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Formulation and Characterization of Liquid Crystalline Transdermal Drug Delivery System of Testosterone

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Abstract **— Present study was focused on the formulation and characterization of liquid crystalline transdermal drug delivery system of testosterone for androgen replacement therapy. Liquid crystalline transdermal gel was prepared using tween 80 and cetostearyl alcohol. Formulation T1 to T5 differs in the ratio of tween 80 and cetostearyl alcohol. Formulations were evaluated on the basis of viscosity, encapsulation efficiency, anisotropy and in vitro drug release study using fabricated diffusion cell. Formulation T1 had appropriate viscosity i.e., 2356.667 cp, highest encapsulation efficiency i.e., 94.26 % w/w and good liquid crystalline property as observed in polarized microscope. In vitro release study found to have zero order release profile in all three formulations. However, formulation T1 had more prominent zero order. Therefore, formulation T1 selected as developed formulation.**

Keywords **— Liquid crystalline system, transdermal drug delivery, gel, in vitro evaluation.**

1. INTRODUCTION

It has been observed that incidence of newer research molecule has limited in last two decades. Therefore, modification in dosages form or release patter of drug may offer another approach in increasing life of existing molecule. This will offer good patient compliance and another approach to research and development industry. Formulations like transdermal patch and gel, controlled release tablets, parenteral microspheres and nanoparticles are some common research field for developing newer dosages form. Among these liquid crystalline transdermal gel is one of the best approach.

Liquid crystalline systems are an intermediate state which exists between solid crystals and isotropic liquid. Liquid crystals (LC) exhibit anisotropy having optical direction. Some property of LC are similar to solids and liquids, they possess both structural order and mobility. LC found to show intense color bands and birefringence under polarizing microscope [1]. The liquid crystalline phase is thermodynamically stable and represents a state of incomplete melting [2].

Liquid crystalline system has semisolid gel or ointment like property. It serves as drug carrier and controlled release system. Skin permeation studies with excised stratum corneum have shown that it has good penetration enhancer property as compared to other carrier system. The high permeation rates were mainly attributed due to presence of surfactant, alcoholic content and other ingredients [3, 4].

Testosterone is a potent androgen class of drug and also known as gonadal hormone or male sex hormone. Plasma concentration levels of testosterone in males are found from 0.3 to 1 µg/dl. Testosterone absorption through gastro intestinal tract is almost complete and also absorbed from buccal and transdermal rout [5].

Testosterone has extensive hepatic metabolism after oral administration. Mainly oral, parenteral and transdermal treatment options are available for testosterone therapy. Conventional oral treatment associated with high first-pass metabolism and parenteral treatment is associated with painful administration. Therefore developing a transdermal gel would be good approach for testosterone [6, 7].

2. MATERIAL AND METHOD

2.1. Materials: Testosterone was kindly provided as gift sample by SPARC, Baroda, India. Cetosteryl alcohol and tween 80 were purchased from Central Drug House Pvt. Ltd., Mumbai, India. All other ingredients were of analytical reagent grade.

2.2. Preparation of liquid crystalline gel: Liquid crystals (LC) were prepared by the method reported by Eccleston and Beattie 1988, with some modification in ingredients and their composition. Cetostearyl alcohol and tween 80 were melted together and double distilled water was added at approximately the same temperature followed by cooling slowly and mixing at 500 rpm stirrer. Testosterone was mixed in the mixture of cetostearyl alcohol and tween 80 and glycerol was mixed with water [8].

2.3. Characterization of liquid crystalline gel: Liquid crystalline gel was characterized on the basis of viscosity, encapsulation efficiency and in vitro release study.

2.4. Viscosity: Viscosity of liquid crystalline gel was determined with the help of Brookfield viscometer (DV-E viscometer, Brookfield, USA) using spindle no 61 at 30 rpm. Viscosity was measured from viscometer display. The liquid crystalline gel was kept at 25±02°C prior to measurement [9] (Kumar and Katare, 2005).

