Journal of Advances and Scholarly Researches in Allied Education
Vol. XV, Issue No. 3, May-2018, ISSN 2230-7540

Effect of Non-Ionic Surfactants on *in-Vitro* Release of Ketorolac Tromethamine

Kamal Saroha[1]* Ajay Aggarwal[2]

[1,2] Institute of Pharmaceutical Sciences, Kurukshetra University, Kurukshetra

Abstract – Niosomes or non-ionic surfactant vesicles are microscopic lamellar structures formed on admixture of non-ionic surfactant of the alkyl or dialkyl polyglycerol ether class and cholesterol with subsequent hydration in aqueous media. They are vesicular systems similar to liposomes that can be used as carriers of amphiphilic and lipophilic drugs. Entrapment efficiency was found to be higher in case of niosome prepared with span60 than niosome prepared with Tween. The amount of release was found to be in order of Span20> Tween60> Tween20> Span60. As the concentration of surfactant is increased in vitro release was increased due to high entrapment. The Stability study of optimized batch revealed that particle size was increased after 3months on increasing the temperature. On the other hand entrapment efficiency was decreased on increasing the temperature.

Keywords: Niosomes, Vesicles, Span, Tween, In Vitro release

----------X----------

INTRODUCTION

Niosomes or non-ionic surfactant vesicles are microscopic lamellar structures formed on admixture of non-ionic surfactant of the alkyl or dialkyl polyglycerol ether class and cholesterol with subsequent hydration in aqueous media. They are vesicular systems similar to liposomes that can be used as carriers of amphiphilic and lipophilic drugs. The method of preparation of niosome is based on liposome technology. The basic process of preparation is the same i.e. hydration by aqueous phase of the lipid phase which may be either a pure surfactant or a mixture of surfactant with cholesterol. After preparing niosomal dispersion, unentrapped drug is separated by dialysis centrifugation or gel filtration. A method of in-vitro release rate study includes the use of dialysis tubing. Niosomes are promising vehicle for drug delivery and being non-ionic; it is less toxic and improves the therapeutic index of drug by restricting its action to target cells. Niosomes are unilamellar or multilamellar vesicles formed from synthetic non-ionic surfactants. They are very similar to the liposomes. Niosomal drug delivery is potentially applicable to many pharmacological agents for their action against various diseases. Niosomes have shown promise in the release studies and serve as a better option for drug delivery system. This class of vesicles was introduced by Handjani – Vila *et al*. They are vesicular systems similar to liposomes that can be used as carriers of amphiphilic and lipophilic drugs. The concept of incorporating the drug into niosomes for a better targeting of the drug at appropriate tissue destination is widely accepted by researchers and academicians. Niosomes represent a promising drug delivery module. They present a structure similar to liposome and hence they can represent alternative vesicular systems with respect to liposomes, due to the niosome ability to encapsulate different type of drugs within their multienvironmental structure (Don *et al*., 1997). Niosomes are thoughts to be better candidates drug delivery as compared to liposomes due to various factors like cost, stability etc. Various type of drug deliveries can be possible using niosomes like targeting, ophthalmic, topical, parentral.

METRIALS AND METHODS

Materials

Ketorolac tromethamine was received as a gift sample from Ranbaxy laboratory ltd.Gurgaon, India. Cholesterol, Tweens , Spans and other chemicals were of analytical grade and used without further purification.

Methods

PREPARATION OF NIOSOMAL GELS

Unilamellar vesicles were prepared by the conventional thin film hydration method. Precisely weighed amount of Drug, Non-ionic surfactant and cholesterol (ratio reported in table) were dissolved in15ml chloroform. The lipid mixture was added to a 100-mL rounded bottom flask, and the solvent was evaporated slowly under reduced pressure at a temperature of 60ºC by a rotary evaporator (company) at 135rpm. The evaporation step was

continued until almost all organic solvent was evaporated and a thin lipid film was deposited on the wall of the flask. The excess, non evaporated organic solvent was removed by keeping the flask in a desiccator under vacuum overnight. The lipid film was hydrated with 10 mL of Phosphate buffered saline (pH 7.4). The hydration was continued for 1 hr., while the flask was kept rotating at 60ºC in the rotary evaporator. The niosomal suspension was further hydrated at room temperature for 2 hrs in order to complete the swelling process. The niosomal suspension was kept to mature overnight at 4˚C.

