

Design and Development of Niosomal Delivery System for Ketoprofen

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Abstract:

Niosomes are efficient carriers for controlled drug delivery, to entrap hydrophilic drugs in the larger interior aqueous layer, whereas, lipophilic drugs in the outer lipid bilayers. Since, the niosomes are biodegradable and non toxic and hence, a good carrier for targeting of therapeutic agents at the site of interest with reduced systemic toxicity. The film formation method was used for the preparation of the niosomes due to simplicity, reproducibility and high drug entrapment efficiency. The various ratios of Surfactant (Span 60) Cholesterol and Dicetyl phosphate (DCP) were used for the preparation of the niosomes. The molar ratio of 47.5:47.5:5 was found to be most suitable in terms of niosomal size drug entrapment efficiency and *in vitro* drug release. The average size of niosomes was observed as 4.5 μ m with drug entrapment efficiency of 62.4%. The *in vitro* drug release study was carried out using dialysis membrane in Phosphate buffer saline (PBS, pH 7.4) for 24 hrs. The result showed a cumulative drug release of 98% in 8 hrs. from the free drug, against 92% drug release in 24 hrs. With optimized niosomal formulation. The optimized niosomal formulation showed a sustained action of about 16 hrs was subjected to *in vivo* studies (anti-inflammatory activity). This formulation was found to be more effective in reducing edema after 2 hrs as compared to the free drug.

Key-word: - Niosomes, biodegradable, film formation method, drug entrapment efficiency, dialysis membrane.

1) Introduction:-

Target oriented drug delivery systems are the areas of the major interest in the modern pharmaceutical research. The selective drug delivery to the target tissues increases the therapeutic efficacy of the drug and reduces its undesirable effect to non target tissues. The concept of drug targeting or site specific drug delivery was introduced first time by Paul Ehrlich in 1909, when he reported 'magic bullet' to deliver a drug to the desired site of action without affecting the non target organs or tissues (Juliano, 1980) by associating the drug with a pharmacologically "inactive carrier" capable of conveying the drug selectively towards its target cells. Niosomes are efficient carriers for controlled drug delivery, to entrap hydrophilic drugs in the larger interior aqueous layer, whereas, lipophilic drugs in the outer lipid bilayers. Since, the niosomes are biodegradable and non toxic and hence, a good carrier for targeting of therapeutic agents at the site of interest with reduced systemic toxicity. Ketoprofen, non-steroidal anti-inflammatory drug, is used for the treatment of rheumatoid arthritis, osteoarthritis, degenerative joint conditions and musculoskeletal disorders, involving long term therapy. Ketoprofen has various side effects like gastritis, peptic ulcer and bleeding, along with short biological half life (0.5-2 hrs) which calls for frequent administration. Thus, a novel and controlled drug delivery system need to be developed in order to increase its therapeutic effects with reduced side effects. The result obtained in our findings reveals that vesicular niosomes may be very useful as a sustained release delivery system of ketoprofen as compared to the free drug.

2) Materials & Method:-

It is given in table 1 & 2.

2.1) Method:-

2.1.1) Preparation of different batches of Niosomes:-

A different batch of Niosomes was prepared using experimental conditions include:

| | | |
|---------------------------|---|---------------|
| Surfactant Concentration | : | 100 μ mol |
| Rotation Time | : | 2 h |
| Hydration Time | : | 1 h |
| Temperature of water bath | : | 50° C |

The entire process of preparation of niosomes has been shown in the flow diagram in fig. 1.

2.1.2) Optimization of formulation:-

Formulation shall be optimized on the basis of -

2.1.2.1) rotation speed of rotary evaporator.

2.1.2.2) surfactant concentration.

2.1.2.3) composition of bilayers etc.

2.1.2.1) Rotation speed of rotary evaporator.

In order to investigate the effect of rotational speed on niosomal formulations, the niosomes were prepared at three different rotations i. e. 60, 80 and 100 r.p.m., at the 100 r.p.m. the maximum number of niosomes possessed an average size of 4.5 μ m.

