Microemulsion Formulations for the transdermal delivery of testosterone

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Introduction

Testosterone is the major circulating androgen in man.[1] Its deficiency is usually associated with adverse effects on body composition, bone density, sexual function, and mood and may also increase cardiovascular risk. The low molecular weight (M.W.=288) and hydrophobic nature (log $P_{o/w}$ = 3.3 and water solubility = 0.039 mg/ml at 37°C) in addition to first pass metabolism are favourable factors for transdermal delivery of testosterone. It is generally agreed that androgen replacement therapy should deliver physiological amounts (3-10 mg/day) of testosterone. This corresponds to targeted fluxes of 4-14 µg cm^{-2} hr^{-1} over a reasonable surface area of 30 cm^2. In this work, microemulsions of different compositions were considered to achieve these objectives. Single phase microemulsions are currently of interest to the pharmaceutical scientist as potential drug delivery vehicles due to their long term stability, ease of preparation, and considerable capacity for solubilization of a variety of drug molecules.

Results and Discussion

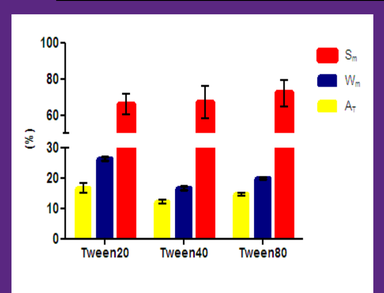

Fig.1 Effect of chain length on total monophasic area, maximum water of solubilization and minimum amount of surfactant needed for solubilization

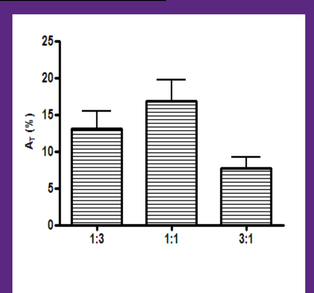

Fig.2 The optimum ratio between surfactant (Tween20) and cosurfactant (Transcutol)

Table 3. Proton NMR chemical shifts of ME F different functional groups after incorporation of Drug (1% w/v) in ME F.

Functional group	δ (ppm) In ME F (δ^0)	δ (ppm) In ME F with 1% drug (δ^1)	Δδ (δ^1- δ^0)
CH_3	0.855	0.888	0.031
CH_2	1.162	1.191	0.029
CH_2CH_2CO	1.543	1.571	0.028
CH_2CH	1.989	2.02	0.031
CH_2CO	2.208	2.23	0.022
OCH_2CH_2O	3.646	3.668	0.022
CH_2OCO	4.171	4.190	0.019
OH	4.653	4.652	-0.001
CH	5.287	5.318	0.031

Table 4. Carbon NMR chemical shifts of ME F different functional groups after incorporation of Drug (1% w/v) in ME F.

Oleic acid				Tween20				Transcutol			
	δ (ppm)				δ (ppm)				δ (ppm)		
Functional group	ME F (δ^0)	ME F with 1% drug (δ^1)	Δδ (δ^1- δ^0)	Functional group	ME F (δ^0)	ME F with 1% drug (δ^1)	Δδ (δ^1- δ^0)	Functional group	ME F (δ^0)	ME F with 1% drug (δ^1)	Δδ (δ^1- δ^0)
CH_3	14.117	14.806	0.689	CH_3	14.088	14.161	0.073	CH_3	14.843	14.916	0.073
CH_2	22.896 29.477 29.631 30.004	22.926 29.513 29.66 30.034	0.073 0.036 0.029 0.030	CH_2	22.896 29.477 29.631 30.004	22.926 29.513 29.66 30.034	0.073 0.036 0.029 0.030	C-OH	60.863	60.914	0.051
								C-O	70.067 72.375	70.126 72.441	0.029 0.066
CH_2CHCO	25.131	25.183	0.052	CH_2CH_2CO	25.754	25.791	0.037				
$CH_2C=C$	27.359	27.396	0.037	CH_2CO	34.086	34.130	0.044				
$CH_3CH_2CH_2$	32.188	32.225	0.037	C-OH	60.863	60.914	0.051				
CH_2CO	34.086	34.130	0.044	C-O	70.067 72.375	70.126 72.441	0.029 0.066				
C=C	129.725	129.71	0.146								
COOH	175.782	175.723	-0.049	C=O	175.782	175.733	-0.049				

Oleic acid functional groups are the most affected by testosterone presence. These results confirms the presence of the drug in the internal oily phase with small amounts at the surfactant/cosurfactant interface.

