International Journal of Pharmacy
Journal Homepage: http://www.pharmascholars.com

Research Article **CODEN: IJPNL6**

IMPROVED RELEASE ORAL DRUG DELIVERY OF METAXALONE

N. Waman, R. Ajage, P. N. Kendre, S.B.Kasture, Veena Kasture*

Department of Quality Assurance Techniques, Sanjivani College of Pharmaceutical Education and Research, Kopargaon, Maharashtra

***Corresponding author e-mail:** veenakastureg@hotmail.com

ABSTRACT

Metaxalone is BCS class II drug having low solubility and high permeability. The solubility and bioavailability of poorly soluble drug was increased by designing microemulsion based drug delivery system of Metaxalone for oral drug administration. The microemulsion was prepared using Tween 80, PEG-400 as surfactant and cosurfactant, sesame and castor oil and water .The formulation was evaluated for globule size, viscosity, RI, pH, conductance, % transmittance and % drug content. The in-vitro intestinal drug diffusion was carried using Frantz diffusion cell and in-vivo drug activity was measured by using animal model. The microemulsions were transparent; particle size was in the range of 45.39 - 271 nm. The viscosity lies between 88 and 95.5cps, pH was found to be 8.12 - 8.17. The Formulated microemulsion had better drug permeation as compared to the pure drug and its marketed dosage form, had good muscle relaxant activity in mice. Study concluded that Metaxalone in microemulsion form exhibited increased solubility and improved drug release.

Key words: Metaxalone, muscle relaxant, rat, Flexura Malvern Zetasiezer

INTRODUCTION

Large number of drug molecules has poor water solubility which results in low oral bioavailability posing difficulty in treatment of various diseases[1]. Many approaches have been developed to increase bioavailability of poorly soluble drugs including particle size reduction, salt formation, and complexation with cyclodextrins, co-solvency, and etc.[2]. Microemulsions act as versatile carrier and are reported to improve permeation and absorption of poorly soluble drugs[3]. Microemulsions are liquid dispersion of water and oil that are made thermodynamically stable and isotropically clear by addition of surfactant and co-surfactant[4]. Microemulsion also offers protection against the enzymatic hydrolysis[5]. Metaxalone, a white crystalline powder, freely soluble in chloroform, sparingly soluble in methanol and ethanol, and practically insoluble in water, is a centrally acting muscle relaxant used to relieve pain caused by strain and sprains[6]. The mechanism of central nervous system depressant action of Metaxalone is not yet known. Metaxalone is devoid of any direct effect on contractile mechanism of striated muscle or on nerve fibers[7]. Because of its low solubility and high permeability it belongs to BCS class II drugs[8]. In this study, an attempt is made to prepare Microemulsion based oral drug delivery to increase bioavailability of Metaxalone. Microemulsions contained varying amounts of Tween 80 as surfactant, PEG-400 as co-surfactant, Sesame oil/ castor oil and water to improve solubility and release of drug.

MATERIALS AND METHODS

Metaxalone was gift sample from Anjelini Pharmaceuticals Ltd. India. Tween 80, Span 80, PEG-400, Sesame oil, castor oil were bought from Research Fine Lab chemicals, Mumbai. All other chemicals were of analytical grade. Tablets of Metaxalone (Flexura, Sun Pharma, India) were purchased from Pharmacy. Swiss albino mice of either sex weighing about 25-30 gm were used for the in-vivo muscle relaxant study. The animals were obtained from National Toxicology Centre, Pune and the animal experiments were approved by the

Institutional Animal Ethical Committee, constituted as per the guidelines of Committee for the Purpose of Control and Supervision on Experiments in Animals (CPCSEA), New Delhi, India.

Solubility Study: The solubility of Metaxalone was determined in various combinations of oil, surfactant and cosurfactant, by Shake Flask Method. For determination of solubility, excess amount of drug was added to 10 ml of each component separately in 50 ml stoppered bottles. The bottles were shaken at 35^0C for 48 hrs at 75 rev/ min. Then contents of each bottle were centrifuged at 3000 rev/ min for 15 min. The supernatant was diluted suitably with chloroform and quantification of Metaxalone was done by UV-Spectroscopic method at 272 nm[9].