Table 1: Composition of niosomal gels

S. No.	Formulation code	Surfactant	Drug: Surfactant: Cholestrol	Quantity(mg)		
				Drug	Surfactant	Cholestrol
1	NG1	T20	1:1:1	100	100	100
2	NG2		1:2:1	200	400	200
3	NG3	T60	1:1:1	200	200	200
4	NG4		1:2:1	200	400	200
5	NG5	S20	1:1:1	200	200	200
6	NG6		1:2:1	200	400	200
7	NG7	S40	1:1:1	200	200	200
8	NG8		1:2:1	200	400	200
9	NG9	S60	1:1:1	200	200	200
10	NG10		1:2:1	200	400	200
11	NG11	S60	1:1:0.25	200	200	50
12	NG12		1:1:0.5	200	300	100
13	NG13		1:1:0.75	200	400	150
14	NG14		1:1:1	200	200	200
15	NG15	T60	1:1:0.25	200	200	50
16	NG16		1:1:0.5	200	300	100
17	NG17		1:1:0.75	200	400	150
18	NG18		1:1:1	200	200	200

Evaluation of niosomal gels:

Visual Appearance, clarity and Ph

Visual appearance and clarity were observed for the presence of any particular matter.The pH of gels was measured using digital pH meter.

Entrapment Efficiency 9:

Entrapment efficiency of niosomal formulations was determined by separating the unentrapped drug. Un-entrapped drug was separated by centrifugation method. Centrifugation of suitably diluted niosomal suspension was carried out at 12000rpm for 20min. The supernatant liquid was analyzed for un-entrapped drug by UV spectrophotometer at 318nm.

% Encapsulation Efficiency = (Total drug- Free drug / Total drug) × 100

In-vitro dissolution studies

The dissolution test was performed using standard USP apparatus II with some medications by using modified paddle using phosphate buffer of pH 7.4. The dissolution medium was phosphate buffer pH 7.4. The temperature was maintained at 37±0.50C. The rpm was 50. Samples of 10 ml was withdrawn at predetermined time intervals 0.5h, 1h, 2h, and up to 12hrs and replaced with fresh and preheated 37±0.50C buffer solution each time. Samples were measured spectrophotometrically at 318nm. The amount released was calculated from regression line of the standard curve developed in the same medium.

Ex-vivo Franz Diffusion cell studies (ex-vivo studies)

Diffusion studies was carried out across abdomen skin by using franz diffusion cell for 8 hr.The rat skin was sandwiched securely between donor and receptor compartment with epidermis site facing the donor compartment. The stirring rate was 600 rpm. Phosphate buffer pH 7.4 was used as medium and was maintained at 37 ± 0.5^0 C. After 1hr of equilibrium 2gm either KT gel on was kept on skin surface. Receptor compartment was filled with 5ml of phosphate buffer pH7.4 Samples (1ml) were collected periodically at 0.5, 1, 2, 3, 4, 5, 6, 7 and 8 hr and assayed for dissolution spectroscopically at 318 nm. Each sample was replaced with equal volume of fresh dissolution medium to maintain the sink condition, and dissolution rate test was repeated thrice and average values were reported.

Drug retention studies

Sufficient quantity of niosomal suspension (after removal of free drug) was sealed in10 ml glass vial and the niosomal gel formulation was sealed in 10 gm collapsible aluminum tube in triplicate, and stored at refrigerated temperature (2-8˚ C) and room temperature (25 + 2˚ C). Specimen (0.5 gm) from each sample was withdrawn at an interval of one week and analyzed for free drug content to determine the leakage rate. The results are recorded and presented in graphical form in figure 1.