The uniformity was more at 100 r.p.m. hence; the effect of rotational speed of vacuum evaporator on size distribution of niosomes was investigated at 100 rpm.

Explain in table no. 3 & fig 2.

2.1.2.2) Surfactant concentration.

The niosome were prepared with concentration of surfactant and found that mixture of surfactant, cholesterol and dicetyl phosphate (in a molar ratio of 47.5: 47.5: 5) were best due-to the average size 4.5 μ m of niosome were formed.Explain in table no. 4 & fig 3.

2.1.2.3) composition of bilayers –

Among the various formulations, the most appropriate ratio of cholesterol: surfactant: DCP was identified as 47.5: 47.5: 5 as it produced stable niosome with maximum entrapment efficiency.Explain in table no. 5.

3) Evaluation of formulation:-

3.1) Microscopic study of niosomal Size -

niosomes were subjected to particle size analysis using optical microscope by standardizing the eye piece micrometer scale with stage micrometer scale.

3.2) *Morphology –*

The niosomal suspensions were evaluated for morphological characteristics using transmission electron microscopy (TEM). Explain in fig no 4, 5 & 6.

3.3) *Determination of drug entrapment efficiency –*

The percent entrapment was calculated using the following formula (Huang, C.H., 1969). Explain in fig no.13.

$$\% \text{ Entrapment} = \frac{\text{Entrapped drug (mg)}}{\text{Total drug added (mg)}} \times 100$$

3.4) *In Vivo & In vitro Study of formulation*

3.4.1) *The in vivo anti-inflammatory studies is carried out by*

carrageenan induced rat hind paw oedema method. Explain in table no 6.

3.4.2) *In-vitro Study is carry out by using dialysis membrane. Explain in table no 7 & fig no.7.*

4) Stability study of Formulation as per ICH Guideline.

Explain in detail in the given data of table & fig. which is given below.

5) Results and Discussion

Among the reported methods for the preparation of niosomes, lipid film hydration technique was used due to its simplicity and reproducibility as compared to others. The formulation variables were optimized with regard to rotations per minute, surfactant concentration, composition and Span 60: Cholesterol: DCP ratio. They were characterized with respect to drug entrapment efficiency, particle size analysis, morphological characteristics and *in vitro* drug release study. The drug entrapment efficiency of various formulations was compared. Based on the data, it was found that niosomes prepared with Span 60: Cholesterol: DCP (47.5: 47.5: 5) gave maximum drug entrapment. Hence, the niosomes were prepared using the above said composition. The photomicrography of the niosomes revealed spherical shape and multilamellar structure of niosomes. The particle size analysis of niosomes using optical microscopy revealed niosomes with a mean diameter of 4.5 μm . The *In vitro* drug release studies of different batches of niosomal encapsulated formulations using pure Surfactant, Surfactant and Cholesterol, and Surfactant, Cholesterol: DCP (47.5 : 47.5 : 5) were carried out using dialysis membrane. These studies were carried out in a self designed diffusion cell over a period of 24 hrs in phosphate buffer saline (PBS). The rate of release of ketoprofen across dialysis membrane from loaded vesicles was slower than that of free ketoprofen solution as a control. The results showed that approximately 98% of drug was released within 8 h from control solution, whereas the release of ketoprofen from the Span 60, Span 60: Cholesterol and Span 60: Cholesterol: DCP was 97, 95 and 92.53 per cent respectively in 24 h. Of these Span 60: Chol: DCP yields slowest rate of release. The release occurred in two phases, an initial burst release lasting for 2 to 7 h followed by sustained but reduced release for 24 h. The biphasic release pattern might be due to size heterogeneity of the vesicles. The comparative release data indicate that, by niosome encapsulation, it is possible to sustain and control the release of drug for a longer duration.