Construction of phase diagrams: Pseudoternary phase diagrams were used to examine the formation of microemulsion using 4 components (oil, surfactant, cosurfactant, and aqueous phase). The diagrams were constructed by water titration method. For the construction of diagrams, surfactant and cosurfactant used in ratios (S:Cos) 1:1, 2:1, 3:1, were mixed with oil in various ratios as 1:9, 2:8, 3:7, 4:6, 5:5, 6:4, 7:3, 8:2, and 9:1 (w/w). Then water was added drop-wise with continuous stirring. After each addition the mixture was examined for turbidity as end point as described earlier[10].

Preparation of microemulsion*:* Microemulsion was prepared on the basis of formula obtained from pseudoternary phase diagram. Predetermined amount of Metaxalone was dissolved in oil. Fixed amount of surfactant and co-surfactant was added to it and the mixture was mixed with small increments of distilled water with continuous stirring[11].

Characterization of microemulsion

Particle size determination: Particle size of optimized microemulsion formulations were determined by dynamic light scattering Malvern Zetasizer Nano-ZS90. Sample preparation was done by diluting 0.1ml of microemulsion in distilled water i.e. dispersion medium[12].

Refractive index and Percent transmittance determination: The refractive index of optimised microemulsion formulations was determined using Abbe's Refractometer. Transparency of optimised microemulsions and their dilution (100 time dilution) was measured using UV-Visible spectrophotometer (UV-1650PC; Shimadzu Co., Kyoto, Japan) at 650 nm against distilled water as blank[13].

pH measurement: The pH of optimised microemulsions was determined using pH meter (LabIndia, India). The pH of microemulsion was measured in triplicate.

Determination of Viscosity: The viscosity of microemulsions was determined using Brookfield Viscometer (LVII, Brookfield Inc., USA) equipped with the spindle No. 4. The measurement was performed at ambient temperature in triplicate[14].

Drug content analysis: The UV-spectroscopic method was used to determine Metaxalone in microemulsions at 272 nm[15].

In-vitro release study: The drug permeability study was performed by using Franz Diffusion Cell. The diffusion cell was fitted with 0.45 µ cellulose acetate membrane (Micro Device Pvt. Ltd, USA) receptor compartment was filled with 12 ml of diffusion medium (20% methanolic phosphate buffer pH 6.8). The diffusion medium was continuously stirred by magnetic stirrer at 50 rev/ min, accurately weighed 1g microemulsion was placed on membrane in donor cell compartment. One ml of sample was withdrawn from the receptor compartment at a predetermined interval up to 5 hours after the application. An equal volume of fresh 20% methanolic phosphate buffer (pH 6.8) was immediately replenished after each sampling. The withdrawn samples were diluted up to 10 ml using diffusion medium and absorbance was measured. The average % drug release from microemulsions, tablets, and plain drug was determined. The release pattern was studied using 0.1N HCl as diffusion medium[16, 17].

In-vitro Intestinal Permeability Study: The method employed was modified from experimental procedure well described in the literature. Male Sprague-Dawley rats (250-300 g) were killed by overdose of pentobarbitone administered by IV route. The duodenal part of the small intestine was isolated and taken for *in-vitro* diffusion study. The tissue was thoroughly washed using cold Tyrode solution to remove the mucous and lumen contents. One side of the duodenum was closed using thread. Then the microemulsion (0.5 ml containing 10mg of drug) was injected in to the lumen by using 1ml syringe, and the second side was tightly closed. Then the tissue was placed in the chamber containing diffusion medium i.e. 20% methanolic phosphate buffer and continuously stirred using magnetic stirrer at 37^0C and supplied with continuous aeration. The samples were withdrawn at predetermined and the absorbance was measured using a UV spectrophotometer. Similar study was also performed using 0.1 M HCl as

diffusion medium. The percentage drug diffusion from microemulsions was compared with marketed tablet and plain drug[18].

In-vivo muscle relaxant activity: The rotarod apparatus was used for muscle relaxant study. The apparatus consists of a metal rod (3 cm diameter) attached to motor. The rod is 75 cm in length and divided into 6 sections by plastic disc, so that 6 mice can be tested simultaneously. The rod is place at a height of 50 cm above the table top to discourage the animal from jumping off the rotating rod. The animals were pretested to demonstrate their ability to remain on the revolving rod (25 rev/ min). Only those animals which remain on rod for 5 min were used for the test. The animals were divided in 6 groups each consisting of 5 animals. Group I served as control and received saline solution, group II served as standard, which received diazepam (1mg/kg, oral), group III and group IV received plain drug and marketed tablet (finely triturated) respectively (5.71 mg/ kg, orally). Group V and group VI received 1.42 mg/kg dose of F-1 and F-2 respectively. Before administering dose, the animals were kept on fasting for 5 hour with free access to water. After 1 hour of administration of dose, the animals were placed on rotating rod and fall off time was recorded [19].

