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Hydrocortisone Micro Emulsions for Parenteral Drug delivery

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ABSTRACT

Microemulsions are the promising vehicle for administration of active pharmaceutical ingredients. It is an isotropic transparent or translucent thermodynamically stable mixture and used for targeted controlled drug delivery system for the effective delivery of hydrocortisone. In present study lecithin based o/w microemulsion was developed for parental drug delivery using hydrocortisone as model drug. Tween 80 and Cremophor–EL were used as co-surfactant and PEG 400 were used as co-solvent; soyabean oil was used as the oil phase. Formulations prepared with the tween-80 were having both clarity and maximum oil entrapment formulation prepared were characterized for color, appearance pH, viscosity, particle size distribution, Refractive index, effect of centrifugal force, freeze thaw cycle, drug content in-vitro release profile and TLC. Prior to stability studies the microemulsion were sterilized by autoclaving. Toxicity studies were performed on Albino mice by injecting them intraperitonialy no mortality was observed, which indicate the safety of these formulations. Therefore the lecithin based microemulsions can be formulated for parenteral drug delivery and obtain sustained or prolonged drug delivery for hydrocortisone having good physical stability.

Keywords: Microemulsions, parenteral drug delivery, thermodynamic stable systems, and toxicity studies.

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INTRODUCTION

Conventionally the model drug (A1) when administered orally[1] usually produces large fluctuation of concentration in the blood stream and tissue and consequently favorable patterns of efficacy and toxicity. Hydrocortisone is widely administered as injection and suspension has a short half life. [2, 3] The parental administration of sparingly soluble active pharmaceutical ingredients are reported to pose major problem in the pharmaceutical industry. Emulsions are useful carrier for administering such drug substance, because of their ability to incorporate drug within their innermost phase for example – Hydrocartisone and diazepam[4,5]. In microemulsion drug may be incorporated into emulsion formulation either by emulsification of drug dissolved in oil phase or by addition of concentrated solution in co-solvent to the commercial IV emulsion.

Lecithin based oil in water microemulsion for parentral delivery would help to improve the therapy in inflammatory condition.

Microemulsion is an isotropic transparent or translucent thermodynamically stable system containing at least 3 components water, oil & surfactant. In combination with a co-surfactant it usually has ultra low interfacial tension, large interfacial area and stabilization capacity for oil & water soluble drug. The water soluble form of hydrocortisone, an A^1 drug can be given by intravenous (IV) injection for rapid action while for prolonged action lipid soluble form can be given by IM injection.

In the present study an attempt was made to control drug delivery system which was designed and developed with a view to enhance the efficacy of the drug and its bioavailability by formulation the drug in the form of microemulsions.

MATERIAL AND METHOD

Material

Hydrocartione (J. P. Glaze India) purified soya lecithin (LucasMoyer), Tween 80 (S.D. fine chemicals) Cremopher – EL (B.A.S.F.).The other entire chemical and the solvents used for formulation are of high analytical grade.

Method

Analysis of drug –

The respective λ max we found to be 239 & 237nm in methanol & saline phosphate buffer PH 7.5 when measured against respective blanks. The data obtained with equations were $Y = 0.045 1x + 0.0265$ $R^2 = 0.9983$ & $Y = 0.0377x + 0.0333$ $R^2 = 0.9982$ for methanol and saline phosphate buffer pH 7.4

Preparation of microemulsion

The ratio of surfactant with an cosurfactent i.e. S / Cos were taken from 0.12 to 0.5. The mixture of S and Cos was then mixed with external phase i.e. water mix of water / co-solvent to given (S + Co5) : water weight ratio of 9:1, 8:2, 7:3, 6:4, 5:5, 4:6, 3:7, 2:8 and 1:9. The water / co-solvent were tried in a ratio of 9:1, 8:2, 7:3 and 6:4. Each mixture was mixed thoroughly using a cyclomixer (Remi) until a homogeneous clear solution was obtained at ambient temp and contact stirring. Point at which turbidity appears was noted. Pseudo ternary phase dig were then plotted to assess the microemulsion clear region and suitable compositions were selected for further studies.

