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Formulation Evaluation and Optimization of Niosomal Gel of Piroxicam

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Abstract: The objective of the present study was to formulate Niosomal gel of Piroxicam to prevent severe gastrointestinal side effects associated with its oral administration as well as to improve the residence time of drug into skin to enhance anti inflammatory activity. Present study was carried out by preparing total nine formulations(A1, A2, A3, B1, B2, B3, C1, C2, C3) of niosomes of piroxicam using appropriate ratio of surfactant and co-surfactant by thin film hydration method and prepared niosomes formulation were evaluated for Vesicle diameter, Drug content, Drug entrapment efficiency, SEM & in-vitro drug release. Best batch thus selected was further formulated as niosomal gel (F1, F2, F3, F4) using different gelling agents that is HPMC, CMC, MC, Sodium alginate.

Prepared gel was evaluated for various physicochemical parameters like Clarity, Homogeneity, Spreadability, Extrudability, pH, Drug content, Viscosity & in-vitro drug release results infants.

Clarity of all formulations were found clear and vesicle were uniformly dispersed in dispersion medium which was confirmed by homogeneity**,** Spreadability varies from 7.2±0.25 – 10.3±0.3**,** extrudability was between 75.67±0.67 – 97.56±1.56**,** pH varies from 5.56 – 6.77**.** Drug content was between 96.44±3.1 – 99.9±1.9 and viscosity varies from 5556 – 8470**.** On the basis of evaluation parameters of niosomal gel, batch F3 was selected as optimized batch.

Keywords: Niosomal Gel, piroxicam, polymers, HPMC, sodium alginate.

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I. INTRODUCTION

Oral route is considered one of the simplest and most commonly route of drug administration. Even though several advantages are there in support, oral therapy has to face many significant drawbacks i.e. poor plasma availability due to pre-systemic metabolism, unpredictable absorption due to degradation by stomach acid and enzymes and unsuitable for unconscious patients.

To overcome these complications there is a need for the development of new drug delivery systems which would improve the therapeutic efficacy and safety of drugs through Transdermal drug delivery system.

Transdermal drug delivery systems deliver the active medicament across the layers of skin. Transdermal delivery systems distribute the active ingredient into the general circulation passing through the skin, viz.; controlled and consistent delivery of drugs.

Criteria for selection of drug suitable for Transdermal drug delivery

- Drug must have optimum physicochemical properties for better penetration through stratum corneum with therapeutic dose less than 10mg.
- The barrier function of the skin and age of patient must be considered before formulation.
- Suitable penetration enhancers should be selected to avoid skin irritation and contact dermatitis.

Niosomes:

Niosomes or non-ionic surfactant vesicles are microscopic lamellar structures formed on the admixture of a non-ionic surfactant of the alkyl or dialkyl polyglycerol ether, cholesterol and phosphate with subsequent hydration in aqueous media. Structurally, they resemble with liposomes and possess equivalent drug delivery potential. Niosomes are tiny lamellar structures (10 to 1000 nm) and consist of an admixture of non-ionic biodegradable, non-immunogenic and biocompatible surfactants and cholesterol. These are amphiphiles allowing entrapment of both hydrophilic and hydrophobic drugs within the bilayer. They are advantageous over conventional dosage forms.

Advantages of Niosomes: Application of Niosomes in cosmetics and therapeutics may offer several advantages:[3, 4]

- The vesicle suspension is water–based vehicle.
- It offers high patient compliance in comparison to other dosage forms. ·
- They are amphiphilic in nature so can accommodate both types of moieties together i.e. hydrophilic and lipophilic.
- Niosomes are osmotically active and stable; also increase the stability of entrapped drug.
- They also act depot and release the drug in controlled manner.
- No special conditions are required for their handling and storage.
- They enhance oral bioavailability and improve penetration of poorly absorbed and permeable drugs respectively.
- They can be targeted to site of action by oral, parenteral as well as topical routes.[12]
- They also improve the therapeutic performance of the drug molecules by delayed clearance, protecting the drug from biological environment and restricting effects to target cells.
- The surfactants used are biodegradable, biocompatible and non-immunogenic.
- The drug delivery rate can be regulated by emulsifying niosomal aqueous dispersion to non-aqueous dispersion.