RESULTS AND DISCUSSION

The solubility data of Metaxalone in different component is shown in **Table 1**. Sesame oil showed higher solubilising capacity as compared to other components. Based on the solubility study, combination of sesame oil or castor oil with Tween 80, Span 80, and PEG-400 could be the most appropriate combination for development of microemulsion. Since the aim was to develop o/w type microemulsion more over physical incompatibility of Span 80 with the mixture of Tween 80 and PEG-400,hence not used for preparation of microemulsion.

Pseudoternary phase diagram: Two different sets of pseudoternary phase diagrams were constructed for two different oils *viz.* sesame oil and castor oil. The diagrams were constructed by water titration method. In first set (**Figure 1**), pseudoternary phase diagram with ratio 3:1 formed clear microemulsion with highest microemulsion existing region, but it is not stable; it showed the phase separation after 24 hrs. The ratio of Tween 80 (2 parts) and PEG-400 (1 part) gives clear and stable microemulsion over 72 hrs. The pseudoternary diagram showed the concentrations of component at microemulsion existing region. Based on the pseudoternary phase diagram proportion of surfactant-cosurfactant mixture (75.95%), water (14.28%) and sesame oil (9.61%) was used for the microemulsion F-1. Similarly, in second set of pseudo-ternary phase diagram, shown in **Figure 2** the (S: Cos of 3:1) i.e. Tween 80 (3 parts) and PEG-400 (1 part) has given a clear and stable microemulsion for 72 hrs with highest microemulsion existing region. Based on the pseudoternary phase diagram, the proportion of surfactant-cosurfactant mixture (64.58%), water (12.12%) and castor oil (23.27) was used for the microemulsion F-2.

Characterization of microemulsion: The optimized microemulsions were subjected for physicochemical characterization. The physicochemical characteristics of microemulsion are shown in **Table 2.** The average globule size of microemulsion was between 45.39 nm and 271.1nm for F-1 and F-2 respectively (**Figure 3)**. Microemulsions showed slightly high viscosity due to large amounts of surfactant and cosurfactant. The percent transmittance of both the formulations was same with and without dilution. It ranges between 94 to 99.80%. The refractive index of both the formulations was slightly high compare to water and pH was slightly alkaline (Table 2). The data of transmittance and refractive index indicate that the formulated microemulsions were clear and transparent. The polydispersity index of formulations was lower than 1, indicates the uniformity in droplet size distribution throughout the formulation. The percent drug content of microemulsion was found to be 98.73% and 97.93% respectively.

In-vitro release study: The average percent release of Metaxalone was determined with the help of Franz diffusion cell. The percent release of microemulsion formulation (F-1 and F-2) was compared with pure drug and marketed formulation i.e. Flexura tablet. The study was performed in different diffusion medium viz. phosphate buffer pH 6.8 and 0.1 N HCl. The results of in-vitro drug release in phosphate buffer pH 6.8 (**Figure 4).** Microemulsion formulation F-1 showed highest drug release i.e. 93.76% as compared to F-2 (90.23%), marketed tablet (37.09%) and pure drug (18.35%). Metaxalone showed slightly higher drug release in 0.1 N HCl as compared to phosphate buffer pH 6.8, indicating better stability in acids than bases. The result of in-vitro drug release in 0.1 N HCl showed in **Figure 5**. The average percent release of Pure Drug, Flexura tablet, formulationsF-1 and F-2 was 23.85 %, 41.57 %, 95.17 %, and 92.59 % respectively. Formulated Microemulsions showed higher drug release compared to pure drug and marketed formulation. The smaller droplet size and solubility enhancing

component like surfactant and co surfactant increased drug release.