Characterization of selected formulation

The selected microemulsions were characterized for color, odor, and visual appearance by the visual observation.

Optical birefringence[6]

The microemulsion were placed in between two polarizing plates and observed for light transmittance than one of the plate was rotated relative to other through 90^0 (Rossed polarizers) and again examined.

Refractive Index

The refractive indexes of selected microemulsion were determined using Abbe's refractometer.

Viscosity[7]

The selected microemulsion was measured using Brookfield viscometer, fitted with T-bar (B) spindle. The selected spindle was lowered into microemulsion system and was allowed to rotate at 10 rpm. The obtained reading was then multiplied by factor shown beside the speed at which measurement was being made.

PH

The pH of selected formulations was measured using digital pH meter. (Universal Enterprises)

Particle Size determination

The size of oil droplets was determined using Coulter N4 plus (Run: 90.0 degrees, Temp. 20^0 C, Unimodal analysis: Polydisperse)

Drug content[8]determination

Differential assay method was used to determine the drug content in formulation as discussed under drug analysis by measuring it's absorbance at λ max 239 (Shimadzu U. V. 160A – U. V. / Visible spectrophotometer).

***In-vitro* release profile**

In *in-vitro* release profile from the microemulsion in (Saline, Phosphate buffer) at pH 7.4 was determined using analysis bag at temp. 37^0 C, $\pm 1^0$ C 24 h. After every withdrawal a sample were replaced by a fresh medium.

Centrifugation

The microemulsion system was centrifuged at 3000 rpm, in 10 cm radius centrifuge tube for 30 min and were examined for any phase separation.

Freeze thaw cycle[9]

The selected microemulsion placed in vials were exposed to temp. 4^0 C and 45^0 C for 24 hr. each (single cycle). Five cycles were carried out for selected microemulsion and were observed for any instability.

TLC of microemulsion

TLC of selected microemulsion was carried out to detect degradation product of drug if any. Specifications for TLC of hydro cortisone is same as described earlier in spectrophotometric analysis and TLC of drug.

RESULTS AND DISCUSSION

The drug procured from Glaro India Ltd. complies with the I.P. limits. The drug the drug was analyzed spectrophotometrically at 239 nm & 237 nm in methanol & saline phosphate buffer pH 7.4 respectively. The line of equation are, Y = 0.045 1x + 0.0265 R^2 = 0.9983 and Y = 0.0377x + 0.0333R = 0.9982 in methanol & saline phosphate buffer pH 7.4 respectively the Beer Lambert low was obeyed over the range 2-20 cm / ml.

TLC was also performed for the detection of degradation & non degradation for drug. For the preparation of microemulsion mixture of surfactant & co surfactant blend and water or co-solvent wire prepared in varying wt. ratio Pseudo ternary phase dig. were constructed to define the extent of microemulsion region from data gathered by titration method. The titration method gives the possibility of making & study of large no. of difference composition [10], [11].

The phase diagram could be chosen to provide right mix of four comments which lead to clear transparent / translucent microemulsion system different ratio of S + Cos water and S + Cos : Water / Co-solvent system. The formulation containing cremophor EL showed turbidity before addition of internal oil phase and were highly viscous in nature. Therefore formulation containing soya lecithin (surfactant) and tween 80 (Co-Surfactant) were selected for further studies. The relative microemulsion containing difference ratio of S/Cos and water / co-solvent

with the parent of oil added is given in Table-1. The various formulations were then characterized for various properties listed in Table-2

Table 1 – Selected Microemulsion Formulation

Batch No.	Surfactant / Co-Surfactant	Solvent / Co-solvent	Oil
A1	1:4	Water PG 8:2	10:23
A2	1:4	Water PG 6:4	8:08
A3	1:6	Water PG 9:1	11:03
A4	1:6	Water PG 7:3	8.08
A5	1:4	Water PEG 400-6:4	9:90
A6	1:6	Water PEG 400 7:3	10:71
A7	1:6	Water PEG 400 6:4	11:50

