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Development and Characterization of Non-Ionic Surfactant Vesicles (Niosomes) for Oral delivery of Lornoxicam

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Abstract

Niosomes are non-ionic surfactant vesicles obtained on hydration of synthetic nonionic surfactants, with or without incorporation of cholesterol or other lipids. They are vesicular systems similar to liposomes that can be used as carriers of amphiphilic and lipophilic drugs. 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. They are lamellar structures that are microscopic in size. They are now widely used as alternative to liposomes. Niosomal dispersion in an aqueous phase can be emulsified in a non-aqueous phase to regulate the delivery rate of drug and administer normal vesicle in external non-aqueous phase. Stable niosome dispersion must exhibit a constant particle size and a constant level of entrapped drug. Span 60 is the better surfactant of all because it is having high phase transition temperature and low HLB (Hydrophilic Lipophilic Balance) so it will form vesicles of good size.one more reason for the selection of span 60 and that was the critical packing factor which is between 0.5 and 1 for this surfactant so it forms spherical vesicles. If CPP factor is below 0.5 it cause micelles to form and if it was above 1 it will form inverted vesicles. Lornoxicam loaded niosomes were prepared by Lipid film hydration method with different surfactant to cholesterol ratio. The niosome formulations were evaluated for FT-IR study,microscopy. The niosomal suspensions were further evaluated for entrapment efficiency, *In vitro* release study, Kinetic data analysis, Stability study. The formulation F4 which showed higher entrapment efficiency of 80.54 ±0.99. Release was best explained by the zero order kinetics. Kinetic analysis shows that the drug release follows super case II transport diffusion. Niosome formulation has showed appropriate stability for 90 days.

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Key words:
Niosomes, span 60, cholesterol and liposomes, lornoxicam.

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INTRODUCTION

Lornoxicam is a non steroidal anti inflammatory drug mainly used as analgesic[1]. The niosomal formulation of lornoxicam helps to sustain the analgesic effect. Sustained release dosage form delivers the drug at a slow release rate over an extended period of time to achieve the objective. The

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short biological half life (about 3-5 hours) and dosing frequency not more than once a day makes lornoxicam an ideal candidate for sustained release [2]. Nowadays considerable interest has been focused on niosomes based targeted drug delivery. Niosomes are non-ionic surfactant vesicles obtained on hydration of synthetic nonionic surfactants, with or without incorporation of cholesterol or other lipids. They are vesicular systems similar to liposomes that can be used as carriers of amphiphilic and lipophilic drugs. 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. This systemic review article deals with preparation methods, characterizations, factors affecting release kinetic, advantages, and applications of niosomes.[3] Niosomal drug delivery has been studied using various methods of administration including intramuscular intravenous, peroral and transdermal. In addition, as drug delivery vesicles, niosomes have been shown to enhance absorption of some drugs across cell membranes, to localize in targeted organs and tissues and to elude the reticulo endothelial system [4].

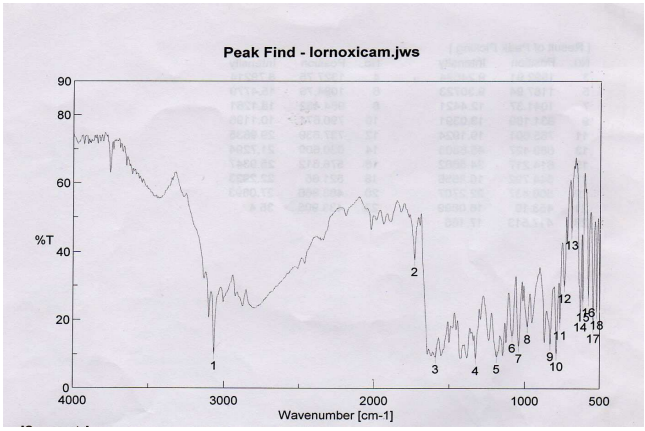
MATERIALS AND METHODS

Lornoxicam obtained as a gift sample from Aeon biologicals Chennai(India). Cholesterol obtained from Merck Specialties Pvt. Ltd., Mumbai (India).Span 60 obtained from national chemicals, Gujrat (India). Chloroform from Suvinadh chemicals, Baroda. Rotary flash evaporator for the preparation of niosomes procured from Popular India, Dialysis membrane for the study of *in-vitro* release obtained from Hi media India. All other materials used and received were of analytical grade.