In-vitro Intestinal Permeability Study: The result of in-vitro intestinal drug release in phosphate buffer pH 6.8 and 0.1 N HCl are shown in **Figure 6 and 7** respectively. In-vitro Intestinal Permeability of F-1 and F-2 was better in both the media compare to pure drug and its marketed formulation i.e. Flexura tablet. Percent Drug release from different formulations were found to be 21.09% for pure drug, 36.59% for Flexura tablet, 87.93% for F-1 and 84.55% for formulation F-2. The average percent release of drug was found to be higher in microemulsions as compared to pure drug and its marketed formulation (Flexura tablet). Percentage Drug release for pure drug, Flexura tablet, microemulsion formulation F-1 and F-2 was found to be 22.00%, 35.51%, 89.78% and 84.171% respectively.

In-vivo muscle relaxant activity: The result for muscle relaxant activity of mice in rota rod test are shown in **Figure 8** Treatment with F-1 formulation was found to be more significant as compared to the vehicle group as there was reduction in the time spent on the rotating rod. Diazepam was a standard drug and showed most significant value amongst all groups. F-2 also possessed more muscle relaxant activity compared to vehicle group. Flexura tablet and pure drug was found to be less potent in muscle relaxant activity may be due to their low solubility. The results indicate that muscle relaxant activity of Metaxalone is significantly increased by microemulsion formulation as compared to pure drug and its tablet.

Stability Study: In stability studies, the physical properties of microemulsions were studied. The microemulsions were found physically stable and there was no sign of creaming, cracking or phase separation in microemulsions. The drug content was found to be slightly reduced may be of degradation of drug. The data of stability study is shown in **Table 3**. After 3 months, the microemulsions were clear and showed no phase separation after centrifugation for 3000 rpm for 30 min. The study showed, better efficacy of F-1& F-2 when stored for longer period, even at varying temperatures.

CONCLUSION

In present study microemulsion based oral drug delivery system of Metaxalone was developed, using Tween 80, PEG-400 as surfactant & cosurfactant. The oil phase selected was Sesame oil/Castor oil. The microemulsion showed the better drug diffusion as well as increased muscle relaxant activity, may be related with its reduced globule size and enhanced solubility. The muscle relaxant activity of Metaxalone will enhance if it is administered in the form of microemulsion orally.

.