Drug content:

Niosomal suspension equivalent to 40mg was taken in 100ml volumetric flask, and then lysed 100ml propane-1-ol by shaking. Then 1ml of it was diluted to 10 ml with phosphate buffer pH 7.4.The absorbance was measured at 318nm and drug content was calculated from the calibration curve.

RESULTS AND DISCUSSION

Results of Vesicle size of ketorolac tromethamine proniosome are presented in (Table7.5), which indicated that Vesicle formed with Span is smaller in size than vesicle formed with Tweens; this is due to greater hydrophobicity of Spans than Tweens. It is indicated that increasing in hydrophobicity decreases surface energy of surfactants resulting in smaller vesicle size. [12] Size of vesicle was reduced when dispersion was agitated. The reason for this is the energy applied in agitation which results in breakage of larger vesicles to smaller vesicles. The size range was found to be from 2.19µm to 6.97µm.

Table 2: Particle size and entrapment efficiency of niosomal formulations (NG1-NG12)

S. No.	Formulation code	Particle size ±S.D	Entrapment efficiency ±S.D
1	NG1	5.54 ±0.06	91.66 ±0.12
2	NG2	5.59 ±0.06	92.72 ±0.20
3	NG3	6.97 ±0.06	94.74±0.10
4	NG4	2.57 ±0.04	95.82 ±0.15
5	NG5	2.44 ±0.05	96.62 ±0.12
6	NG6	2.54 ±0.05	97.68 ±0.14
7	NG7	52.32 ±0.05	94.70 ±0.33
8	NG8	6.41 ±0.09	95.69 ±0.14
9	NG9	5.43 ±0.05	96.05 ±0.69
10	NG10	2.35 ±0.07	90.35 ±0.53
11	NG11	2.21±0.06	91.95 ±0.83
12	NG12	2.19 ±0.06	93.70 ±0.53

Entrapment efficiency was found to be higher in case of niosome prepared with span60 than niosome prepared with Tween this is due to fact that Span 60 is more hydrophobic than Tween, which act as solid at room temperature and showed higher phase transition temperature (Tc), low HLB value and long alkyl chain length [15] and results are shown in (Table 7.5).Entrapment efficiency was higher in Span60 as compared to Span 20; and Tween 60 as compared to tween 20 because longer chain surfactant produces high entrapment. Surfactants with long alkyl chains generally give larger vesicles. This might be the reason for the higher entrapment efficiency of vesicles prepared with longer alkyl chain surfactants.

Table 3: Cumulative drug release of Niosomal formulations* (NG1-NG12)

