

FORMULATION DEVELOPMENT AND EVALUATION OF ONDANSETRON HCL NATURAL VESICLE OF LIPOSOME FOR CHEMOTHERAPY INDUCED NAUSEA VOMITTING

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Abstract: aim of present work was evaluation of liposomes by 3^2 factorial design study of ondansetron Hcl liposome for physicochemical characterization was carried out by using scanning electron microscopy, zeta sizer, particle size analyser and freeze fracture performed. The optimized batch of liposome has zeta potential was (-55.12 mv) and the vesicle size found to be 272.9 nm (PDI = 0.200). In-vivo release study performed using guinea pig skin through franz's cells for (24 hr) by RP-HPLC. Liposome suspension shows higher flux than plane liposomes by hyton and chains analysis. Gel prepared by using carbopol (940) shows pseudoplastic flow. Ondansetron Hcl undergoes first-pass metabolism, so its bioavailability

may be improved when delivered through transdermal route. Here attempt to increase delivery of ondansetron Hcl by virtue liposomal based vesicular system.

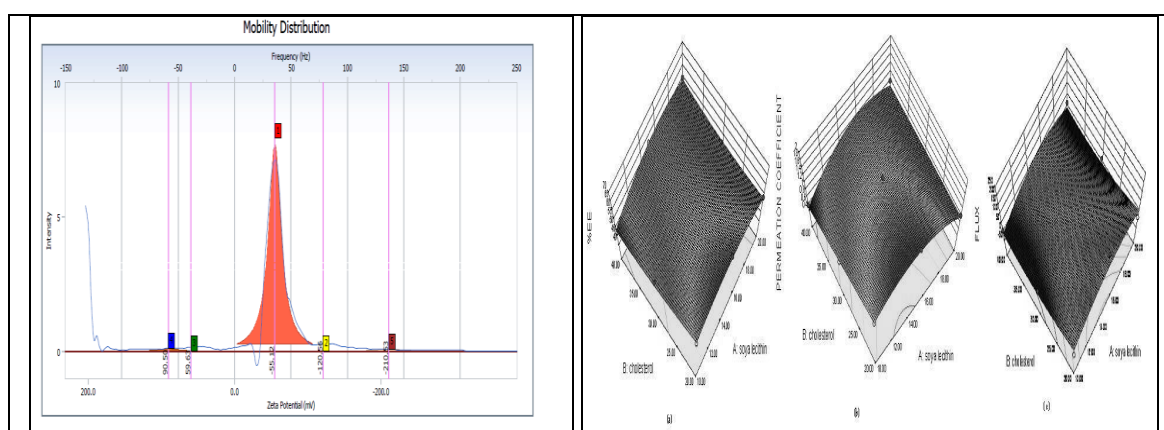


Fig: stability and response surface methodology of vesicle

KEYWORDS: vesicle, 3^2 design, ondansetron HCl, Liposomes, soya lecithin.

1. INTRODUCTION

Cancer Treatment suffers from side effects of nausea and vomiting which are the most complaints by patients. To prevent or minimize these side effects of anticancer treatments, antagonists for 5-hydroxytryptamine subtype-3 (serotonin) such as tropisetron, ondansetron, granisetron and dolasetron, known as serotonin receptor antagonists have been widely administered either parenteral or orally on a daily basis. The transdermal delivery of antiemetic drug is an interesting concept, and seems to be beneficial in a great many patients with chemotherapy induced nausea vomiting.

