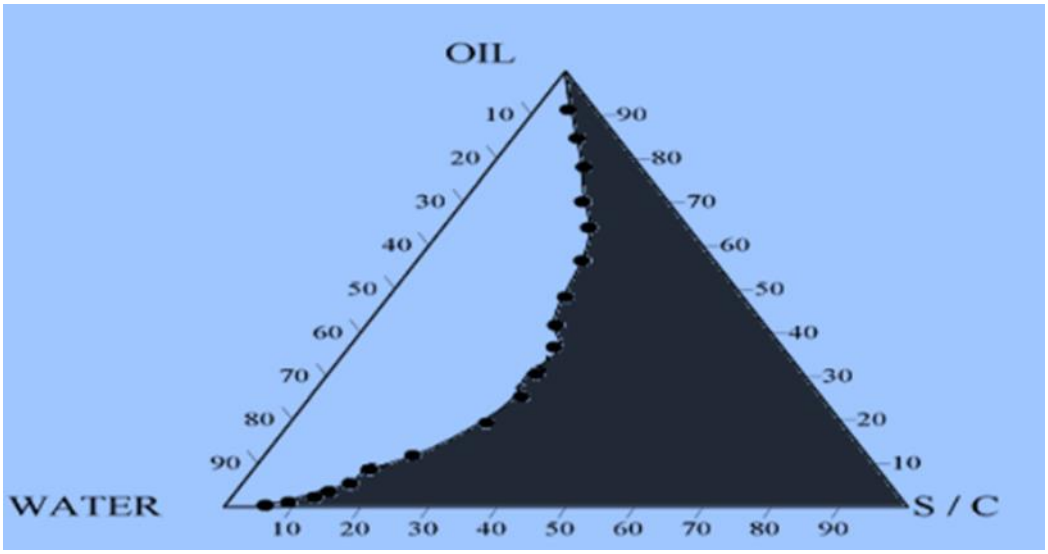

Figure 2: Pseudo ternary phase diagram for 2:1.

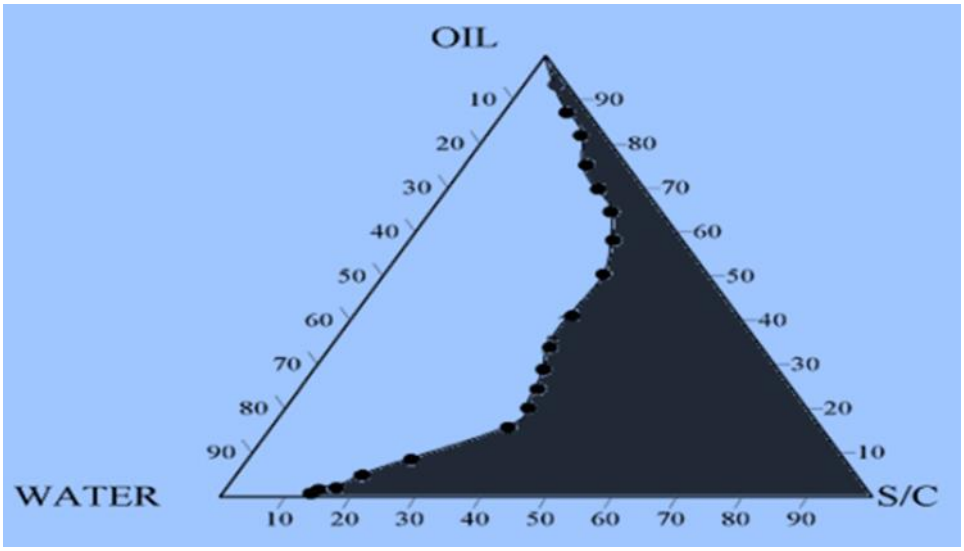

Figure 3: Pseudo ternary phase diagram for 3:1.

Table 5: Composition of batches for Terbinafine hydrochloride micro emulsion.

Code	S_{mix} ratio	% w/w composition		
		% Oil	S_{mix}	% Water
ME1	1:1	35	65	5
ME2	1:2	60	35	5
ME3	1:3	35	60	10
ME4	2:1	50	40	10
ME5	3:1	40	55	5

Table 6: Evaluation parameters of prepared ME Terbinafine formulations.

Batch	Transmittance (%)	pH	Refractive index	Viscosity (cp)	Drug content (%)	Solubility mg/ml
ME1	99.3 ± 0.08	3.56 ± 0.08	1.3548±0.007	64.23±2.1	98.37± 0.08	27.87±0.08
ME2	99.27 ± 0.11	3.76 ± 0.12	1.3420 ± 0.008	65.46±3.7	99.32 ± 0.34	28.87±0.11
ME3	99.42 ± 0.23	3.82 ± 0.07	1.3718 ± 0.004	70.56±5.77	99.61 ± 0.03	29.87±0.08
ME4	98.57 ±0.09	3.44 ± 0.08	1.3620 ± 0.008	68.43±3.34	99.52 ± 0.02	25.87±0.09
ME5	98.63 ± 0.21	4.12 ± 0.09	1.3518±0.016	69.36±4.74	98.43 ± 0.04	31.87±0.07