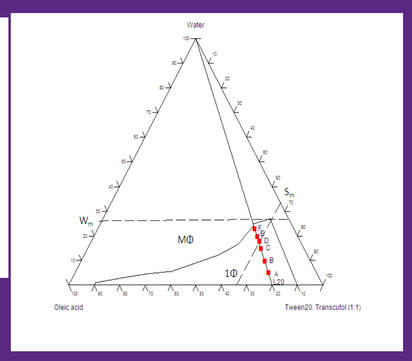

Fig.3 Oleic acid / Tween20 / Transcutol / Water phase diagram where the mixing ratio of Tween20 : Transcutol is 1:1. 1Φ is the area of one phase region, MΦ is the area of multiple phase regios . Wm is the maximum amount of solubilized water, Sm is the amount of surfactant needed to obtain maximum water solubilization and L20 is a dilution line where the initial oil concentration is 20% (w/w).

Where is testosterone in the microemulsion droplets?

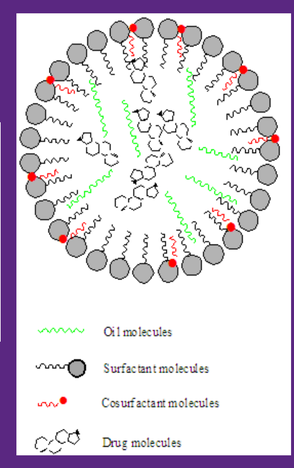

Fig.6 Schematic diagram showing the position of testosterone and microemulsion components and their interactions.

Methodology

I- Construction of Phase diagram

II- Characterization of microemulsions by
a) Particle size determination using a Malvern zetasizer
b) Conductivity measurements
c) pH
d) Rheological measurements
e) FTIR, and ^{1}H-NMR and ^{13}C-NMR spectroscopy

III- Alteration of microemulsion microstructure after drug loading

IV- *In vitro* permeation of testosterone from selected microemulsions

V- Data Analysis
Results fitted to Fick's second law of diffusion to derive values of KH and D/H^2

$$Q = \{KH\}C_{veh}\left[\left(\frac{D}{H^2}t - \frac{1}{6} - \frac{2}{\pi^2}\sum_{n=1}^{\infty}\frac{(-1)^2}{n}\exp\left(\frac{-Dn^2\pi^2.t}{H}\right)\right)\right]$$

Permeability coefficient was deduced from the relation:

$$K_p = (KH)\times\left(D/H^2\right) = \frac{K.D}{H}$$

And the steady-state flux J_{ss} from:

$$J_{ss} = K_p \times C_{veh}$$

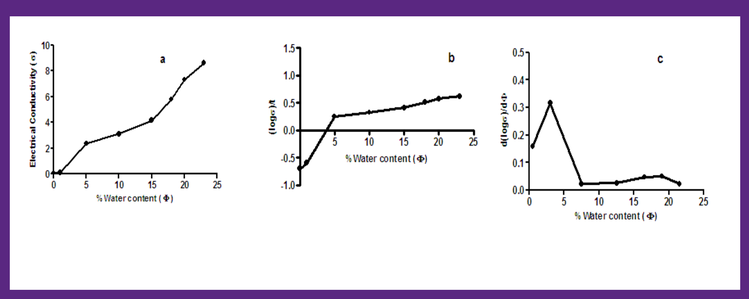

Fig.4. Plot of (a) electrical conductivity (σ) , (b) (log σ) / t and (c) d(log σ) / dΦ as a function of percentage water content (Φ) along the dilution line L20
A percolation threshold occurs at Φ=2.8 where w/o microemulsion converts to o/w microemulsion.

Table 1 Selected microemulsion formulations (%w/w).

	A	B	C	D	E	F
Oleic acid	19	18	17	16.2	16	15.4
Tween20	38	36	34	32.9	32	30.8
Transcutol	38	36	34	32.9	32	30.8
Water	5	10	15	18	20	23

Table 2 Changes in the physical parameters of microemulsions after loading with drug (1% w/v).