Ondansetron HCl is a potent and selective 5-hydroxytryptamine (5HT-3) receptor antagonist with antiemetic activity indicated for the prevention or treatment of nausea and vomiting associated with cytotoxic chemotherapy radiotherapy and postoperative nausea and vomiting. Ondansetron HCl is rapidly absorbed from the gastrointestinal tract and reaches maximum concentration in serum after approximately 1.6 hr. Ondansetron HCl undergoes first-pass metabolism so its bioavailability may be improved when delivered through transdermal route. So there is a need to develop a transdermal formulation of Ondansetron HCl which increases patient compliance. The word 'vesicle' having a biological origin actually means a bubble of liquid within a cell. Technically a vesicle is a small, intracellular, membrane-enclosed sac that stores or transports substances within a living cell. Touitou (1998) discovered and investigated lipid vesicular systems embodying ethanol in relatively high concentration and named them Ethosomes. The basic difference between Liposomes and Ethosomes lies in their composition. The high concentration of ethanol (20-50%) in ethosomal formulation could disturb the skin lipid bilayer organization. Touitou (1998) discovered and investigated lipid vesicular systems embodying ethanol in relatively high concentration and named them Ethosomes. Ethanol acts as a penetration enhancer through the skin. The mechanism of its penetration enhancing effect is well-known. Ethanol penetrates into intercellular lipids and increases the fluidity of cell membrane lipids and decrease the density of lipid multilayer of cell membrane. Increased cell membrane lipid fluidity caused by the ethanol of Ethosomes results increased skin permeability. So the Ethosomes permeates very easily inside the deep skin layers, where it got fused with skin lipids and releases the drugs into deep layer of skin. Liposome have problem of drug leakage which is overcome by using Ethosome. Stability of vesicle is enhanced by use of the ethanol. Ondansetron HCl BCS -3 drug, so permeation of the vesicle containing Ondansetron HCl enhanced virtue of ethanol effect of ethanol and ethosomal effect of Ethosomes. Literature reveals that no work is reported on ondansetron in

gel based vesicular delivery of antiemetic drug is an interesting concept but its clinical use has found limited application due to remarkable barrier properties of the outermost layer of the skin. Literature also suggest that Ethosomes has better stability than Liposomes, niosomes and more permeation than Liposomes and liquid drug solutions. First time attempt to develop liposomal and ethosomal TDDS for antiemetic drugs for the treatment of chemotherapy induced nausea and vomiting (CINV). Development of sustain release ethosomal and liposomal transdermal gel of ondansetron HCl. Attempt to increase permeation of ondansetron HCl through liposomal based system. Prolonged drug release Reduce dose frequency Improve patient compliance. The animal experiments was approved by Institutional Animal Ethics Committee (IAEC) of Government College of Pharmacy, Aurangabad India (Ref. No. GCPA/IAEC/2012/555- Date: 4/6/2012) and carried out as per the guidelines of the committee.

2. MATERIAL AND METHODE

Ondansetron HCl from (Cipla Mumbai), Was a Kind Gift Soya Lecithin from (ResearchLab), Cholesterol from (Dipa Laboratory Chemicals), Carbopol 940 From (Noveon), All Other Chemicals Was of Analytical grade. Animal guinea pig from Wockhardt .The animal experiments was approved by Institutional Animal Ethics Committee (IAEC) of Government College of Pharmacy, Aurangabad, India (Ref. No. GCPA/IAEC/2012/555- Date: 4/6/2012).

2.1. PREPARATION OF LIPOSOME

Preliminary Batches of the Liposomes was prepared by using soya lecithin (50-200 mg) and cholesterol (20 -50 mg) as independent variable. The optimized batch (F4) was selected by 3² Factorial design (Table1). In this method physical dispersion where the lipid mixture of different phospholipids soya lecithin and charge inducing substances i.e. stearic acid (30 mg) and cholesterol components are dissolved in chloroform: methanol mixtures (2:1 v/v) in a round bottom flask along with the hydrophobic drug (Ondansetron HCl) . This is followed by Evaporation using a rotary evaporator at temperature 50°C the transition temperature of the phospholipids to obtain a thin film on the wall of flask. Adding phosphate buffer pH 7.4 containing drug into the flask then carries out hydration of the lipid film. The flask is then shaken or rotated above the Transition temperature. The obtained liposomal dispersion is then allowed to stand for two hours at room temperature (Fig.11).

2.2 Preparation of Liposomal Gel

Liposomal suspension containing Ondansetron HCl was incorporated into Carbopol 940 (20% w/w) as a gelling agent with constant stirring using a Teflon-coated magnetic bead, and the resulting mixture was then refrigerated at 4°C for 24 hr to obtain a completely hydrated, homogeneous and clear solution. After solution as removed from refrigerator placed at room temperature, until it forms a completely hydrated, homogeneous, and clear gel. (Table 2).