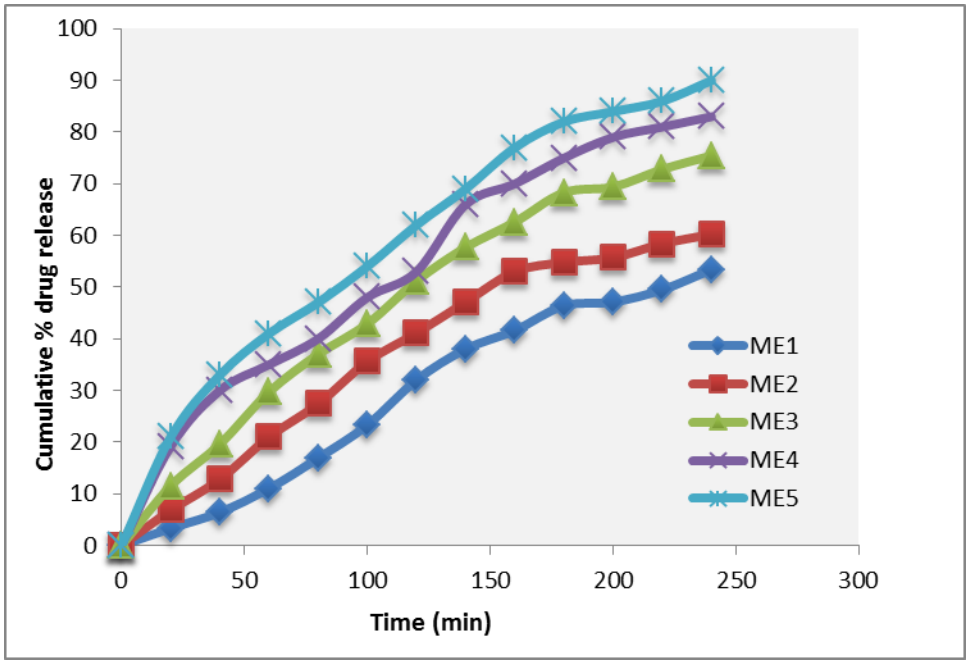

Figure 4: *In vitro* study of prepared Terbinafine hydrochloride micro emulsion formulations.

Table 8: Different release models for Terbinafine hydrochloridemicro emulsion formulations.

Batch	Kinetic model	Parameters
ME1	Peppas and Korsmeyer	R = 0.965, K1 = 4.234, n = 0.750
ME2	Peppas and Korsmeyer	R = 0.974, K1 = 3.147, n = 0.854
ME3	First order	R = 0.952, K1 = 5.61, n = 0.750
ME4	Peppas and Korsmeyer	R = 0.934, K1= -0.070
ME5	Peppas and Korsmeyer	R = 0.963, K1 = 6.812, n = 0.772

RESULTS AND DISCUSSION

Solubility of Terbinafine hydrochloride was checked in different oil to select the oil for the preparation of micro emulsion formulation. On the basis of solubility Capmul Pg-12 was selected as the oil and on the basis of emulsification efficiency and solubility Tween 80 was selected as the surfactant and Propylene glycol as the co-surfactant.

Given Terbinafine hydrochloride sample has shown maximum absorption (λ_{max}) at 250 nm. FTIR spectroscopy was used to detect any kind of interaction between Terbinafine hydrochloride and used oil (Capmul Pg-12), surfactant (Tween 80), co-surfactant (Propylene glycol). No change in peak was found, that indicate compatibility between them.

Ternary phase diagram was prepared using oil (Capmul Pg-12), surfactant (Tween 80), co-surfactant (Propylene glycol) in different ratio to identify the micro emulsion existing zone from which appropriate concentration ranges of components of micro emulsion can be obtained. The ternary phase diagrams of all the ratios are shown in Figure 6 to Figure 8. Formation of micro emulsion systems (the shaded area) was observed at room temperature. Phase behavior investigations of this system demonstrated the suitable approach to determine the water phase, oil phase, surfactant concentration, and co surfactant concentration with which the transparent, one-phase, low-viscous micro emulsion system was formed.

Total five formulations were developed to enhance the solubility of the Terbinafine hydrochloride. Prepared formulations were further studied for different parameters including percent transmittance, drug content, pH determination, refractive index, viscosity, drug release.

The percent transmission carried out on UV spectrophotometer at 638 nm was found to be in the range of 98.47 ±0.09 to 99.2 ± 0.08% for all which confirms good transparent nature of formulations.

For the micro emulsion formulations, the pH value was found to be in the range of 3.34 ± 0.08 to 4.02 ± 0.09.

The refractive index for the micro emulsion formulations was found to be in the range of 1.3418±0.016 to 1.3818 ± 0.004.

The drug content was found to be in the range of 98.47± 0.08 to 99.62 ± 0.02 % in the micro emulsion formulations.

The Viscosity was found to be in the range of 65.23±2.1 to 71.56±5.77% in the micro emulsion formulations. The viscosity of the micro emulsion increased with increasing concentration of the surfactant. It was seen that after 4 hours of diffusion, the drug released from the formulation ME5 faster and more than that of the other ratios i.e., 91.2±0.06%.

In present study PCP disso Version 2 software was used in for the estimation of release pattern. Models for the release kinetic profile are shown in Table 13. *In-vitro* release data were plotted in 2 different models i.e. first, and Korsemeyer peppas. It was observed that release was governed by the diffusion process.

CONCLUSION

ME are clear systems of with a droplets diameter>500 nm[1]. Due to small droplets size, they may serve an excellent carrier for drugs having poor water solubility. Aqueous phaseconsists of salt(s), and/or other ingredients, while oil consist of hydrocarbons and olefins. There is need of high shear in the preparation of emulsions, but for ME, there is no need of high shear, they simply formulated by the mixing of different ingredients.

Present study concludes successful delivery of terbinafine hydrochloride by the means of micro emulsion formulations.

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