RESULT AND DISCUSSION

Preformulation study

FT-IR spectra of lornoxicam were recorded.Main peaks was there at 3068.19 for C=C stretching, 1733 for C ≡ C, 1592.9 for the primary and secondary amines and amides(-NH group), 1327.5,1187.9, 1084,1041 for the amines(-C-N group), 831,790 for the aromatic group, 765, 737,689.47,630 for the C-X group, 1041.37 for S=O stretching.So the drug was found to be pure compared to pure drug which is shown in the table below.



FTIR spectra of lornoxicam

Table 24: Peak no. and position of lornoxicam compared with pure drug

Peak no:	Position	Pure lornoxicam	Groups present	Range of groups
1	3068.19	3067.06	C=C stretching	3100-300
3	1592.91	1580.39	-NH	1640-1550
4,5,6,7	1327.5,1187,1084,	1323.36,1185.64,1092.93	-C-N	1350-1000
9,10	831	828.83	Aromatic	900-690
11,12,13	765,737,689.47	764.87,726.7,688.7	-C-X	785-540
7	1041.37	1055.33	S=O	1030-1060

Solubility study

10 mg of lornoxicam is freely soluble in 0.1N NaOH after heating.

Preparation of niosomes of lornoxicam

The niosome formulations were prepared by lipid film hydration technique. Drug (lornoxicam) is freely soluble in 0.1N NaOH after heating. non ionic surfactant and cholesterol were weighed (surfactant:cholesterol in µmol) and dissolved in chloroform methanol (2:1) in a 100 ml round bottom

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flask. A thin lipid film was formed under reduced pressure in a rotary flash evaporator, temperature was maintained at 60°c or above. The film was then hydrated by 10 ml of PBS* pH 7.4 at a temperature above the glass transition temperature of the surfactant with gentle shaking. The niosome suspension obtained was sonicated for 5 min which forms small sized vesicles. The stabilized MLVs were used for further studies.

Table 1: Compositions of Niosomal batches of Lornoxicam

Formulation No.	Ratio (µmol)(surfactant: cholesteol)	Surfactant (mg)	Cholesterol (mg)
F_1	200:200	86	77.32
F_2	220:180	94.74	69.6
F_3	240:160	103.34	61.87
F_4	260:140	111.96	54.14
F_5	280:120	120.57	46.4
F_6	300:100	129.18	38.67
F_7	320:80	137.79	30.93

Drug content used-15mg per batch

Evaluation of niosomes

Microscopy

The prepared vesicles were studied under 400 x magnifications to observe the formation of vesicles. Some unevenness of vesicles that observed under the study may be due to drying process under normal environment condition. The photomicrograph of niosomes is shown in the figure below.

Figure 1: Photomicrograph of lornoxicam niosome in a dry glass slide

Entrapment efficiency of various formulations

Entrapment efficiency was studied for all the 7 formulations to find the best in terms of entrapment efficiency. Higher entrapment efficiency of the vesicles of span 60 is predictable because of its higher alkyl chain length. The entrapment efficiency was found to be higher with the F4 (80%), which may have an optimum cholesterol surfactant ratio to provide a high entrapment of lornoxicam. The niosomal formulations having high surfactant concentration (F5, F6and F) have the higher entrapment efficiency which might be due to the high fluidity of the vesicles but it depends upon the cholesterol amount. Very low cholesterol content (F7) was also found to cause low entrapment efficiency (65%), which might be because of leakage of the vesicles. It was also observed that very high cholesterol content (F1) had a lowering effect on drug entrapment to the vesicles (68%). This could be due to the fact that cholesterol beyond a certain level starts disrupting the regular bi-layered structure leading to loss of drug entrapment. The higher entrapment may be explained by high cholesterol content (~50% of the total lipid). There are reports that entrapment efficiency was increased, with increasing cholesterol content and by the usage of span-60 which has higher phase transition temperature. The larger vesicle size may also contribute to the higher entrapment efficiency. Entrapment efficiency showed by various formulations are specified in Table no:2

Table 2: Entrapment efficiency of various formulations

S. No.	Formulation No	Molar ratio (span60 : Cholesterol)	Entrapment efficiency* %
1	F1	200:200	68.34±1.42
2	F2	220:180	72.88±0.44
3	F3	240:160	76.47±0.93
4	F4	260:140	80.52±0.99
5	F5	280:120	75.54±0.58
6	F6	300:100	70.65±0.88
7	F7	320:80	65.26±1.27