2.3. Characterization of Vesicles

2.3.1. *In-vivo* Permeation Studies

The guinea pig skin was mounted on modified franz diffusion cell. In-vivo evaluation of permeation rates of preliminary and optimized liposomal (F4) batches was performed respectively and drug solution containing same concentration of Ondansetron HCl through guinea pig skin was studied (As control). At the predetermined sampling intervals, aliquots of 1 ml was withdrawn periodically and replaced with the same volume of fresh receptor fluid (20% PEG). Skin Permeation was studied for 24 hr. Experiments for preliminary batches was performed in triplicate. Drug concentrations was measured by RP-HPLC method. After the experiment the skin was cut into pieces and kept in 20% v/v (PEG-400) in water for 24hr to determined skin drug content. Then solution was filtered and analyzed by RP-HPLC method. From this amount of drug remain in skin was determined By Hyton and Chien Equation (table 1, 2 and Fig:11,12)

$$C_n^1 = C_n (V_t/V_t - V_s)(C_n^1 - 1/C_n - 1)$$

2.3.2. Entrapment Efficiency Determination

Liposomal Suspension prepared by Thin Film Hydration Method Respectively was further optimized for the entrapment efficiency. The prepared Ethosomes was kept over night at 4°C and ultra centrifuged (Megafuge 1.0 R, Heraeus, Hanau, Germany) for 5 hr at 14000 rpm. The free (unentrapped) Ondansetron HCl concentration was determined in the supernatant by RP-HPLC. The Ondansetron HCl entrapment percentage was calculated from the following formula:

$$EE = [(Q_t - Q_s)/ Q_t] * 100$$

2.3.3. Skin Irritation Studies

The skin irritation potential of the optimized formulation (F4) batch of Liposome was investigated in guinea pigs. Skin irritation following single application (single insult

challenge) was assessed by a visual erythema scoring method (Figure 1).shows formulation suitable for transdermal formulations.

2.3.4. Vesicle Size and Size Distribution

Vesicle size of optimized (F4) batch of Liposomes was determined using zeta sizer (Beckmann coulter counter) (Figure 2).shows vesicle size of 372.9 nm.

2.3.5. Microscopic Examination

MicroscopyOlympus® Cx31 Equipped With Magnus Pro.V.3.0. Software of the Optimized Optimized F4 Formulations of Liposome Revealed the Presence of Liposomal vesicle (Figure 3)shows vesicle of liposome in sample.

2.3.6. Zeta Potential Analysis

Zeta potential of optimized (F4) batch of Liposomes was determined using zeta sizer (Beckmann coulter counter) (Figure4). which was initially calibrated according to Beckmann instrument specification .it was found to be -55.12 mv.

2.3.7. Surface Morphology Evaluation

Scanning electron microscopy (Jsm-760 Of Philips) Photomicrographs of optimized (F4) batch of Liposomes vesicle was taken using a scanning electron microscope to study the surface morphology of Vesicle (Figure 5).

2.3.8. Evaluation of Liposomal and Ethosomal Gel Formulations

The gel formulation containing Ondansetron HCl was evaluated for pH, viscosity, consistency and clarity, drug content uniformity, histopathology (Table3,4 and Figure3,4).

2.3.9. Freeze Fracture Analysis

Vesicle characterization, the samples, after. centrifugation for 30 min at room temperature (Microcentrifuge Ole Dich. NCL Pune),was examined by means of the freeze fracture microscopy technique: samples were impregnated with 30% glycerol and then frozen in partially solidified Freon 22, freeze fractured in a freeze fracture device (-105 8C, 10–6 mm Hg) and replicated by evaporation from a platinum/carbon gun. The replicas were extensively washed with distilled water, picked up onto Formvar-coated grids and examined with a Philips CM 10 transmission electron microscope. (Figure10) .