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Table 1:- List of Drug/chemicals:-

| Sr. No. | Materials/Chemicals | Manufacturer |
|---------|--------------------------------|--|
| 1. | Ketoprofen | Hindustan Biosciences Ltd., Hyderabad |
| 2. | Cholesterol | Loba Chemie Pvt. Ltd., Mumbai |
| 3. | Dicetyl phosphate | Sigma Aldrich, USA |
| 4. | Span 60 (Sorbitan monosterate | S.d. Fine Chem Ltd., Mumbai |
| 5. | Disodium hydrogen phosphate | Qualigen Fine Chemicals, Mumbai |
| 6. | Potassium dihydrogen phosphate | Qualigen Fine Chemicals, Mumbai |
| 7. | Sodium chloride (AR Grade) | Qualigen Fine Chemicals, Mumbai |
| 8. | Diethyl ether | Central Drug House (P) Ltd., New Delhi |
| 9. | Methanol (AR Grade) | Qualigen Fine Chemicals, Mumbai |
| 10. | Chloroform | Spectrochem Pvt. Ltd., Mumbai |
| 11. | Triton X 100 L.R. | S.d. Fine Chem. Ltd., Mumbai |
| 12. | Sephadex G-50 | Sigma Aldrich, USA |
| 13. | Acetone | Qualigen Fine Chemicals, Mumbai |

| | | |
|-----|-----------------|------------------------------|
| 14. | Sodium acetate | S.d. Fine Chem. Ltd., Mumbai |
| 15. | Dialysis tubing | Sigma Aldrich, USA |

Table 2:- List of Equipments:-

| Sr. No. | Equipment | Manufacturer |
|---------|----------------------------------|--|
| 1. | UV-Visible Spectrophotometer | Perkin Elmer EZ 301 Double beam |
| 2. | Digital pH meter | Systronics |
| 3. | Electronic Balance | A & D Japan |
| 4. | Rotary vacuum evaporator | Steroglass, Italy |
| 5. | Microscope | Olympus (India) Pvt. Ltd., Delhi |
| 6. | Vacuum Pump | Ital Scientific, Genova |
| 7. | Magnetic Stirrer with hot plate | Remi Sales & Engg. Ltd., Mumbai |
| 8. | Research Centrifuge | Remi Sales & Engg. Ltd., Mumbai |
| 9. | Digital Vernier Caliper | Mitutoyo digimatic, Japan |
| 10. | Transmission electron microscope | Fei-Philips Morgagni 268 D |
| 11. | Water Bath | Narang Scientific Works Pvt. Ltd., Delhi |
| 12. | Diffusion Cell | Fabricated |

The entire process of preparation of niosomes has been shown in the flow diagram.