***In-vitro* release profile**

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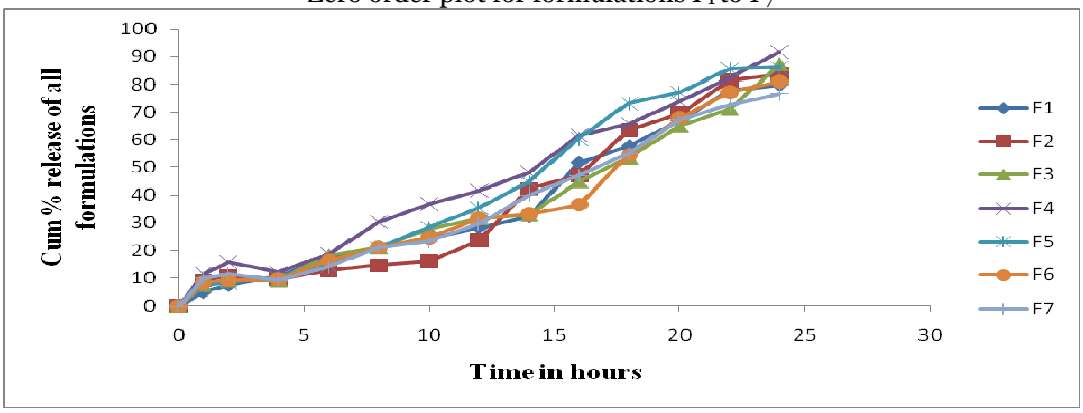
The release study was conducted for all the 7 formulations. Most of the formulations were found to have a linear release and the formulations were found to provide approximately 90% release within a period of 24 hours. Cholesterol, which has a property to abolish the gel to liquid transition of niosomes, this found to prevent the leakage of drug from the niosomal formulation. The slower release of drug from multilamellar vesicles may be attributed to the fact that multilamellar vesicles consist of several concentric sphere of bilayer separated by aqueous compartment. The above specified three best formulations F4, F5, and F6, were found to give a cumulative release of 91.68%, 86.11% and 81.02% respectively over a period of 24 hrs, the higher release from the formulation F4 may be because of its optimum cholesterol content. Formulations F1, F2 having the highest cholesterol content showed the lowest release over 24 hours, they provide a release of 79.97%, 83.62% respectively.

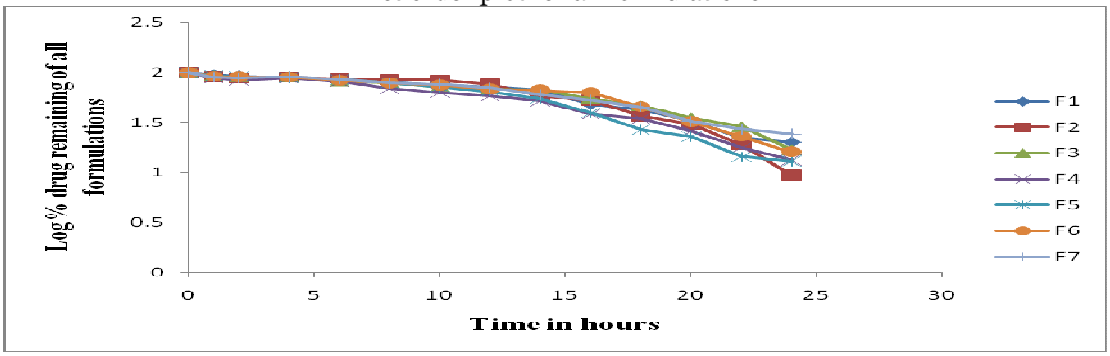
Table 3: *In-vitro* release profile of all formulations

TIME	2hr In Hcl	4hr In ph7.4	6hr	8hr	10hr	12hr	14hr	16hr	18hr	20hr	22hr	24hr
Formulation	CUMULATIVE DRUG RELEASE											
F_1	7.5	10.54	17.6	21.23	24.4	28.3	32.5	51.86	57.8	66.98	77.95	79.97
FF_2	10.83	9.69	12.8	14.58	16.0	23.7	42.1	47.07	63.4	69.54	81.25	83.62
FF_3	9.16	9.15	18.3	21.08	27.7	31.7	33.1	44.94	53.4	65.06	71.24	87.17
F_4	15.83	12.03	18.6	30.4	36.9	41.6	48.1	61.55	65.6	73.9	82.32	91.6
F_5	8.33	10.54	14.5	21.08	28.4	35.4	44.8	60.38	73.2	77.20	85.2	86.1
F_6	9.16	9.69	16.2	21.19	24.7	31.6	33.2	36.63	54.5	67.83	77.10	81.02
FF_7	11.66	9.26	14.0	21.08	23.3	29.8	40.0	47.07	55.0	67.51	72.73	76.71

