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DEVELOPMENT OF NEOSOMAL GEL FORMULATIONS OF PIROXICAM FOR THE TREATMENT OF RELIEVING PAIN DURING MENSTRUAL CRAMPS

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Abstract: *Over the past several years, treatment of infectious diseases and immunisation has undergone a revolutionary shift. With the advancement of biotechnology and genetic engineering, not only a large number of disease- specific biological have been developed, but also emphasis has been made to effectively deliver these biologicals. Niosomes are vesicles composed of non-ionic surfactants, which are biodegradable, relatively nontoxic, more stable and inexpensive, an alternative to liposomes. the current deepening and widening of interest of niosomes in many scientific disciplines and, particularly its application in medicine. Piroxicom is a non steroidal anti-inflammatory drug (NSAID) that exhibits anti-inflammatory, antirheumatoid,arthritis, analgesic, and antipyretic activities in animal models. Piroxicom like other non steroidal anti-inflammatory drugs causes side-effects on the gastro-intestinal system and other systems of the body. Because of these side effects the patient compliance may reduce. The best alternative route for administration of PIR is transdermal route.*

Keywords: *Piroxicam, Niosomes, Surfactanst*

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INTRODUCTION:

Basically there are three route of drug administration oral, topical & parentral. Among that topical i.e. skin provide efficient route for API administration. Stratum corneum in epidermal layer found to be major barrier for penetration of API through or in to the skin.

Topical drug delivery system means delivery of API through or in to the skin for direct treatment of cutaneous disorder or the cutaneous manifestation.

Topical drug delivery systems include a large variety of pharmaceutical dosage form like semisolids, liquid preparation, sprays and solid powders. Most widely used semisolid preparation for topical drug delivery includes gels, creams and ointments.

Fungus infection (Mycoses) is a human infection is broadly of two types. Superficial & deep seated (systemic) superficial infection is by far common & comprises the various types of tinea or ringworm affecting the skin, hair & nails. Superficial mycoses having two types surface infection & cutaneous infection. In cutaneous disorder mostly fungal infection occurs superficially. Novel topical drug delivery systems include noisomes, liposomes, and solid lipid nanoparticles etc. which are highly effective for topical route of drug administration.
Conventional preparation like Ointment, gel, cream, emulsion shows problem of drug penetration as well as API deposition. So to overcome this problem there is need to develop novel formulation act as carrier for better penetration through topical formulations.

Niosomal gels contain nanometric systems embedded in a gel. Nanometric systems have a greater surface area, which renders them highly satisfactory for the application of drug substances promoting a homogeneous drug release. Such structures have been investigated as alternatives to the classical formulations based on chemical skin permeation enhancers. Additionally, the nanostructure systems have nano size so it is easy for application to the skin in dermatological product

In the present study it has been aimed at developing a niosomal drug delivery system of piroxicam by solvent evaporation technique.

The objective of the present study is to enhance the dissolution release profile of piroxicam. This was developed by using, span 80 and cholesterol as a carrier, surfactant, lipid respectively.

List of Materials used for formulation

SI.No	Materials	Supplied by
1	Piroxicam	Gift sample from Dr.Reddy's Laboratories Ltd., Hyd
2	Cholesterol	S.D.Fine Chemicals, Mumbai.
3	Span 60	S.D.Fine Chemicals, Mumbai.
4	Methanol	Merck Specialities Pvt. Ltd., Mumbai.
5	Chloroform	Merck Specialities Pvt. Ltd., Mumbai.
6	carbopol	S.D.Fine Chemicals, Mumbai.

METHODOLOGY:

ANALYTICAL STUDIES:

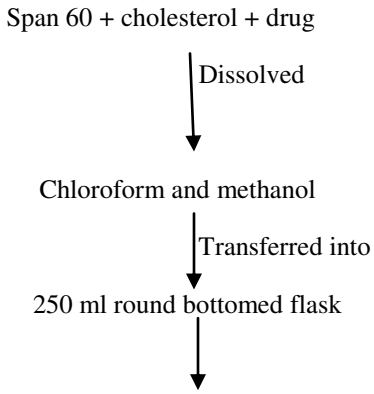
Construction of standard graph

For the spectrophotometric analysis stock solutions of piroxicam was prepared by dissolving 10 mg of the drug in 10 ml distilled water to obtain a final concentration of 1 mg/ml. Serial dilutions were made to prepare diverse sample solutions of concentrations ranging from 2–20 µl/ml. The solutions were analyzed at an absorption maximum of 304 nm against the blank.