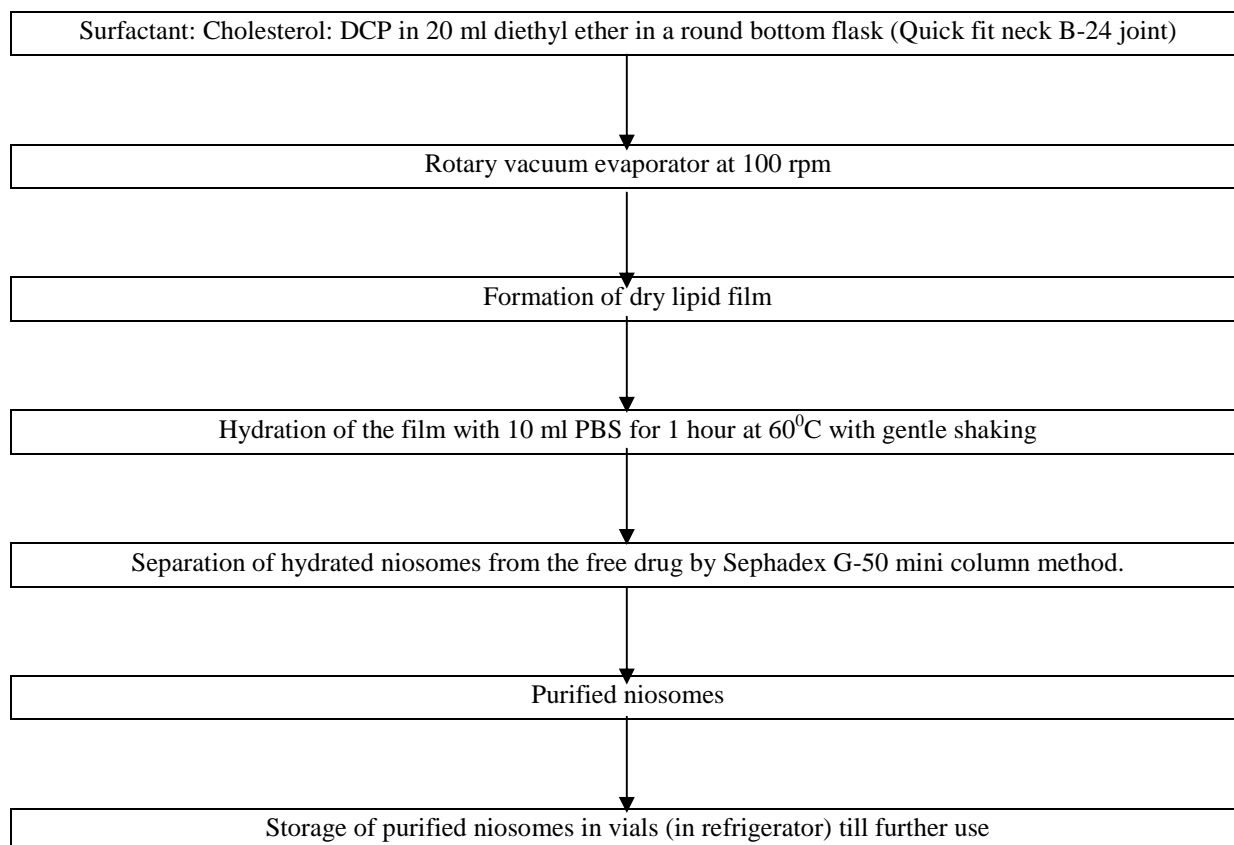


Fig 1: Flow diagram showing preparation of niosomes of ketoprofen

Table 3: The effect of rotational speed of rotary vacuum evaporator on the size distribution of niosomes

| Rotational Speed (rpm) | Size Range (μm) | Mean size (μm) | Average number of Niosomes (n = 3) |
|------------------------|------------------------------|-----------------------------|------------------------------------|
| 100 | 0-3 | 1.5 | 13.66 ± 1.24 |
| | 3-6 | 4.5 | 40.00 ± 3.29 |
| | 6-9 | 7.5 | 23.66 ± 2.05 |
| | 9-12 | 10.5 | 16.33 ± 0.82 |
| | 12-15 | 13.5 | 5.66 ± 0.12 |
| | 15-18 | 16.5 | 1.33 ± 0.00 |

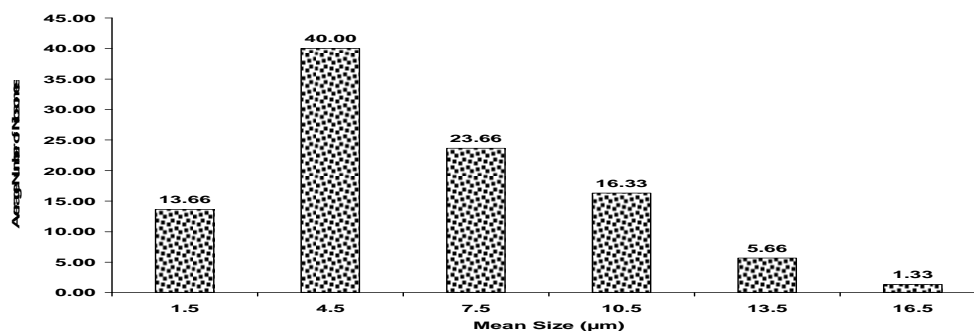


Fig. 2: Size distribution of niosomes prepared at 100 r.p.m.