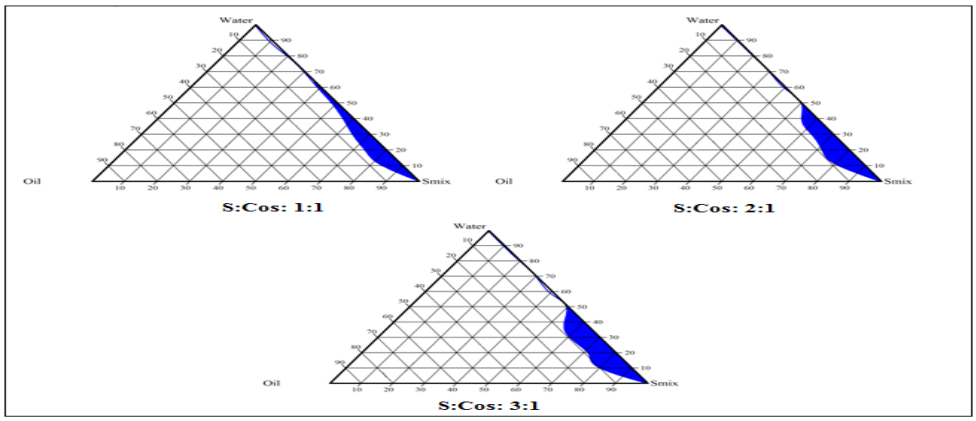

Figure 1: Pseudoternary phase diagrams of microemulsion containing sesame oil

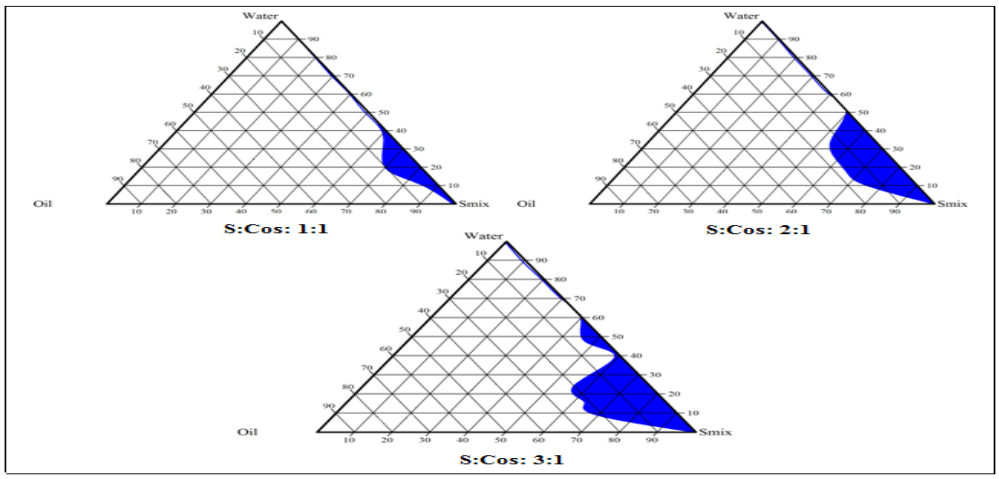

Figure 2: Pseudoternary phase diagrams of microemulsion containing castor oil

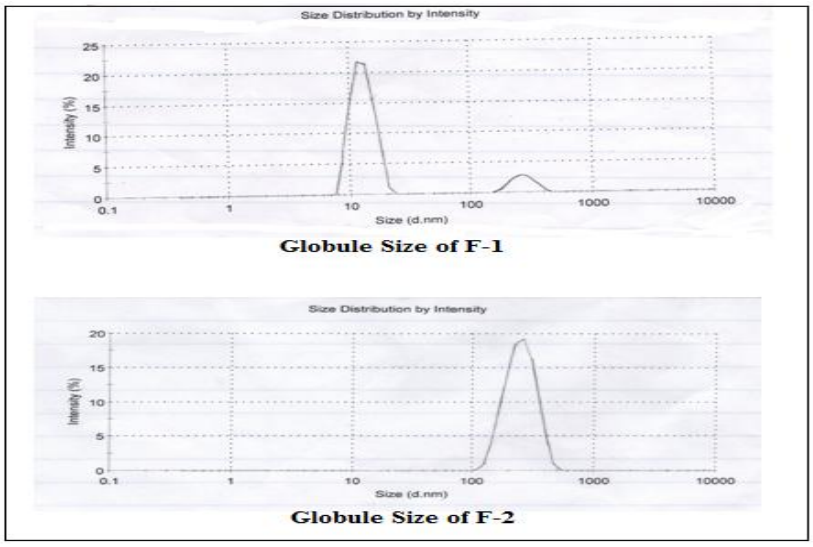

Figure 3: Globule size determination of microemulsions

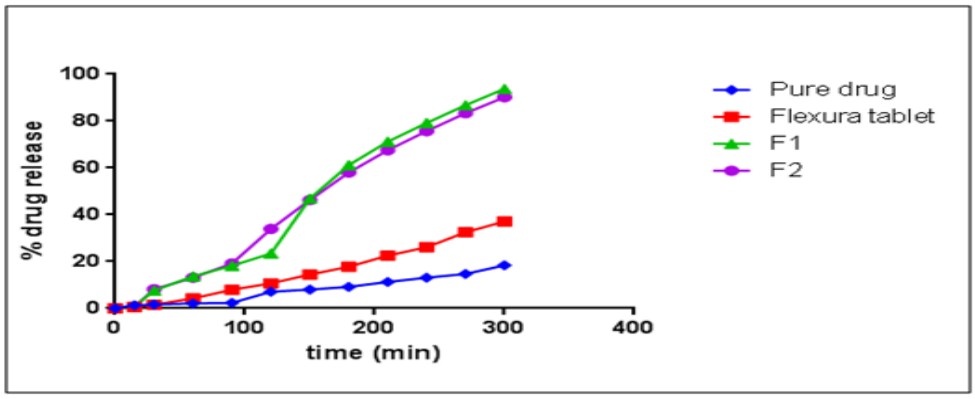

Figure 4: Percent drug release of pure drug, Flexura (marketed) tablet, Formulation F-1and F2 in phosphate buffer pH 6.8