ME	OH frequency (cm^{-1})		σ (µS/cm)		η (Pa.s)		pH	
	Unloaded	Loaded	Unloaded	Loaded	Unloaded	Loaded	Unloaded	Loaded
A	3449	3442	2.39 ± 0.16	2.35 ± 0.21	0.047 ± 0.011	0.036 ± 0.027	5.24 ± 0.01	5.30 ± 0.03
B	3436	3433	3.11 ± 0.27	3.63 ± 0.29	0.046 ± 0.012	0.049 ± 0.020	5.15 ± 0.04	5.14 ± 0.02
C	3434	3436	4.18 ± 0.64	5.04 ± 0.60	0.050 ± 0.016	0.062 ± 0.008	5.04 ± 0.03	4.97 ± 0.01
D	3426	3433	5.82 ± 0.53	6.35 ± 0.48	0.039 ± 0.018	0.062 ± 0.007	5.03 ± 0.03	4.97 ± 0.02
E	3431	3434	7.34 ± 0.23	7.20 ± 0.54	0.037 ± 0.014	0.040 ± 0.017	4.89 ± 0.02	4.90 ± 0.03
F	3401	3402	8.63 ± 0.59	8.71 ± 0.32	0.061 ± 0.007	0.073 ± 0.037	4.45 ± 0.03	4.45 ± 0.01

No statistical significant differences between loaded and unloaded microemulsions at P < 0.05.

According to these results, the drug is present in the oily phase.

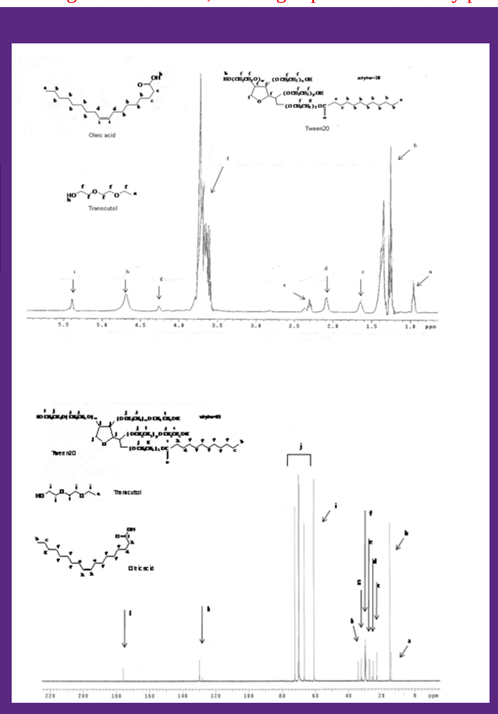

Fig.5 Proton NMR and Carbon NMR spectra of microemulsion F.

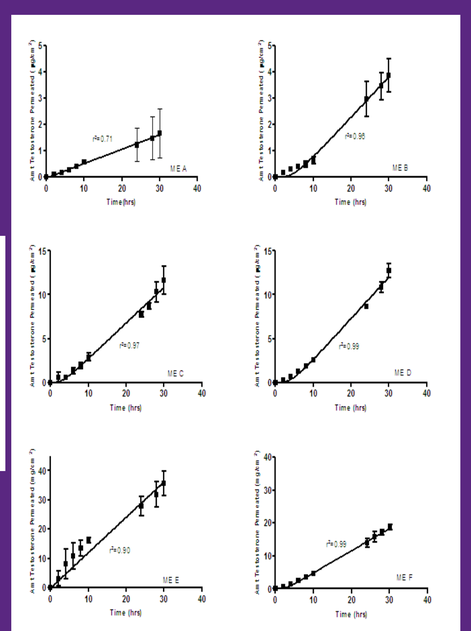

Fig.7 Permeation of testosterone (1%) from the selected Oleic acid / Tween20 / Transcutol / Water microemulsions and fitting of the results to Fick's second law of diffusion.

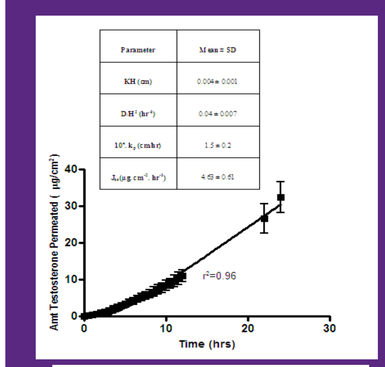

Fig.8 Permeation of testosterone (3%) from microemulsion E. The results were fitted to Fick's second law of diffusion.

Flux reached targeted values.

Conclusion

The microemulsion system studied offers a potential vehicle for the transdermal delivery of testosterone.

References

[1] Leichtnam ML, Rolland H, Wuthrich P, Guy RH. 2006. Identification of penetration enhancers for testosterone transdermal delivery from spray formulations. J Control Release 113:57-62.

[2] Leichtnam ML, Rolland H, Wuthrich P, Guy RH. 2006. Testosterone hormone replacement therapy: State-of-the-art and emerging technologies. Pharm Res 23:1117-1132.