Time (hr)	NG1	NG2	NG3	NG4	NG5	NG6	NG7	NG8	NG9	NG10	NG11	NG12
0.5	0.92± 0.23	2.45± 0.67	1.33± 0.47	0.48± 0.04	1.22±0 .09	0.27±0 .02	3.62±0. 29	2.36± 0.56	1.32± 0.38	1.03±0.1 9	3.62±0 .58	2.46±0.0 6
1	1.67± 0.14	3.27± 0.82	2.47± 0.69	1.29± 0.08	2.17±0 .38	1.00±0 .4	4.39±0. 56	3.40± 0.29	2.87± 0.25	3.00± 0.08	7.39± 0.39	5.40±0.1 9
2	2.35± 0.15	6.75± 0.36	4.76± 0.83	2.48± 0.46	3.39±0 .58	2.09±0 .45	5.2±0.4 8	5.70± 0.67	3.99± 0.84	5.09± 0.39	10.2± 0.09	10.79± 0.28
3	4.26± 0.08	8.01± 0.56	6.31± 0.39	4.19±0. 56	4.72±0 .37	3.95±0 .29	7.29±0. 78	7.18± 0.28	4.32± 0.48	7.95± 0.49	14.29± 0.49	13.18± 0.45
4	8.25± 0.26	10.43± 0.18	8.38± 0.93	6.29±0. 39	6.58±0 .47	4.60±0 .59	9.28±0. 67	9.00± 0.58	6.58± 0.76	11.60± 0.58	17.28± 0.89	16.08± 0.78
5	10.14 ± 0.45	12.67± 0.26	10.90± 0.29	8.48±0. 89	8.69±0 .78	5.08±0 .87	11.67± 0.46	10.48± 0.78	8.69± 0.48	14.08± 0.29	21.67± 0.48	20.48± 0.56
6	17.25 ± 0.23	16.01± 0.35	12.11± 0.58	10.36± 0.39	10.60± 0.58	6.96±0 .45	14.19± 0.67	12.19± 0.48	10.60 ± 0.58	23.96± 0.48	28.19± 0.67	23.19± 0.67
7	22.12 ± 0.16	20.26± 0.45	16.01± 0.47	12.29± 0.28	12.89± 0.8	8.87±0 .76	16.75± 0.89	13.27± 0.29	13.69 ± 0.28	29.87± 0.57	32.75± 0.39	26.47± 0.38
8	28.19 ± 0.08	24.34± 0.34	21.64± 0.39	15.19± 0.89	13.81± 0.47	10.59± 0.3	17.99± 0.68	16.89± 0.48	15.81 ± 0.29	37.59± 0.27	34.99± .58	30.89± 0.47

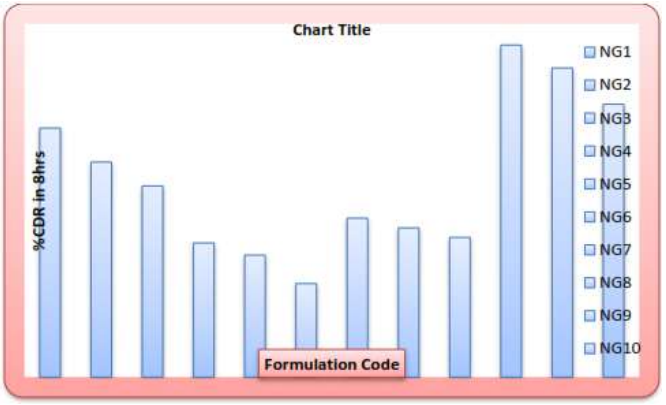

Figure 1: % Cumulative Drug Release of formulations NG_1-NG_{12}

In vitro release studies are often performed to predict how a delivery system might work in an ideal situation as well as give some indications of its in vivo performance since drug release indicates the amount of drug available for absorption. In-vitro release of Span was high as compared to tween .The amount of release was found to be in order of Span20> Tween60> Tween20> Span60.This was due low phase transition temperature of Span 20. Span 20 showed the release in range of 1:1.5:1>1:1:1>1:0.5:1 37.59%, 34.99%, 30.89% in 8hrs respectively. The release of KT from the niosomes of different surfactants was found dependent on the chain length of surfactants. As the chain length increases, the release gets sustained for longer duration Phase transition temperature of span 60, span 20 is 53˚C and16 ˚C, respectively [27]. The reduced permeation of SSD from niosomes of span 60 can be attributed to their high transition temperatures, which may have made them in a highly ordered gel state at the permeation temperature of 37 °C. On the other hand, the lower transition temperatures of span 20 may have made them in the disordered liquid crystalline state and completely fluid, hence; they were more permeable for the drug at 37 °C. Similar is the effect of phase transition temperature on the release of drug from the niosomes manufactured by using different tweens. As the concentration of surfactant is increased in vitro release was increased due to high entrapment.