Formulation of Niosomes

NIOSOMES were prepared by using slurry method (13). The composition of different proniosomal formulations is represented in (Table 4.3).

In brief, accurately weighed amounts of lipid mixture comprising of span 60 and cholesterol as per formulation ratios were dissolved in 20ml of solvent mixture containing chloroform and methanol (2:1). The resultant solvent solution was transferred into a 250ml round bottom flask. The flask was attached to a rotary flash evaporator (Hei-VAP advantage/561-01300, Heidolph, Germany) and the organic solvent was evaporated under reduced pressure at a temperature of 45±2^{0}C. The obtained niosomes were stored in a tightly closed container for further evaluation.



The flask was attached to a Rotary flash evaporator and organic solvent was evaporated under reduced pressure at a temp. of 45±2ºc

After ensuring the complete removal of solvent, the resultant pronisomes were collected and stored in a closed container.

Preparation of Gel: Carbopol 934 was taken as polymer for the formation of Gel. 1% Carbopol was chosen for preparing gel. Weighed amount of Carbopol 934 was taken in a dry beaker and to this water was added and kept aside for swelling of carbopol for 3 hours. After complete swelling of carbopol , slowly stir with glass rod and to this add few drops of Tri ethanol amine (TEA) and this turns the preparation into gel. To tis gel the prepared NIOSOMES were added.

Fig.1: Schematic representation of Proniosomal formulation of Piroxicam.

Table 1: Formulation of NIOSOMES

Formulation code	Drug (Piroxicam)	Surfactant	Cholesterol	Solvent (2:1)
NG1	**20**	Sapn 60	100	Chloroform and methanol
NG2	**20**	Sapn 60	100	Chloroform and methanol
NG3	**20**	Sapn 60	100	Chloroform and methanol
NG4	**20**	Sapn 60	50	Chloroform and methanol
NG5	**20**	Sapn 60	50	Chloroform and methanol

Evaluation

Morphological evaluation of prepared proniosome powders by Scanning Electron Microscopy

The surface morphology of the pro-niosomes was evaluated by scanning electron microscopy. The proniosome gel was placed on a cavity glass slide and few water was added drop wise along the side of the cover slip. The formation of vesicles was monitored through a microscope and photomicrograph was taken.

Percentage Drug Entrapment

The PDE of Piroxicam NIOSOMES was calculated after determining the amount of unentrapped drug by dialysis[38]. The dialysis was performed by adding the niosomal dispersion to a dialysis tube (donor compartment) and then dipping the tube into a beaker containing 200 mL of PBS pH 7.4 with 0.05% SLS (receptor compartment) on a magnetic stirrer, rotated at a speed of 80 to 120 rpm for 3 hours. After 3 hours, the solution in the receptor compartment was

estimated for unentrapped drug at 304 nm by using a UV spectrophotometer[27].

$$Percent\ Entrapment = Total\ drug - Diffused\ drug/totaldrug X100$$

***In vitro* diffusion study**

In vitro dissolution study of proniosomal gel was perfomed by using franz diffusion cells by taking phosphate buffer 6.8 pH. The volume of diffusion medium used was 20 ml and maintained at a temperature of 37 ± 0.5ºC with paddle speed set at 50 rpm throughout the experiment. An aliquot of 5 ml was collected at predetermined time intervals 30 min, 1, 2, 3, 4, 5, 6, 7 hrs respectively and replaced with fresh buffer to maintain constant volume[40]. Samples were analysed for Piroxicam using UV-Visible spectrophotometer at 304 nm.

Fourier transform infrared (FT-IR) spectroscopy

Infrared spectra of pure drug, and optimized proniosomal formulation were obtained using FT-IR spectrophotometer (Bruker, Alpha-T, Lab India) by the conventional KBr pellet method[13].