Table 4: the effect of variable ratio of surfactant, cholesterol on size distribution of Niosomes.

| Ratio of Surfactant : Cholesterol : DCP | Size Range (µm) | Mean size (µm) | Average number of Niosomes (Mean ± SD) (n = 3) |
|---|-----------------|----------------|--|
| 47.5 : 47.5 : 5 | 0-3 | 1.5 | 36.33 ± 2.94 |
| | 3-6 | 4.5 | 51.33 ± 4.32 |
| | 6-9 | 7.5 | 8.66 ± 1.70 |
| | 9-12 | 10.5 | 3.00 ± 0.0 |
| | 12-15 | 13.5 | 1.66 ± 0.33 |
| | 15-18 | 16.5 | 1.0 ± 0.0 |

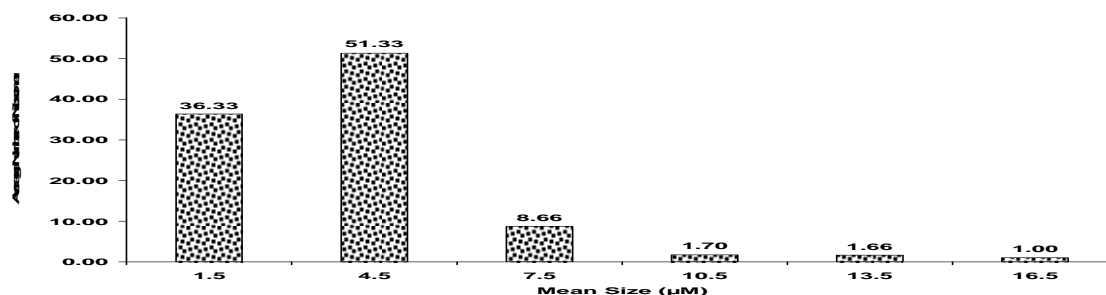


Fig. 3: Size distribution of niosomes prepared with a mixture of surfactant, cholesterol and DCP (47.5 : 47.5 : 5)

Table 5: Effect of varying composition of surfactant, cholesterol and DCP on Entrapment Efficiency

| Composition of Bilayer | | Percent Entrapment |
|------------------------|--|--------------------|
| B1 | Pure surfactant (100 µ mol) | 52.19 ± 0.79 |
| B2 | Surfactant : Cholesterol : : 50 : 50 | 61.84 ± 1.26 |
| B3 | Surfactant : Cholesterol : DCP (47.5 : 47.5 : 5) | 62.45 ± 0.34 |

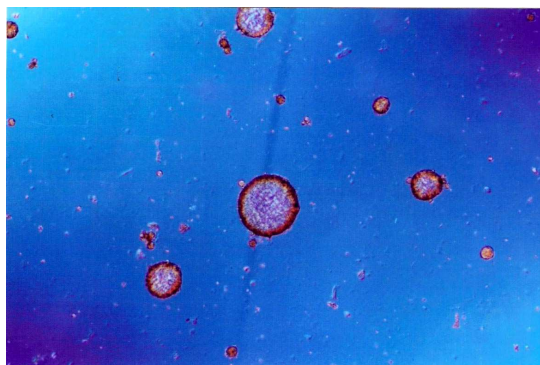


Fig. 4:- Niosomes prepared using surfactant (100 μ mol)