3. Statistical Analysis Optimization

F4 batch showing max entrapment 63.65% 3^2 factorial. carbopol (940), flux 20.65 ($\mu\text{g}/\text{cm}^2/\text{hr}$), permeability coefficient 1.8(cm/hr) was selected for further studies by 3^2 factorial optimization figure. ANOVA on the basis of p-value was found to be less than 0.05 at 95% Confidence limit by student-t test. (Figure 6).

4. RESULTS

Vesicle size of optimized F4batch of Liposomes was found in nano range (372.9 nm). It was observed that increase in concentration of ethanol reduces vesicle size which leads to enhancement in permeation and flux. Polydispersity index of 0.200nm indicates that vesicles are monodispersed with distribution of vesicles from 372.9 nm to 942.3 nm range. Microscopic examination of the optimized Liposome batch F4 formulations revealed the presence of vesicles. Zetapotential of optimized Liposome F4 batch was found to be -55.12 mv.% entrapment efficiency of optimized Liposome F4 batch was found to be 63.65% re. Flux of optimized Liposome F4 batch was found to be 20.65 ($\mu\text{g}/\text{cm}^2/\text{hr}$) respectively. Permeability coefficient of optimized Liposome F4 batch was found to be 1.8 (cm/hr). Surface morphology analysis performed by using scanning electron microscopy. skin sensitivity test shows no erythema for optimized F4 batches so suitable for transdermal application. Cumulative release for optimized F4 batches with plane Liposome and listed in Figure (8). Liposomes so proved to be better drug delivery for Ondansetron HCl.


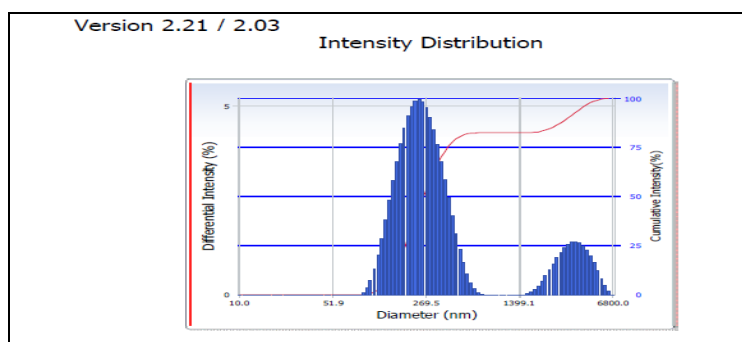
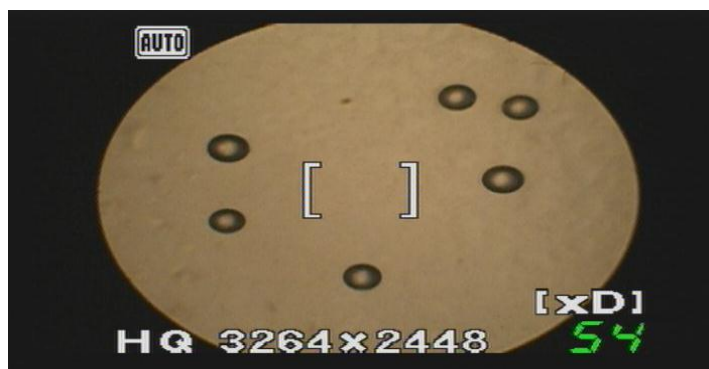
Visual observation	Erythema score	Conclusion	Suitability
	0	No erythema	suitable
For Liposome			