5. ANALYTICAL METHODS

5.1. Development of UV spectroscopic method

Preparation of calibration curve: The standard curve was prepared in the concentration range of 2–20 µl/ml. Different volumes of standard stock solutions, containing 2-20 µg mL^{-1} of drug were transferred to 10ml volumetric flasks and volume was made up with methanol. The absorbance was measured at 304 nm against the corresponding reagent blank. The drug concentrations of piroxicam were analyzed by UV-Spectrophotometer at 304 nm (fig. 2).

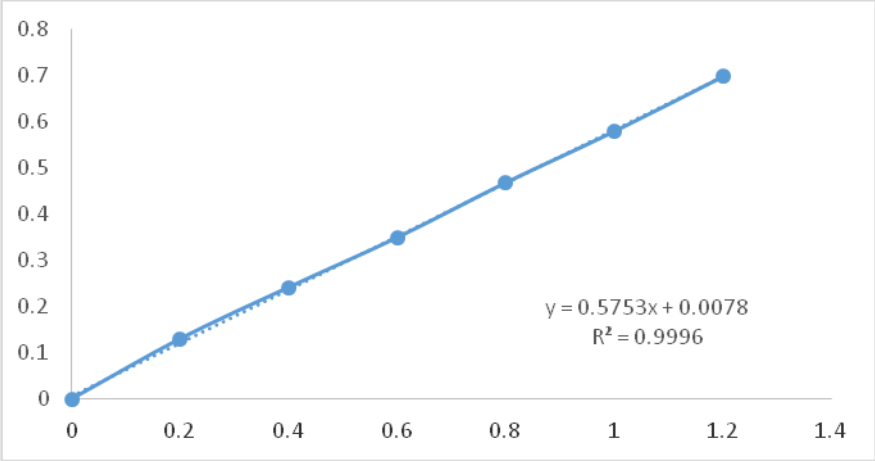


Fig.2:Standard graph of Piroxicam

Table 2:Standard graph of Piroxicam

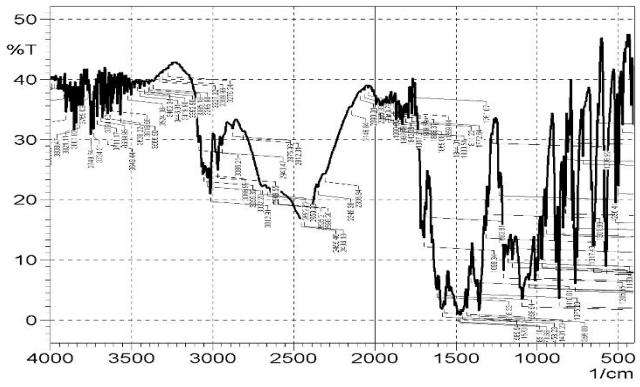
conc(mg/ml)	abs
0	**0**
0.2	**0.1307**
0.4	**0.2423**
0.6	**0.3502**
0.8	**0.4689**
1	**0.5801**
1.2	**0.6987**

Table 3: Optical Parameters

Parameters (Units)	**Values**
	Piroxicam
λ max/ nm	304 nm
Linearity Range (µg/ml)	0-1.2
Slope , *b*	0.5753X

FTIR:

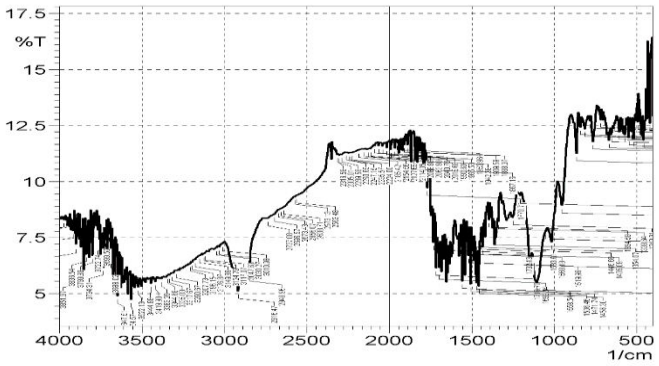
The FTIR was performed for both pure drug and formulation, and the results clearly indicated that there is no incompatibility between pure drug and formulation.