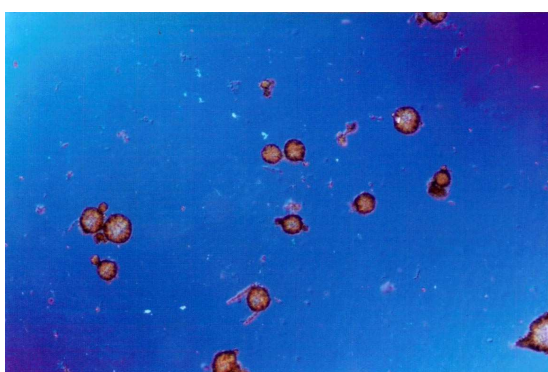


Fig 5:- Niosomes prepared using surfactant : cholesterol : : 50 : 50

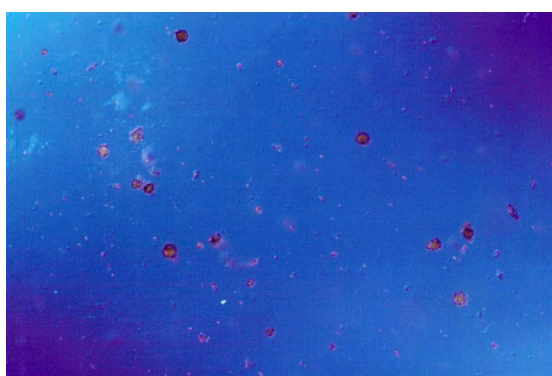


Fig 6:- Niosomes prepared using surfactant: cholesterol: DCP (47.5: 47.5: 5)

Table 6: Effect of Free and Niosomes Encapsulated Ketoprofen on Development of Oedema after Intra-planter Injection of Carrageenan

| Treatment | % Inhibition of Paw Oedema * (Mean ± SD), n = 6 | | | | |
|------------------------------|--|--------------------------|---------------------------|--------------------------|--------------------------|
| | 1h | 2h | 3h | 4h | 5h |
| Free Ketoprofen 0.3 mg/kg | 50.22 ±2.59 | 38.46 ±3.58 | 30.12 ± 2.74 | 22.25 ±3.24 | 10.38 ±1.86 |
| Free Ketoprofen 3mg/kg | 72.48 ±1.42 ^a | 66.32 ±2.56 ^a | 48.12 ± 0.34 ^a | 38.34 ±1.26 ^a | 20.24 ±1.26 ^a |

| | | | | | |
|------------------------------|-------------|--------------------------|---------------------------|--------------------------|--------------------------|
| Niosomal Ketoprofen 0.3mg/kg | 50.34 ±2.16 | 48.21 ±1.24 ^a | 45.21 ± 2.34 ^a | 42.34 ±0.24 ^a | 36.42 ±0.88 ^a |
|------------------------------|-------------|--------------------------|---------------------------|--------------------------|--------------------------|

^aSignificant difference as compared to free Ketoprofen (0.3 mg/kg) treatment,

Table 7: *In vitro* release data of ketoprofen from niosomal and non niosomal formulation

| Time (hr) | Control | Span 60 | S:C | S:C:D |
|-----------|---------|---------|-------|-------|
| 0 | 0 | 0 | 0 | 0 |
| 1 | 12.32 | 5.36 | 3.64 | 2.25 |
| 2 | 25.32 | 15.38 | 8.97 | 6.74 |
| 3 | 49.53 | 19.85 | 14.25 | 10.56 |
| 4 | 55.36 | 25.38 | 22.86 | 15.79 |
| 5 | 69.23 | 34.66 | 35.96 | 22.35 |
| 6 | 82.39 | 46.33 | 45.26 | 35.84 |
| 7 | 89.45 | 58.27 | 58.27 | 48.28 |
| 8 | 98.36 | 71.85 | 65.98 | 56.98 |
| 12 | | 85.96 | 79.64 | 72.24 |
| 16 | | 93.87 | 88.35 | 82.3 |
| 24 | | 97.64 | 95.46 | 92.53 |