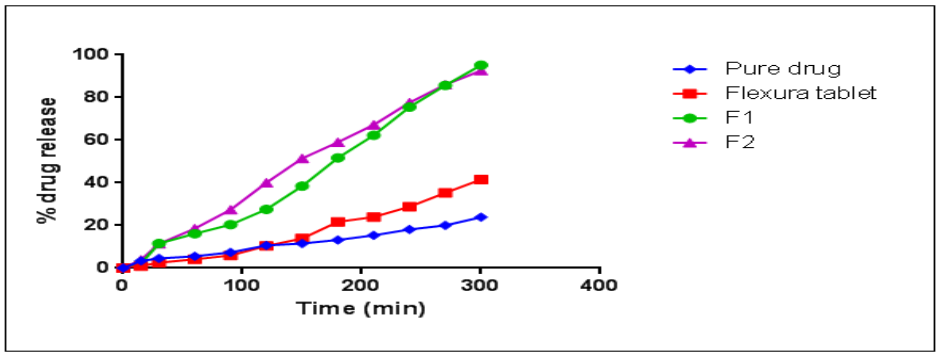

Figure 5: Percent drug release of pure drug, Flexura (marketed) tablet, Formulation F-1and F-2 in 0.1 N HCl

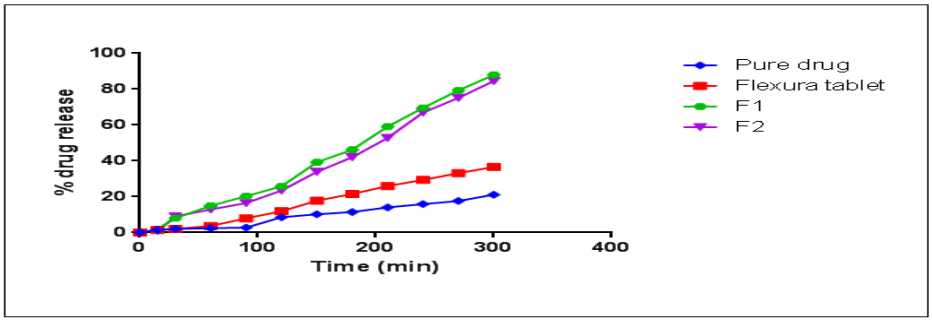

Figure 6: Percentage drug release from duodenum in phosphate buffer pH 6.8

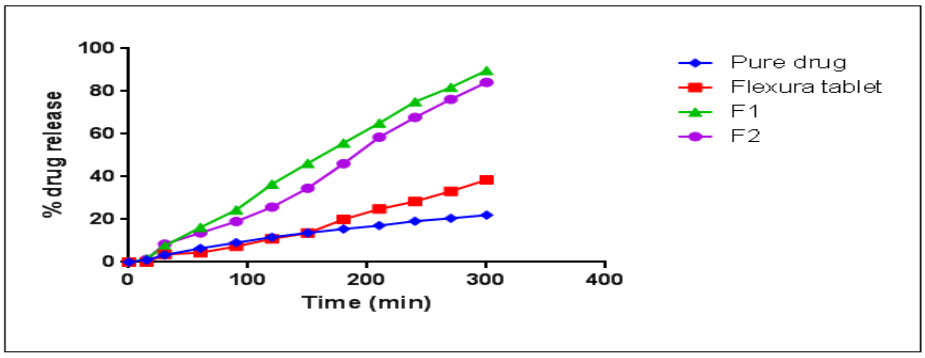

Figure 7: Percentage drug release from duodenum in 0.1 N HCl

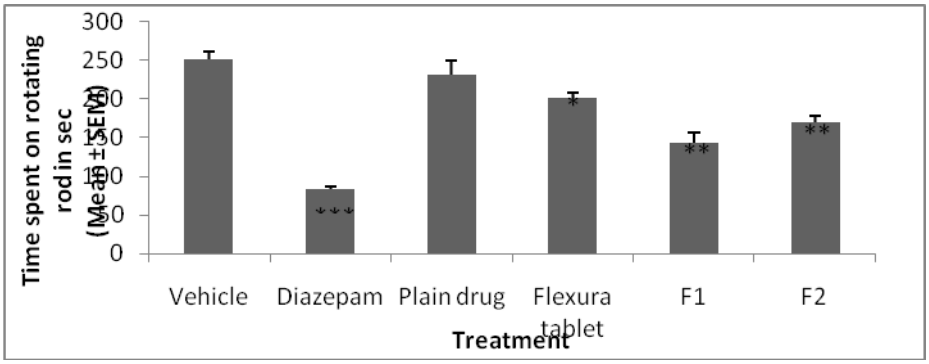

Figure 8: Effect of different formulations on muscle relaxant activity Values are mean ± SEM of 6 mice