2.5. Encapsulation efficiency (EE): The liquid crystalline gel was placed in dialysis tube (Dialysis membrane-110, HiMedia Laboratories Pvt. Ltd., India) and were dialyzed for two hour and then one hundred miligram of liquid crystals were taken from dialysis bag and dissolved in methanol in 10 ml of volumetric flask. After suitable dilution testosterone was determined by

spectrophotometrically at 241 nm [10]. Entrapment efficiency of liquid crystalline gel was calculated as per following equation:

$$EE\% = \frac{\text{Amount of testosterone found in liquid crystals}}{\text{amount of testosterone added during preparation of liquid crystals}} X\ 100$$

2.6. Microscopic analysis: Presence of liquid crystalline gel properties were examined by polarizing light microscope (Nikon, Melville, NY) in bright field and between crossed polarizer. Thin film of liquid crystalline gel was spread on glass slide and covered with cover slip to examine in microscope. The suitable microphotograph of liquid crystalline gel was taken in plane and polarized light [11-13].

2.7. In vitro release study: The in vitro release study was performed using fabricated diffusion cell [14,15]. Dialysis tube was used in the study as the permeation barrier (Dialysis membrane-110, HiMedia Laboratories Pvt. Ltd., India). Dialysis tube as semipermeable membrane was mounted on the receptor compartment of the diffusion cell and liquid crystalline gel was applied on the donor compartment. The receptor compartment contained 50 ml of 40% v/v PEG 200 in phosphate buffer (pH-6) at 50 rpm. During the experiment temperature was maintained at 37°C±02°C using water bath. Samples of 5 ml were withdrawn at a time interval of one hour upto eight hours and withdrawn samples were analyzed by spectrophotometrically at 241 nm.

3. Results and Discussion

Liquid crystalline gel was prepared using Cetostearyl alcohol and tween 80 and double distilled water was added at approximately the same temperature followed by cooling slowly and mixing at 500 rpm stirrer. It was stored in wide mouth tightly closed container for evaluation. Five different combinations were selected for the preparation of Liquid crystalline gel varying in the composition of Cetostearyl alcohol and tween 80.

Liquid crystalline gel was characterized on the basis of viscosity, encapsulation efficiency and in vitro release study. Viscosity is an important parameter for appropriate consistency of gel as it should be like an ointment. Therefore viscosity of the system was determined with the help of Brookfield viscometer (DV-E viscometer, Brookfield, USA) using spindle no 61 at 30 rpm. Viscosity was measured from viscometer display. It was found from 1653.333 to 2356.667 cp in formulation T1 to T3. Formulation T1 had highest viscosity and also suitable for gel. Formulation T4 and T5 did not have gel like consistency. The results of viscosity data is given in table 2.

Maximum quantity of drug entrapped was determined in term of encapsulation efficiency The liquid crystalline gel was placed in dialysis tube (Dialysis membrane-110, HiMedia Laboratories Pvt. Ltd., India) and were dialyzed for two hour and then one hundred miligram of liquid crystals were taken from dialysis bag and dissolved in methanol in 10 ml of volumetric flask. After suitable dilution testosterone was determined by spectrophotometrically at 241 nm. It was found from 81.68 to 94.26%. Formulation T2 had lowest EE and formulation T1 had higher EE which may be due to presence of appropriate composition of cetostearyl alcohol and tween 80. The higher EE represent for good formulation i.e. formulation T1.

Polarizing light microscope is a useful tool to determine presence of liquid crystalline system. Therefore, polarizing light microscope is used for determination of presence of liquid crystals. Figure 1 represents photomicrograph of liquid crystalline system in which presence of birefringence proves the presence of liquid crystals [13].

The in vitro release study was performed using fabricated diffusion cell of formulation T1, T2 and T3. Study was performed for eight hours and samples were withdrawn in one hour interval. All three formulations showed controlled release property. Formulation T1 showed 79.33 % drug release in eight hour and formulation T3 showed 99.23 %. The r^2 value of in vitro release data were determined to find best fit model for different model like Zero order, First order, Higuchi Matrix and Peppas-Korsmeyer [16]. All formulations showed zero order release profile, however formulation T1 shown more prominent. T1 formulation has good consistency on the basis of viscosity data, higher encapsulation efficiency and good crystalline property. All these parameters make T1 formulation as developed formulation.

4. Conclusion

Formulation T1, T2 and T3 showed good property, however formulation T1 had best results among all formulation. Formulation T1 may be applied easily on skin and having controlled release property. It is also proposed to do in vivo study for future plan and may prove to be good formulation.