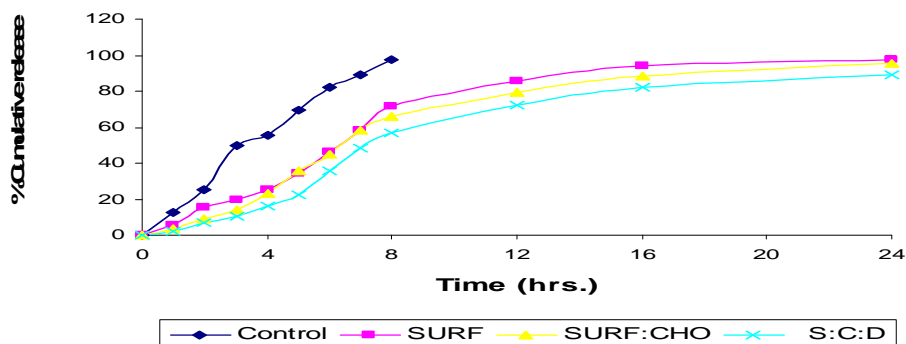


Fig. 7: Cumulative release profile of ketoprofen from niosomal formulation

Table 8: Effect of temperature on drug retention of niosomes using Surfactant : Cholesterol : DCP (47.5 : 47.5 : 5)

| Time | Drug Entrapment (%) | | |
|----------------------|---------------------|--------------|--------------|
| | 4-7 °C | 30 ± 2 °C | 40-45 °C |
| 1 st week | 60.48 ± 0.96 | 58.92 ± 0.34 | 54.32 ± 0.74 |
| 2 nd week | 56.34 ± 1.24 | 55.44 ± 0.53 | 49.24 ± 0.86 |
| 3 rd week | 54.86 ± 0.22 | 53.27 ± 1.24 | 47.38 ± 0.98 |
| 4 th week | 52.24 ± 0.86 | 50.12 ± 1.36 | 42.21 ± 0.12 |

Table 9: Aggregation and disruption behaviour of ketoprofen niosomes at various temperatures.

| Time | 4-7 °C | | Room Temperature 30 ± 2 °C | | 40-45 °C | |
|----------------------|-------------|------------|-------------------------------|------------|-------------|------------|
| | Aggregation | Disruption | Aggregation | Disruption | Aggregation | Disruption |
| 1 st week | + | - | + | - | + | - |
| 2 nd week | ++ | - | + | 1 | + | 1 |
| 3 rd week | +++ | - | + | 2 | - | 2 |
| 4 th week | +++ | 1 | ++ | 2 | - | 2 |

Degree of aggregation: Degree of disruption (out of 100 vesicles):

- | | |
|-------------|-----------|
| + 5-10%; | 1— 0-5; |
| ++ 10-20%; | 2— 5-10; |
| +++ 20-30%; | 3— 10-15; |
| ++++ 30-40% | 4— 15-20 |