SHIMADZU

	Peak	Intensity	Corr. Inte	Base (H)	Base (L)	Area	Corr. Are
1	472.58	32.47	9.894	480.29	462.93	7.307	0.886
2	497.65	22.29	15.705	503.44	482.22	10.048	1.426
3	515.01	17.459	21.964	522.73	505.37	9.698	2.601
4	572.88	8.916	4.567	576.74	530.44	25.473	0.532
5	619.17	34.049	4.098	623.03	603.74	7.557	0.279
6	650.03	9.24	16.064	659.68	624.96	25.584	6.334
7	717.54	27.229	8.092	723.33	680.89	19.2	0.763
8	752.26	10.415	6.56	756.12	725.26	18.82	0.781
9	763.84	6.068	12.387	775.41	758.05	16.679	4.138
10	781.2	16.531	12.237	790.84	777.34	8.147	1.138
11	800.49	30.756	2.813	802.41	792.77	4.499	0.251
12	810.13	27.91	4.965	813.99	804.34	5.044	0.36
13	825.56	18.97	10.942	831.35	815.92	9.179	1.34
14	839.06	15.33	10.928	846.78	833.28	9.283	1.442
15	864.14	3.598	18.243	871.85	852.56	17.75	5.308
16	883.43	9.605	13.89	904.64	873.78	22.682	4.023
17	945.15	15.586	7.447	950.94	906.57	25.908	1.142
18	970.23	10.046	8.836	979.87	952.87	21.904	2.767
19	995.3	8.239	3.643	999.16	981.8	15.478	0.65
20	1012.66	6.504	5.966	1018.45	1001.09	18.504	2.172
21	1051.24	6.623	1.773	1055.1	1020.38	35.489	1.549
22	1091.75	3.546	2.335	1099.46	1066.67	41.581	2.241
23	1151.54	10.021	3.985	1161.19	1134.18	24.544	1.48
24	1168.9	13.18	0.547	1172.76	1163.11	8.344	0.076
25	1180.47	10.804	2.441	1193.98	1172.76	19.672	1.017
26	1205.55	8.256	8.405	1226.77	1196.91	25.551	2.469
27	1236.41	21.947	5.343	1253.77	1228.7	14.161	0.662
28	1276.92	30.698	0.729	1278.85	1265.35	6.691	0.088
29	1301.99	18.845	5.334	1307.78	1280.78	16.667	1.197
30	1317.43	14.897	4.37	1323.21	1309.71	10.275	0.776
31	1356	1.577	7.973	1367.58	1325.14	52.345	11.587
32	1375.29	5.61	1.164	1383.01	1369.5	16.371	0.585
33	1410.01	7.51	2.773	1413.87	1402.3	11.844	0.781
34	1431.23	1.977	3.956	1437.02	1415.8	28.322	3.562
35	1458.23	1.408	1.344	1465.95	1438.94	44.013	3.478
36	1473.66	0.825	0.808	1483.31	1465.95	33.371	2.311
37	1489.1	0.981	0.794	1502.6	1485.24	30.773	1.251
38	1568.54	5.268	1.364	1562.39	1552.75	11.383	0.266
39	1570.11	2.438	1.118	1572.04	1562.39	14.07	0.969
40	1585.54	1.811	2.765	1608.69	1573.97	52.936	6.935
41	1618.33	5.061	2.792	1631.83	1610.61	25.671	2.33