Table 2- Physico-Chemical Characteristics of Selected Formulation

	Characteristics	A1	A2	A3	A4	A5	A6	A7
1	Colour and Odour	Light yellow and pleasant colour						
2	Appearance	Translucent						
3	Refractive Index	1.448	1.449	1.447	1.451	1.446	1.453	1.446
4	Optical Birefringence	Complies.						
5	Viscocity (CPL)	350	400	600	550	430	320	800
6	PH	7.21	7.46	7.29	7.31	7.14	7.34	7.30
7	Particle size (nm)	31.4	206.4	566.4	93.85	65.4	47.5	23.5
8	Drug Content (W/W)	96.61 ± 0.01	93.96 ± 0.09	93.30 ± 0.05	97.94 ± 0.07	95.29 ± 0.05	94.62 ± 0.09	92.63 ± 0.05
9	Cum % drug release in 24 hr.	77.80 ± 0.08	79.79 ± 0.09	81.18 ± 0.08	92.92 ± 0.02	70.86 ± 0.06	69.78 ± 0.08	76.55 ± 0.05
10	Configuration	No change						
11	Freeze thaw cycling	No change						
12	TLC	No drug degradation was detected						

On the characterization studies, observation indicated that all microemulsion were optically isotropic colloidal dispersion, translucent, homogeneous, multiphase apparently liquid and were stable at room temperature is based on the principle of light transmittance thro polarized plate Microemulsion appeared compactly black when observed through crossed polarizer.The formulation A1 & A6 had particle size in the range of 30-50 nm and viscosity in the range of 300-350 cps. Hence A1 & A6 micro emulsions were kept for accelerated stability studies made on the viscosity, particle size and cumulative parent-drug release in 24 hrs.

The formulations were sterilized and then sterilized formulations were evaluated for physicochemical properties (Table 3) the sterilized sample found to comply with test for sterility. The accelerated stability studies of sample were carried at 4^0 C, room temp. 37^0 C $\pm 2^0$C & 45^0 C $\pm$ 2^0C for period of 1 month samples were weekly evaluated and were found no change in color, visual appearance, centrifugation, freeze thaw cycle during accelerated stability study.

Table 3: Physiochemical Characteristics of A1 & A6 Microemulsion after sterilization

Sr. No.	Characteristic	Formulation	
		A1	A6
1.	Colour & Odour	Light yellow and pleasant order	
2.	Appearance	Translucent	
3.	Refractive Index	1.446	1.451
4.	Viscosity (CPS)	268	256
5.	pH	7.12	7.31
6.	Particle size (nm)	30.1	46.4
7.	Drug Content (% w/w)	96.69 ± 0.001	94.46 ± 0.003
8.	Cum % drug release in 24 Hr.	82.79± 0.003	75.82± 0.005
9.	Centrifugation	No Change	
10.	Freeze Thaw cycling	No Change	
11.	TLC	No drug degradation was detected	

Result of accelerated stability studies were reported in Table 4.No degradation detected by TLC and *in-vitro* release profile of selected formulation showed, no significant change during the studies.

Table 4 Accelerated Stability studies of A1 & A6

Characteristic	Observation after 4 week									
	Initial		4^0		Room Temp.		37^0		45^0	
	A1	A6	A1	A6	A1	A6	A1	A6	A1	A6
pH	7.12	7.31	7.12	7.31	7.12	7.31	7.12	7.31	7.12	7.31
Viscosity (CPS)	268	256	266	255	266	255	266	254	265	255
Drug Content (w/w)	96.49 ± 0.07	94.46 ±0.01	96.58 ±0.01	94.76 ±0.03	96.76 ±0.03	94.56 ±0.05	96.62 ±0.05	94.62 ±0.03	96.76 ±0.05	94.47 ±0.07

CONCLUSION

Therefore it can be concluded that lecithin – based microemulsion could be formulated for parental drug delivery to obtain sustained / prolonged drug delivery for hydrocortisone combined with good physical stability. It is recommended that *in-vivo* anti-inflammatory efficacy studies should be carried out.

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