CONCLUSION

The in-vitro release from optimized batch of niosomal gel was found to be 37.59% in 8hrs. From the study we concluded that Spans gave more release as compared to tweens. As concentration of surfactant increased, % release was increased. Upon storage due to less physical stability of conventional niosomes particle size increased. While entrapment efficiency was decreased on increasing the temperature. Proniosomes can be prepared to increase the stability of niosomes.

REFERENCES

1. Handjani-Vila RM., Ribier A., Rondot B and Vanlerberghe G. (1979). Dispersions of lamellar phases of non-ionic lipids in cosmetic products. International JournalCosmetic Sciences; 1: pp. 303-314.

2. Malhotra M., Jain NK (1994). Noisome as Drug Carriers. Indian Drugs. 31(3): pp. 81-86.

3. Don A., Van H., Joke AB and Hans E. (1997). Non ionic surfactant vesicles containing estradiol for topical application. Centre for drug research. pp. 330-339.

4. Parthasarathi G., Udupa N., Umadevi P. and Pillai G.K. (1994). Niosome encapsulated of vincristine sulfate: improved anticancer activity with reduced toxicity in mice. Journal Drug Target; 2(2): pp. 173-182.

5. Baillie A.J., Florence A.T., Hume L.R, Rogerson A., and Muirhead G.T. (1985). The preparation and properties of niosomes-non-ionic surfactant vesicles. J. Pharm Pharmacol; 37(12): pp. 863–868.

6. Namdeo A., Mishra P.R., Khopade A.J. and Jain N.K. (1999). Formulation and evaluation of niosome encapsulated indomethacin. Indian Drugs; 36(6): pp. 378-380.

7. Rogerson A., Cummings J., Willmott N., Florence A.T. (1988). The distribution of doxorubicin in mice following administration in niosomes. Journal Of Pharm Pharmacology; 40(5): pp. 337–342.

8. Khandare JN., Madhavi G., Tamhankar BM (1994). Niosomesnovel drug delivery system. The Eastern Pharmacist; 37: pp. 61- 64.

9. Chauhan S., Luorence MJ (1989). The preparation of polyoxyethylene containing non-ionic surfactant. Vesicles; 41: pp. 6.

10. Yoshioka T., Sternberg B., Moody M Florence AT. (1992). Niosomes from Span surfactants Relations between structure Journal Pharmceutics andPharmcology, 44: pp. 1044.

11. Jayaraman CS., Ramachandran C., Weiner N. (1996). Topical delivery of erythromycin from various formulations: an in vivo hairless mouse study. Journal of Pharmaceutical Sciences; 85(10): pp. 1082-1084.

12. Moser P., Arvier MM., Labrude P., Vignerson C. (1990). Hemoglobinniosomes. II. In Vitro interactions with plasma proteins and phagocytes. Pharm ActaHelv; 65: pp. 82-92.

13. Chauhan S.,Luorence M.J. (1989). The preparation of polyoxyethylene containing non-ionic surfactant vesicles. Journal of Pharceutics and Pharmacology; 41: pp. 6.

14. Sheena I.P., Singh U.V., Kamath R., Uma Devi P., and Udupa N. (1998). Niosomalwithaferin A, with better tumor efficiency. Indian journal. Pharmceutical Sciences; 60(1): pp. 45-48.

15. Weissman G., Bloomgarden D., Kaplan R., Cohen C., Hoffstein S., Collins T., Gotlieb A., Nagle D. (1975). A general method for the introduction of enzymes, by means of immunoglobulin-coated liposomes, into lysosomes of deficient cells.ProcedingThe National academy Of Sciences; 72(1): pp. 88-92.

16. Cummings J., Staurt J.F. and Calman K.C. (1984). Determination of adriamycin, adriamycinol and their 7-deoxyaglycones in human serum by high-performance liquid chromatography. Journal of Chromatography; 311: pp. 125-133.

Corresponding Author

Kamal Saroha*

Institute of Pharmaceutical Sciences, Kurukshetra University, Kurukshetra