Figure 1: Skin Irritation Study

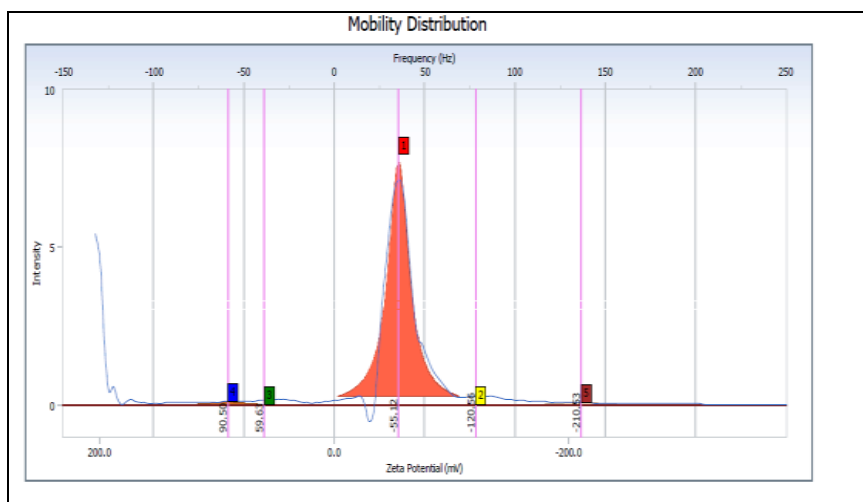


* F4 batch

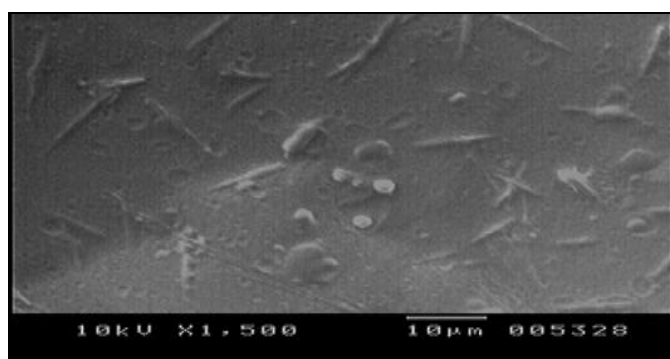
Figure 2: Vesicle Size of Liposome F4



*Liposome F4

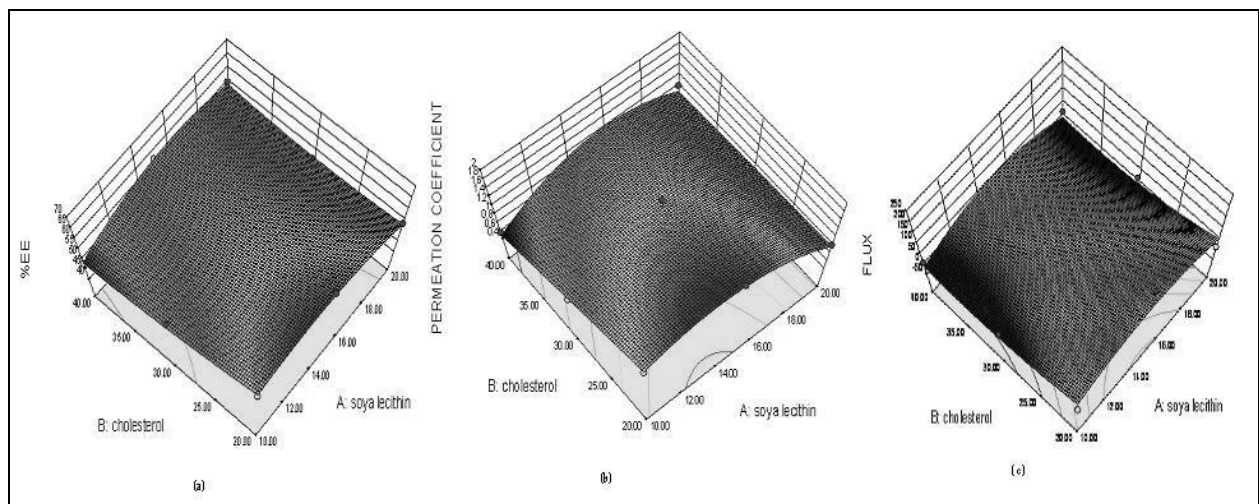
Figure 3: Microscopic Examination of Liposome F4 so on upgradation respectively