Fig 3: pure drug-piroxicam



SHIMADZU

	Peak	Intensity	Corr. Inte	Base (H)	Base (L)	Area	Corr. Are
1	418.67	12.613	1.809	422.42	406.99	12.662	0.136
2	457.14	11.855	0.807	459.07	441.71	15.631	0.318
3	491.86	12.666	1.007	495.72	486.08	8.471	0.162
4	518.87	11.922	0.956	522.73	507.3	13.9	0.186
5	530.44	12.228	0.457	538.16	524.66	12.241	0.133
6	545.87	11.96	0.912	551.66	540.09	10.476	0.17
7	569.02	12.095	0.271	570.95	561.3	8.724	0.045
8	603.74	12.217	0.662	617.24	596.02	19.133	0.249
9	630.74	12.573	0.135	634.6	619.17	13.809	0.032
10	651.96	12.116	0.287	655.82	646.17	8.787	0.052
11	665.46	11.835	0.42	669.32	657.75	10.599	0.067
12	717.54	12.765	0.508	731.05	711.76	17.062	0.149
13	754.19	12.354	0.131	756.12	738.76	15.409	0.025
14	763.84	11.782	0.794	775.41	756.12	17.661	0.307
15	781.2	12.706	0.23	786.98	777.34	8.608	0.042
16	813.99	12.356	0.559	831.35	794.7	32.887	0.312
17	840.99	12.423	0.534	850.64	833.28	15.589	0.182
18	864.14	11.25	1.648	879.57	852.56	24.654	0.619
19	954.8	8.933	1.897	976.01	898.86	75.047	2.468
20	1014.59	7.308	1.441	1037.74	977.94	64.604	1.964
21	1053.17	7.766	0.03	1055.1	1039.67	17.039	0.009
22	1107.18	5.488	0.226	1111.03	1055.1	66.497	0.631
23	1149.61	6.603	0.81	1197.83	1136.11	67.87	0.639
24	1207.48	9.363	0.153	1215.19	1199.76	15.812	0.05
25	1249.91	8.4	0.229	1255.7	1222.91	34.391	0.136
26	1338.64	8.222	0.542	1342.5	1332.86	10.205	0.098
27	1354.07	7.455	0.131	1356	1342.5	14.844	0.012
28	1394.58	8.304	0.758	1400.37	1390.72	10.279	0.222
29	1435.09	7.09	0.931	1438.94	1427.37	12.948	0.294
30	1446.66	7.299	0.21	1448.59	1440.87	8.583	0.023
31	1456.3	5.341	1.745	1460.16	1450.52	11.528	0.49
32	1471.74	5.494	1.529	1483.31	1467.88	16.278	0.6
33	1506.46	5.431	2.488	1512.24	1502.6	11.247	0.625
34	1519.96	6.711	1.072	1527.67	1514.17	15.467	0.495
35	1558.54	6.566	2.397	1560.46	1546.96	15.337	0.627
36	1568.18	7.104	0.761	1572.04	1562.39	10.787	0.175
37	1583.61	7.434	0.267	1599.04	1579.75	21.602	0.3
38	1699.34	5.971	1.124	1701.27	1691.63	11.411	0.461
39	1716.7	6.155	1.774	1724.42	1710.92	15.383	0.513
40	1732.13	7.29	1.429	1735.99	1726.35	10.629	0.391
41	1770.71	9.721	1.486	1776.5	1764.93	11.327	0.319

Fig 4: optimised formulation

Entrapment Efficiency:

Proniosomes have generated interest as a topical formulation and to achieve the desirable therapeutic effect of Niosomes as drug carriers, they must be loaded with sufficient amount of active compound. Proniosomes prepared with non-ionic surfactants of alkyl ester including Span (sorbitan esters) and Tween (polyoxythylene sorbitan esters) were utilized to determine the encapsulation of associated Piroxicam and vesicle size. As shown in Table 6, encapsulation efficiency of proniosomes formed from formulation NG1, NG3, NG4, NG5 proniosome gel exhibit lower encapsulation efficiency when compared to NG2. The results of entrapment efficiency are shown in the fig 3. Piroxicam was best encapsulated by niosomal gel prepared using Span 40 when compared to other grades and this was attributed to the fact that S40 is solid at room temperature, showed higher phase transition temperature and low permeability. The encapsulation efficiency of S40 at 59.50% was much higher than S20, T60 and T80 at 23.84%, 28.84%, 17.24% and 15.84%. Furthermore S40 was optimized based on the encapsulation efficiency by taking different ratios of surfactant and lecithin and encapsulation percentage is determined. Table 7 shows the effect of various ratios of sorbitan fatty acid esters and lecithin on the encapsulation of Piroxicam in niosomal gel.

Table 4: Encapsulation percentage of various Niosomal Gel Formulations

Sl. No	Niosomal code	Encapsulation percentage (%)
1.	NG1	23.84 ±1.4
2.	NG2	59.50 ±2.3
3.	NG3	23.84 ±1.6
4.	NG4	28.84 ±2.0
5.	NG5	17.24 ±1.9

Table 5: Niosomal gel formulations with various ratios of sorbitan fatty acid esters and lecithin:

Sl. No	Niosomal code	Ratios		Piroxicam (mg)	Cholesterol (mg)
		SPAN 40	Lecithin		
1.	NG1	1	1	10	20
2.	NG2	2	1	10	20
3.	NG3	1	2	10	20
4.	NG4	3	1	10	20
5	NG5	1	3	10	20

The encapsulation percentage obtained by different ratios of sorbitan fatty acid esters and lecithin were almost same with slight difference that is formulations having more of surfactant have encapsulation slightly higher than those with higher lecithin ratio. Table 8 shows the encapsulation percentage of different formulations. The encapsulations Percentage of different formulations of Span 40 are shown in the fig 4.