Zero order plot for formulations F_1 to F_7



First order plot for all formulations



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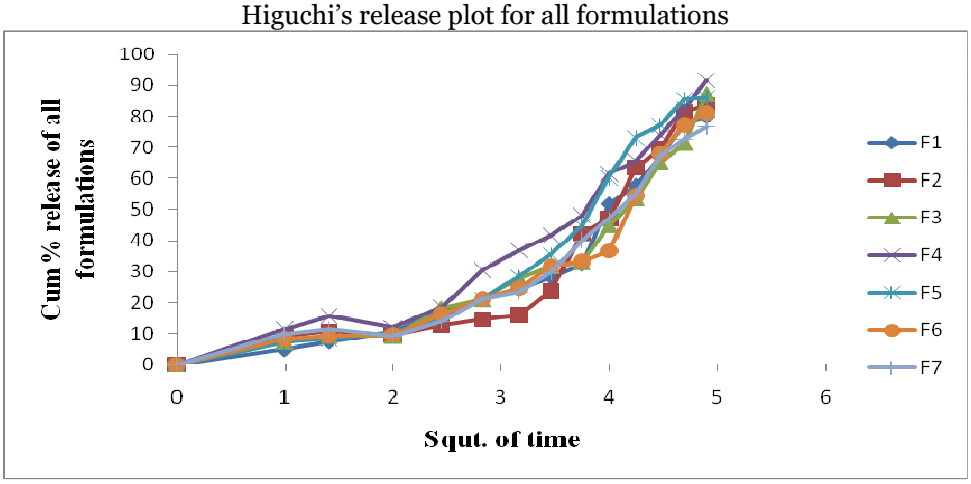
Higuchi's release plot for all formulations



Peppa's release polt for all formulations

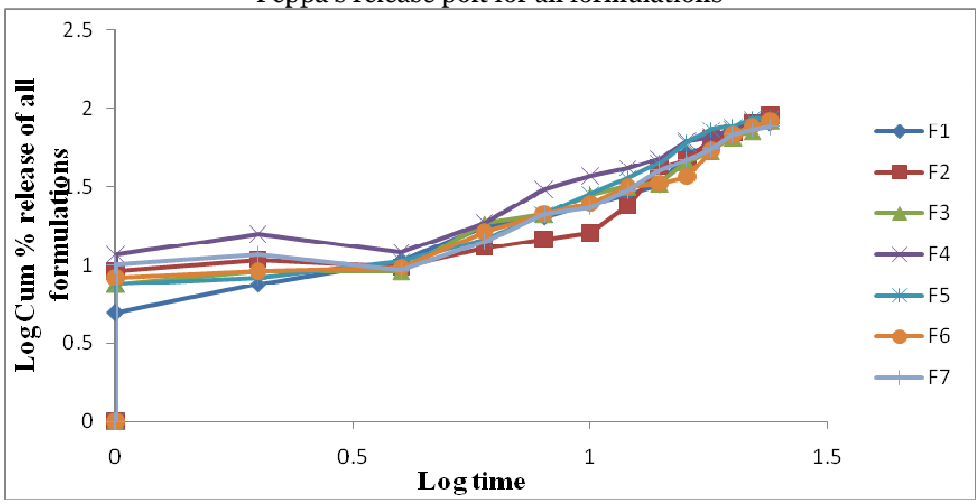


Table 4: Drug release kinetic data

No.	'r' coefficient values for				'n' value for
	Zero order plot	First order plot	Higuchi's modal plot	Peppa's modal plot	
F1	0.983	0.882	0.932	0.891	1.184
F2	0.979	0.891	0.944	0.885	1.198
F3	0.988	0.888	0.927	0.873	1.204
F4	0.995	0.897	0.967	0.869	1.213
F5	0.991	0.906	0.963	0.889	1.187
F6	0.983	0.922	0.961	0.891	1.161
F7	0.989	0.906	0.948	0.896	1.153

Drug release kinetic data

The zero order plots showed the zero order release characteristics of the formulation, which was confirmed by the correlation value. In order to find out the mechanism of drug release, the *in vitro* drug release data was graphically treated according to Higuchi's equation and the graphical fit for the *in vitro* data was used to conclude the mechanism of the drug release involved in the delivery system. Correlation value of Higuchi's plot revealed that the mechanism of drug release is diffusion. The *in vitro* kinetic data subjected to log time log drug release transformation plot (peppa's model), all the value ranges from 1 to 1.2704 revealed the fact that the

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drug release follows a super case II transport diffusion.