Table 1: Solubility of metaxalone in different component

Sr. No.	Component	Solubility (mg/ml)
1.	Tween 80	33.29
2.	Span 80	51.66
3.	PEG 400	21.95
4.	Sesame oil	56.29
5.	Coconut oil	4.799
6.	Isopropyl myristate	0.306
7.	Castor oil	27.50
8.	Soya oil	29.97

Table 2: Physicochemical characterization of F-1 and F-2

Sr. No.	Parameter	Microemulsion formulation	
		F-1	F-2
1.	Average droplet size (d. nm)	45.39	271.1
2.	Viscosity at 25^0C (cps)	88.7±0.030	95.5±0.045
3.	Refractive index	1.456±0.01	1.462±0.03
4.	pH	8.17±0.02	8.12±0.05
6.	%Transmittance		
	i. Without dilution	94.18	96.83
	ii. 100 times dilution	99.60	99.77
7.	Polydispersity index	0.191	0.356
8.	% Drug content	98.73%	97.93%

Microemulsion formulation F-1 contain sesame oil and F-2 contain castor oil

Table 3: Observations of stability study of microemulsions

Sr. No.	Time	Temp. cycle	% Drug content		Centrifugation test		Appearance	
			F-1	F-2	F-1	F-2	F-1	F-2
1.	1st month	4^0C	98.36	97.72	No phase separation		No change	
		RT	98.70	97.79				
		45^0C	98.21	97.54				
2.	2nd month	4^0C	97.83	97.36	No phase separation		No change	
		RT	97.71	97.28				
		45^0C	97.58	97.09				
3.	3rd month	4^0C	97.26	97.12	No phase separation		No change	
		RT	97.24	96.87				
		45^0C	96.98	96.57				

REFERENCES

1. S.Talegaogkar ,K.R. Khar , A. Adnan andA.J. Farhan . AAPS PharmSciTech. 2009 December; 10(4): 1093–1103.
2. N.Sarkhjiya, M.Nakum, V.Patel . Int. Bull. Of Drug Res. 2012; 1(1): 54-83.
3. S.N.Ahammed, K.K.Shrinivasan,M.R. Kumar. Int.J.of Curr. Pharm. Res. 2013; 5(2): 10-14.
4. J.Swarbrick Encyclopedia of Pharmaceutical Technology. Inform healthcare Inc., USA 2007; 3: 1561-1564.
5. E.Gundogdu, I.G.Alvarez, E.Karasulu Int. J. of Nanomed. 2011; 6: 1631-1640.
6. M.N.Carrol, W.R.Luten,R.W.Southward. Arch. Int. Pharmacodyn. Ther. 1961, 130, 280–298.
7. T. Peter, U. Jason. Ther.2004, 26 (9), 1355-67.
8. R.Chou, K.Peterson and M.J.Helfand. Pain Sym. Manag. 2004, 28(2), 140-175.
9. B.Kumar, S.Jain, S.Prajapati, M.Alok. Inter.J.of Pharm. Sci. and Res. 2010; 1 (6): 57-74.
10. K..Jha, R.Karki. Int. J. of Drug Dev. & Res. 2011; 3(4): 336-343.
11. S.Mandal, S.S.Mandal andK.K. Sawant Int J of Drug Del. 2010; 2: 69-75.
12. S. Khokhra and A.Diwan. Int. J.of Drug Dev. and Res. 2010; 3(1): 191-196.
13. B.Sarkar S. Hardenia . J of Adv. Pharm. Edu. and Res. 2011. 1(4): 195-200.
14. R.Shah,S.C.Madgum,S.S.Patil and N. Niakwade.Ind. J. of Pharm. Res. 2010; 9(1): 5-11.
15. C.R.Patel, R.V.Kumbahune, P.V.Kabr,A.R.Harish andLVG Narund,(2012) J Anal Bioanal Techniques ,3:137
16. S.Solanki, B.Sarkar ,R.Dhanwani. Int. Scholarly Res. Network 2012: 1-4.
17. R.R.Shah , N.S.Naikwade andC.J. MagdumInd.J. of Pharm.Res. 2009; 2 (3):557-561.
18. P.K.Ghosh, R.J.Majithiya,M.L. Umrethia, S.R.Murthy. AAPS PharmaSciTech 2006; 7(3): 1- 6.
19. P.Sinoria,R.IrchhaiyaB.,Sharma G.,Sahu ,and K Santosh. Ind. J Pharmacol 2011;43(60):710-713.