* Liposome F4

Figure 4: Zeta Potential Analysis of Liposome F4

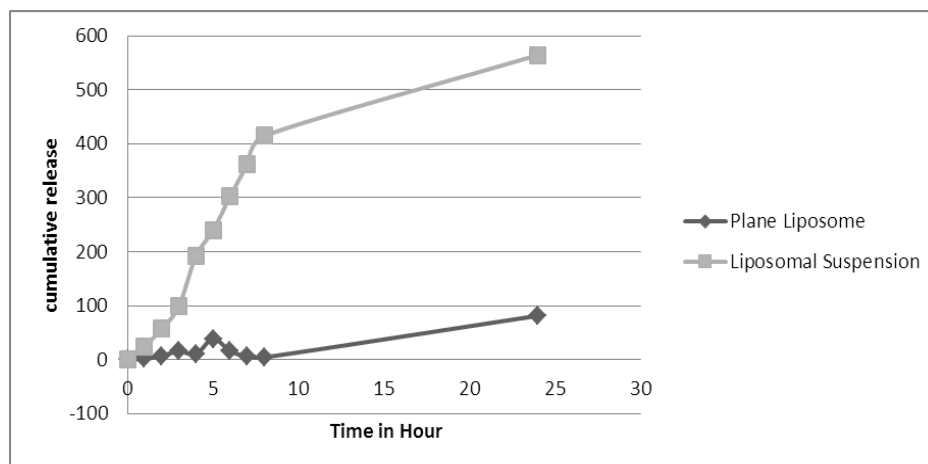
*Liposome F4

Figure 5: Surface Morphology Study of Liposome E4



* response surface plot for Liposomes F4

Figure 6: optimization Graphs for Liposomes F4



* Liposome E4

Figure 7: cumulative release for Liposome E4

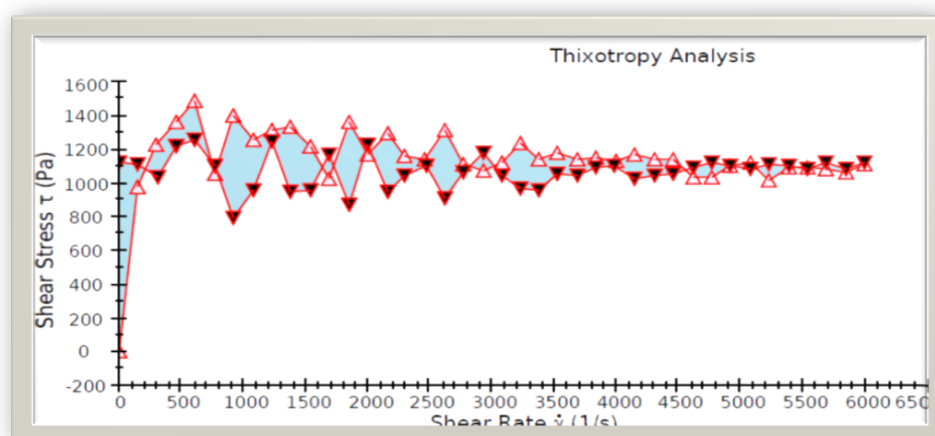


Figure 8: Thixotropic Analysis

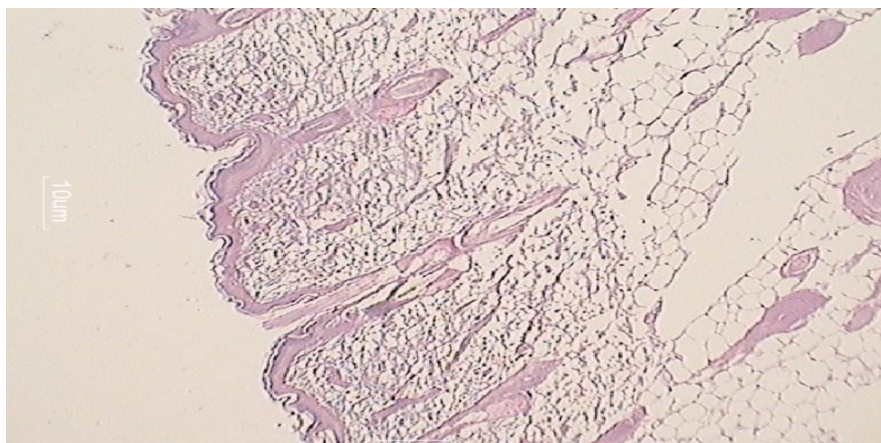


Fig 9: Histopathology of Guinea pig skin with F4 Liposome

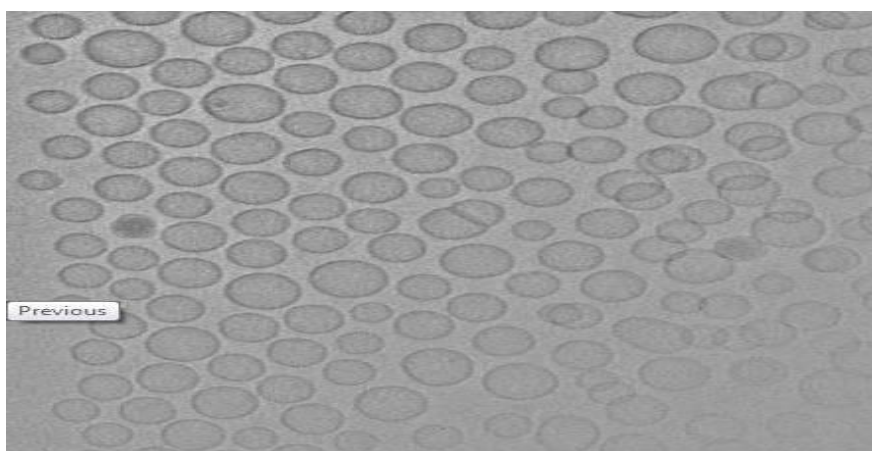


Fig10: Freeze Fracture of F4 Liposome

A		B		C		D		E		F		G	
In-vitro permeability study													
Sample name		Onda in NMP 20 mg/ml						Date		07-07-2013			
Diffusion cell no.				4									
Diffusion cell volume (ml)		Vr		14									
Surface area exposed (cm^2)		A		6.15									
donor cell drug conc		Cd		20000									
Sampling volume		Vs		1									
Sampling hr		Measured conc in receptor medium		Actual drug conc in receptor cell		Drug loss in sampling		Sum total of previous measured samples		Cumulative amt of drug permeated		Cumulative amt of drug permeated per unit area	
t		Cn		Vr.Cn		Vs.Cn		Vs .Σ Cm		Q		Q/cm^2	
1		0.2762		3.8668		0.2762		0.2762		3.8668		0.6287	
2		1.3694		19.1716		1.3694		1.6456		20.8172		3.3849	
3		3.0482		42.6748		3.0482		4.6938		47.3686		7.7022	
6		16.211		226.9540		16.2110		20.9048		247.8588		40.3022	
12		54.0327		756.4578		54.0327		74.9375		831.3953		135.1862	
24		119.7569		1676.5966		119.7569		194.6944		1871.2910		304.2750	
48		222.2222		3111.1108		222.2222		416.9166		3528.0274		573.6630	
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Fig11: Spreadsheet template for quantification and non-linear regression analysis of data generated from *in vitro* skin permeation study.