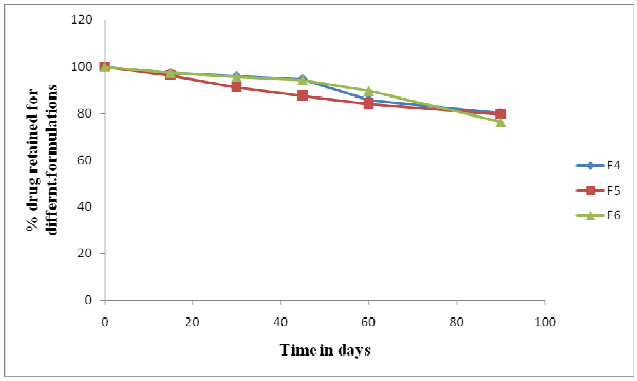
Stability Study

Physical stability

Physical stability was carried out to investigate the leaching out of the Lornoxicam from niosomes. The best formulation F4 was kept at refrigerated temperature (2-8ºc), room temperature and 40ºc (75%RH) as three different groups. Stability chamber was used for the third group. The group which kept at refrigerated temperature showed promising results of 80% drug retained after 90 days ,the group which is kept at room temperature gave 71% drug retained and the group which is kept at 40ºc,75% RH gave only 65% drug retained after 90 days. So the best three formulations kept at refrigerated temperature for a period of three months. The percentage of Lornoxicam retained in the span 60 vesicle after a period of three months were 80.22% , 77.25%, 75.13% and respectively for formulations F4 (260:140), F5 (280:120) and F6 (300:100). Also the results indicate that more than 80% of Lornoxicam was retained in the niosomal formulation for a period of 90 days. From this it can be concluded that vesicles are stable enough to store under refrigeration temperature with least leakage. The leakage of drug from F6 may be due to its higher surfactant content and lower cholesterol which formed a leaking vesicle.

Table 22: Percentage of Lornoxicam retained on refrigerated storage

SL NO:	Days Stored	F4 Percent retained	F5 Percent retained	F6 Percent retained
1	0	100	100	100
2	15	97.44	96.42	98.92
3	30	95.96	91.30	95.77
4	45	94.71	87.58	94.39
5	60	85.84	84.19	89.65
6	90	80.13	79.55	76.25



Test of Significance

The stability data analyzed for significant difference between retention patterns of drug in three different niosomal formulations on storage. The test value showed no significant difference (P>0.05) between the stability data of formulations from each other.

Table 23: Test of Significance

Formulations	F4-F5	F5-F6	F4-F6
P-value	0.0743	0.9286	0.1873

Zeta potential analysis

The formulation F4 which was subjected to zeta potential analysis had a zeta value of +29mv, which is a measure of net charge of niosomes. This higher charge on the surface of vesicle produce a repulsive force between the vesicles which made them stable, devoid of agglomeration and faster settling, providing an evenly distributed suspension. From this it can be concluded that formulation F4 provides much stable niosomal suspension.

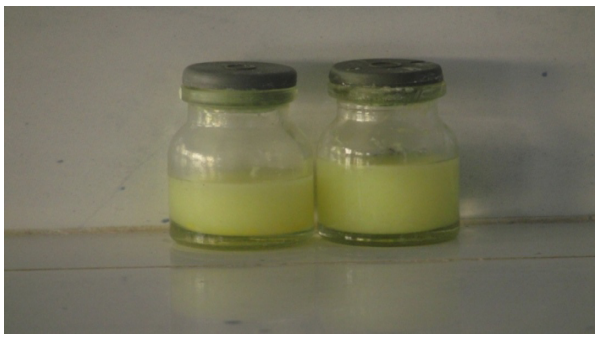


Figure 14: Lornoxicam loaded niosomes (Formulation F4)

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CONCLUSION

This study suggests that niosomal formulation can provide consistent and prolonged release of lornoxicam from different niosomal formulations. It will lead to sustained action of the entrapped drug that reduce the side effects associated with frequent administration of the drug and potentiate the therapeutic effects of the drug.

The concept of incorporating the drug into liposomes or 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. Niosomes are thoughts to be better candidate's 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, Oral, ophthalmic, topical, parentral, etc. By considering certain factors lornoxicam a hydrophobic drug which can be better entrapped in the cholesterol surfactant multilamellar vesicles by lipid film hydration method.Lipid film hydration method is the best method of preparing multilamellar vesicles as it is important in the case of a hydrophobic drug. When compared to proniosomes niosomes occur some stability problems due to the state of the formulation but as a advantage from proniosomes niosomes are easy to prepare and the carriers which are using for the proniosome preparation like sorbitol and maltodextrin are hygroscopic and it absorbe moisture. Selection of the carrier in the proniosomal formulation requires more attention as it affects some factors like flexibility in surfactant and other component ratio, surface area, efficient loading, etc

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