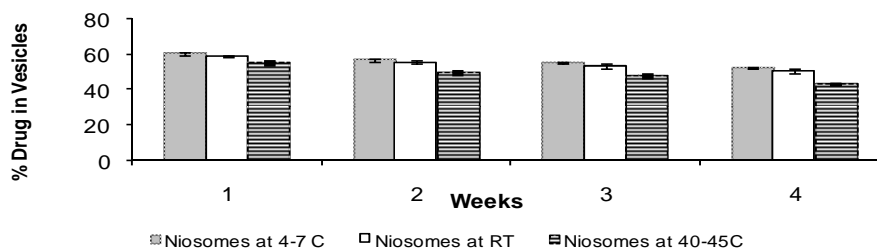


Figure 8: Effect of temperature on drug leakage from niosomal vesicles

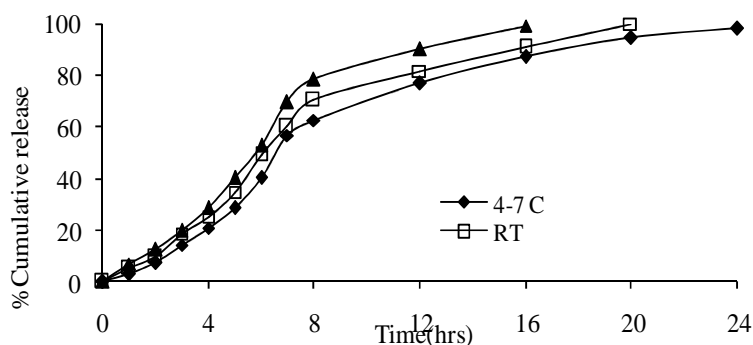


Figure 9: Cumulative release profile of ketoprofen from niosomal formulation after 1st week

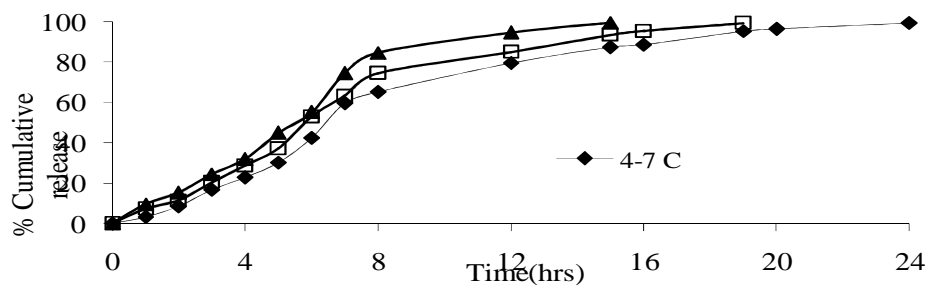


Figure 10: Cumulative release profile of ketoprofen from niosomal formulation after 2nd week

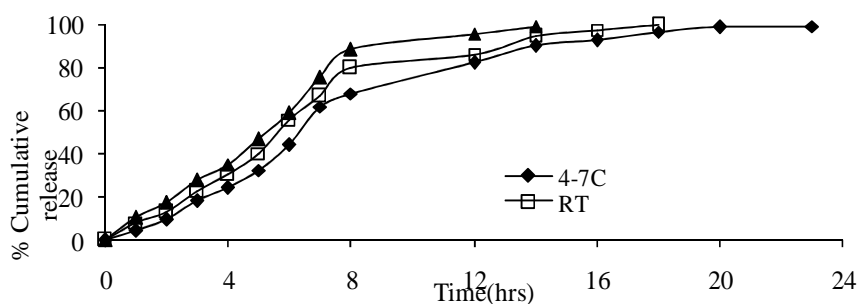


Figure 11: Cumulative release profile of ketoprofen from niosomal formulation after 3rd week

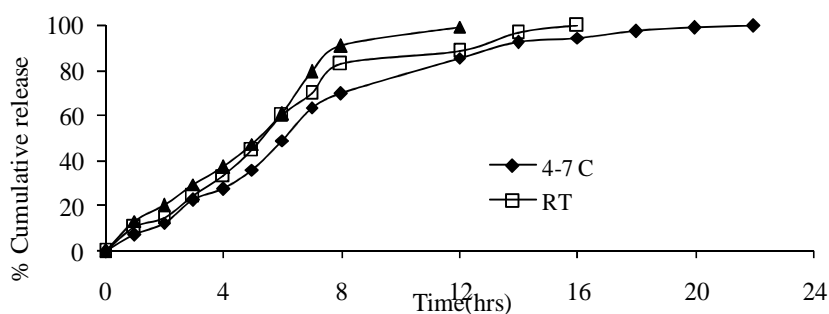


Figure 12: Cumulative release profile of ketoprofen from niosomal formulation after 4th week

| Composition of Bilayer | Percent Entrapment |
|--|--------------------|
| Surfactant : Cholesterol : DCP (47.5 : 47.5 : 5) | 62.45 ± 0.34 |

Fig 13. Composition of bilayers.

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