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TABLE 1: Formula of Liquid Crystalline Gel

Ingredients	Formulation Code				
	T1	T2	T3	T4	T5
Testosterone (mg)	100	100	100	100	100
Tween 80 (ml)	10	5	15	0	20
Cetostearyl alcohol (g)	10	15	5	20	0
Glycerol (ml)	1	1	1	1	1
Double distilled water q.s. (ml)	50	50	50	50	50

TABLE 2: Evaluation of Testosterone Liquid Crystalline Gel

Formulation Code	**Viscosity (cp)**	**EE (% w/w)**	**Polarizing light microscopy**
T1	2356.667	94.26	A
T2	1730.00	81.68	A
T3	1653.333	86.24	A
T4	-	-	-
T5	-	-	-

All values represents, n = 3, EE; encapsulation efficiency, A= anisotropy

TABLE 3: Model fitting of in vitro drug release data obtained from liquid crystalline formulations

Formulation code	**Zero order**	**First order**	**Higuchi Matrix**	**Peppas-Korsmeyer**
	r^2	**r^2**	**r^2**	**r^2**
T1	0.9910	0.8739	0.9297	0.9836
T2	0.9892	0.8976	0.9392	0.9723
T3	0.9814	0.8734	0.9182	0.8936

r^2= correlation coefficient

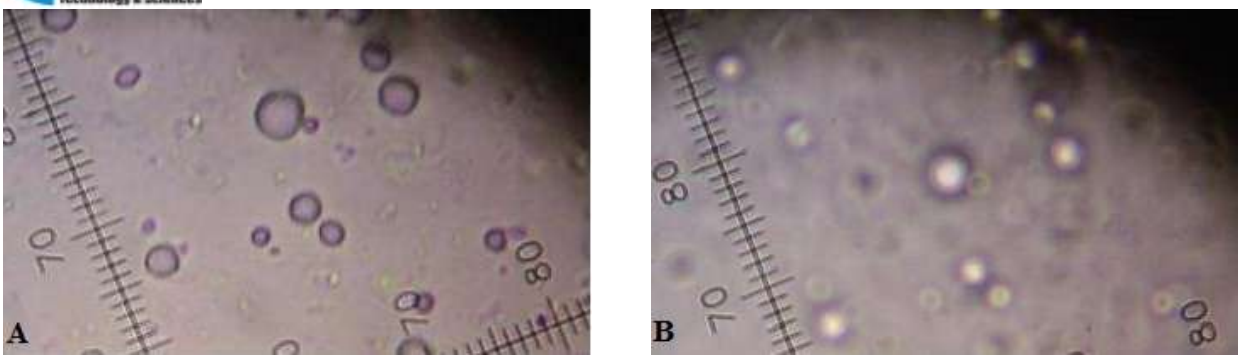

FIGURE 1: PHOTOMICROGRAPH OF LIQUID CRYSTALLINE FORMULATION T1 USING (A), OPTICAL MICROSCOPE AND (B), POLARIZING LIGHT MICROSCOPE AT 40X

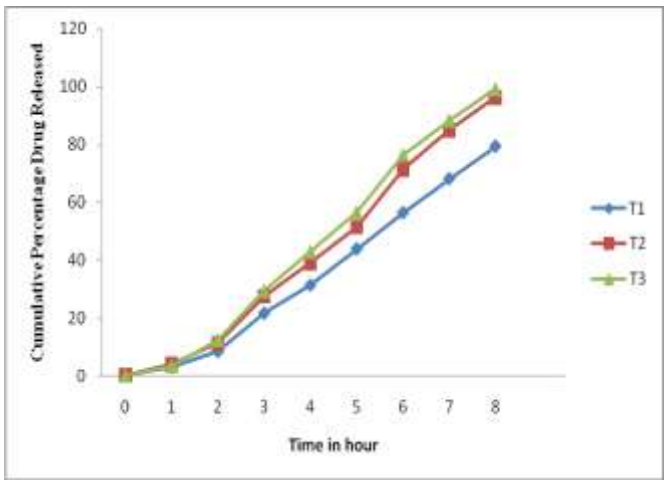

FIGURE 2: DRUG RELEASE DATA OBTAINED FROM LIQUID CRYSTALLINE FORMULATIONS VS TIME