Table 6: Encapsulation percentage of different formulations

Sl. No	Niosomal code	Ratios		Encapsulation percentage (Percentage)
		SPAN 40	Lecithin	
1.	NG1	1	1	66±1.0
2.	NG2	2	1	65 ±1.9
3.	NG3	1	2	57.4 ±1.6
4.	NG4	3	1	61.2 ±2.1
	NG5	1	3	57.2 ±1.5

***In-vitro* Studies**

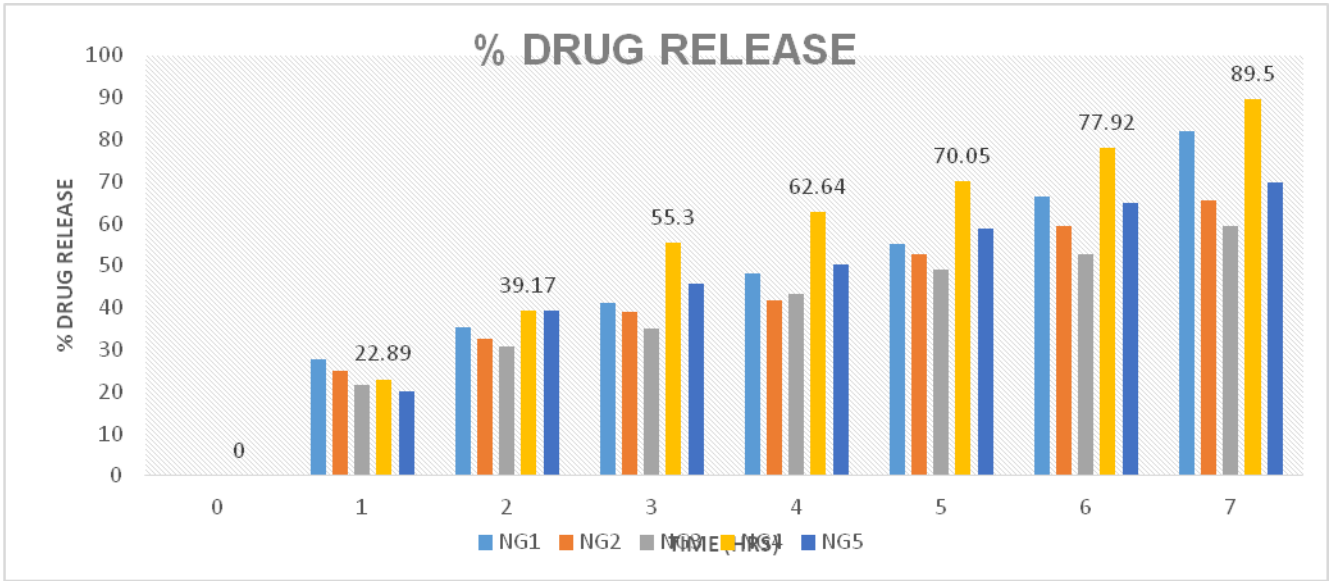
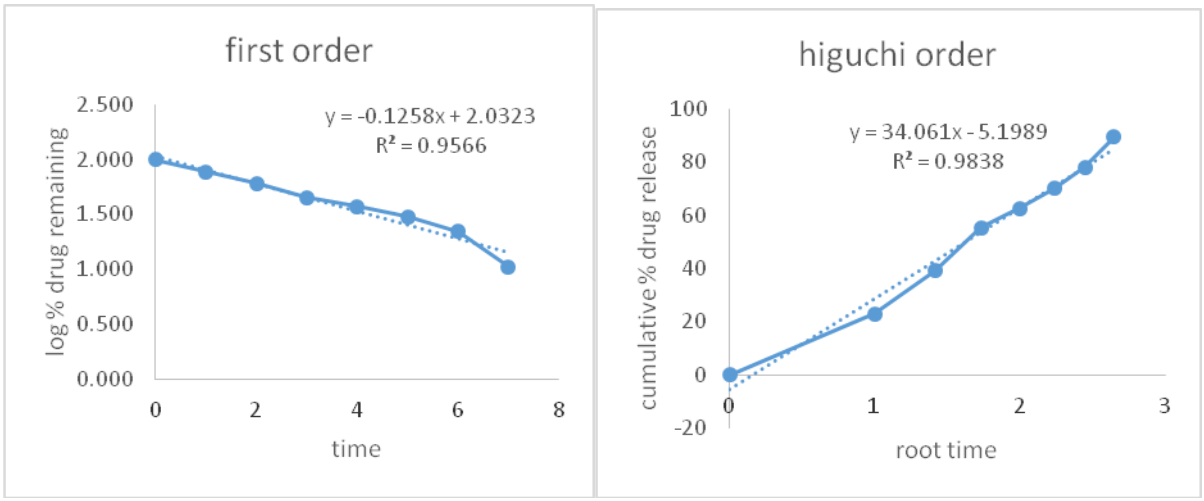