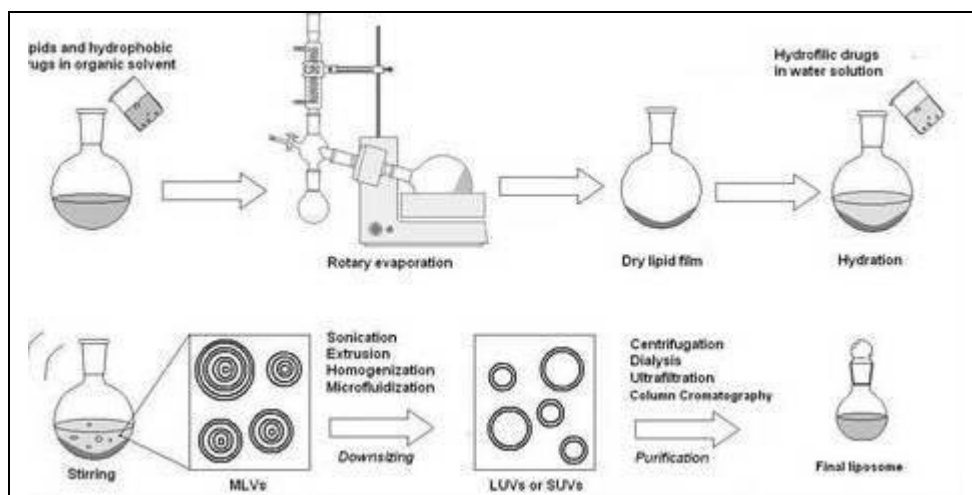


Fig12: Preparation of liposome

Fig 13: Experimental set up for *in vitro* permeation studies

TABLES

Table 1: 3²Liposomal Factorial Design

Batch code	ONDA HCl mg	Soya lecithin Mg	Cholesterol Mg	Stearic acid Mg	Entrapment%	Flux $\mu\text{g}/\text{cm}/\text{hr}$	Permeability coefficient $\text{nt} \times 10^{-3}$
F1	8	10.00	20.00	30	59.53	17.47	1.546
F2	8	20.00	30.00	30	51.12	6.36	0.564
F3	8	10.00	30.00	30	55.04	9.5	0.8
F4	8	15.00	20.00	30	63.65	20.65	1.8
F5	8	15.00	30.00	30	57.48	19.84	1.761
F6	8	20.00	20.00	30	53.51	11.26	0.999
F7	8	20.00	40.00	30	55	11.27	1
F8	8	15.00	40.00	30	57	9.2	0.816
F9	8	10.00	40.00	30	48	6.3	0.559

*liposomal factorial Design

Table 2: Liposomal gel composition

Composition	Ingredients	Quantity (w/w %)
Composition	Ingredients	Quantity (w/w %)
Plain Ondansetron HCl	ONDA HCl	8 (w/w %)
	Carbopol 940	20 (w/w %)
	Water	80 (V/V %)
Ethosomal Gel	Liposomal suspension (F4)	80 (V/V %)
	Carbopol 940	20 (w/w %)

Table 3: Liposomal gel evaluation

Formulation code (F4)	pH	Viscosity (cp)	Clarity	Content Uniformity
Liposomal gel	5.7	29.32 ± 0.26	+	97.43%

* + = Poor ++ = Good +++ = Excellent

Table 4: Comparison of Liposome Parameters

Sr.no	Parameter	Liposome
1	% EE (%)	63.65
2	Particle size (nm)	372.9
3	Flux (µg/cm ² /hr)	20.65
4	Permeability coefficient (cm/hr)	1.8
4	P.D	0.200
5	Zeta potential	-55.12

5. DISCUSSION

In the present study an attempt was made to formulate, optimise and develop liposomal transdermal system of Ondansetron HCl with the aim to have rapid onset of action which will last for prolonged period of time. Then Liposomes was prepared by thin film hydration method by keeping soya lecithin and cholesterol as independent factor .optimization was carried by 32factorial design. Two independent variables soya lecithin and cholesterol was used against entrapment efficiency, permeabilitycoefficient and flux as dependent variables. F4 batch showing max entrapment63.65, flux 20.65 (µg/cm²/hr) and permeability coefficient (1.8cm/hr) was selected for further studies.liposomal gelcontaining liposomal suspension (F4) and Carbopol 940 as gelling agent (20 % w/w) was prepared and compared with plain gel containing same drug concentration for in vitro drug release. Comparative *In-vitro* drug release study of plain drug solution and drug in liposomal suspension containing gel was carried out for 24 hours it was found that cumulative release and flux of liposomal suspension containing was more than plane liposomal gel containing suspension showed enhanced permeation as compared to plain gel (Figure 8).

6. CONCLUSION

Liposomal suspension shows increase in permeation than drug solution with same drug concentration. Finally, it can be concluded that Ondansetron HCl can be successfully formulated in gel based Lipoosomal TDDS which can be used to achieve faster onset of action as compared to Plane Liposomes and the formulation can still prolong the drug delivery for more than 24 hours. However it requires further study on human cadaver skin, in vivo study and establishment if *In-vitro* relations. Increase permeation of ondansetron HCl through liposomal based system.

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