Fig 5: In vitro drug release profile for Niosomal Gels

Table 7: Release kinetics of optimized formulations in in-vitro drug release

time (t)	root (t)	cumulative (%) release q	log (t)	log(%) release	log (%) remain	release rate (cumulative % release / t)
0	0	0	0.000	0.000	2.000	0.000
1	1.000	22.89	0.000	1.360	1.887	22.890
2	1.414	39.17	0.301	1.593	1.784	19.585
3	1.732	55.3	0.477	1.743	1.650	18.433
4	2.000	62.64	0.602	1.797	1.572	15.660
5	2.236	70.05	0.699	1.845	1.476	14.010
6	2.449	77.92	0.778	1.892	1.344	12.987
7	2.646	89.5	0.845	1.952	1.021	12.786



RELEASE KINETICS:

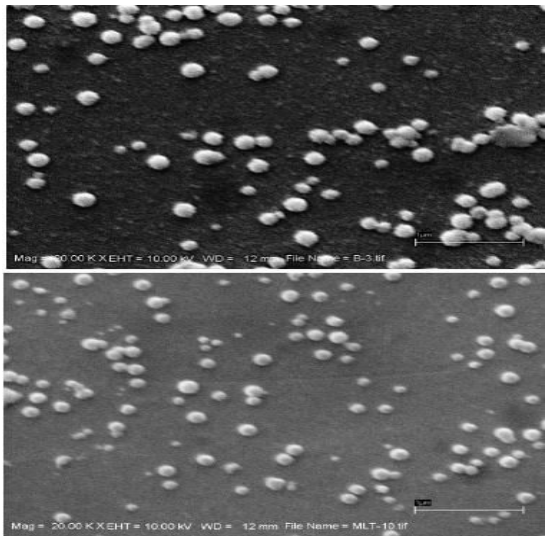
The Release kinetics of the optimized formulations studied in in-vitro drug release are given in the tables

Different Kinetic model of the Formulations NG2, NG3, NG4 and NG5 are shown in the figure.

Thus it is evident from the study that NG4 formulation of Piroxicam niosomal gel showed good stability characteristics, prolonged release of entrapped Piroxicam with enhanced penetration and retention of drug in the skin facilitating local action thus achieving the main objectives in the development of formulation for Therapy.

To ascertain the drug release mechanism and release rate data of the various formulations, the data's were model fitted by Drug Kinetic Models. The models selected were Zero order, First order, Higuchi Matrix, Weibull, Korsemayer Peppas, Hixon-Crowell. The release pattern was found to be first Order and the best fit model was found to be higuchi order

Scanning Electron Microscopy:



CONCLUSION:

Studies were conducted with various levels of amount of cholesterol and span 60 to optimize proniosomal. All formulations were evaluated for the different Physico-chemical characteristics.Formulated proniosomes gave satisfactory results for entrapment efficiency. *In Vitro* drug release behavior was improved.There is no significant difference between the FTIR patterns of the optimized formulation of proniosomal gel and to that of the pure drug.

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