Types of Niosomes:

The niosomes are classified on the basis of number of bilayer, size and the method of preparation. Various types of niosomes are as follows:

1. Multi lamellar vesicles (MLV, Size-0.05 μm)
2. Large unilamellar vesicles (LUV, Size-0.10 μm).
3. Small unilamellar vesicles (SUV, Size-0.025-0.05 μm)

II. MATERIALS AND METHOD

Piroxicam was obtained as a gift sample from Mr. Vijay Singh Bisht, Jubilant life science, Sodium alginate, Methyl Cellulose, HPMC and CMC was purchased from Sheila enterprises, Dehradun, Methyl Paraben, Propyl Paraben were purchased from CHD ltd. New Delhi. Glycerin and other required ingredient are available by Gyani Inder Singh Institute of Professional studies, Dehradun, Uttarakhand. The entire chemical used was of analytical grade and were used without further purification. Deionized distilled water was used throughout the studies.

Method of preparation of niosomes of piroxicam

Niosomes of Piroxicam were prepared by lipid hydration method according to the composition in following table:

Table 1: Formulation design of niosomes of Piroxicam

Formulation code	Amount of drug (mg)	Surfactant used	(Surfactant: cholesterol) weight ratio
A1	10	Span 20	0.5:0.5
A2	10		0.5:1.0
A3	10		0.5: 1.5
B1	10	Span 60	0.5:0.5
B2	10		0.5:1.0
B3	10		0.5:1.5
C1	10	Span 80	0.5:0.5
C2	10		0.5:1.0
C3	10		0.5:1.5

Mixture of surfactant (Span 20, 60, 80) and cholesterol (equivalent to 50 mg) were dissolved in 10 ml of chloroform. The solvent was slowly evaporated using a rotary flash evaporator (at 80 rpm, 60°C) under low pressure to produce thin lipid film. In another conical flask, weighed amount of drug (according to dose) was transferred and dissolved in required quantity of Phosphate buffer saline (pH 7.4). The mixture was sonicated for 5 min. by the hand and again resonicated for 5 min. The prepared niosomes were allowed to equilibrate at room temperature. Niosomal dispersion was then kept in refrigerator at 4°C.

Evaluation of piroxicam niosomes:

Drug Encapsulation efficiency:

Niosomal dispersion of Piroxicam thus prepared was subjected to centrifugation on a Refrigerated Centrifuge at 14000 rpm and 4° C for 30 min duration each with 10 min gap to separate free drug from entrapped drug. On completion of centrifugation process, the supernatant was siphoned off carefully and entrapped drug was left behind in the sediment.

The niosomes were separated from the supernatant and about 0.1 ml of this was added to 10 ml methanol in a volumetric flask and drug content was determined spectrophotometrically at 356 nm using drug free formulation as a blank. The pellet obtained after centrifugation was added in methanol and sonicated for 10 min. The drug concentration was determined. Drug Encapsulation

Efficiency (%) was calculated as follows:

$$EE\ \% = [(T-C)/T] \times 100 \quad (1)$$

Where, T = total amount of drug (calculated both in supernatant and sediment)

C = amount of drug found only in the supernatant.

Preparation of piroxicam niosomal gel

Niosomal gel of Piroxicam was prepared by using niosomal dispersion and 4% sodium alginate. Initially, weighed amount of polymer was gently sprinkled in a beaker comprised of 10 ml boiling distilled water and stirred at high speed on magnetic stirred till hazy dispersion was formed. Afterwards, glycerol and propylene glycol were added followed by parabens. Niosomal dispersion (equivalent to dose) of piroxicam was added to above mixture and homogenized until uniform gel was formed. It was then sonicated to remove bubbles. Finally, distilled water was added to make up the weight up to 100 g.

Similarly, Piroxicam gels were also prepared with HPMC, Methyl cellulose and Carboxy methyl cellulose using predetermined concentrations of polymers.

Table no. 2: Formulation design of Niosomal gel of Piroxicam

INGREDIENTS	**FORMULATION CODE**			
	F1	**F2**	**F3**	**F4**
Niosomal dispersion (ml)	10	10	10	10
Sodium alginate (gm)	4			
Methyl Cellulose (gm)		4		
HPMC (gm)			4	
CMC (gm)				4
Methyl Paraben (gm)	0.2	0.2	0.2	0.2
Propyl Paraben (gm)	0.02	0.02	0.02	0.02
Glycerin (gm)	10	10	10	10
Propylene Glycol (gm)	10	10	10	10
Water to (gm)	100	100	100	100

Evaluation of niosomal gels

Niosomal gels of Piroxicam thus prepared were subjected to various evaluation parameters viz.; clarity, homogeneity, Spreadability, Extrudability, pH, drug content, viscosity (Brookfield's viscometer (DV II model) at 100 rpm using spindle number 64) and *in-vitro* diffusion study which revealed that gel prepared with HPMC exhibited good results and considered as best niosomal gel. Percentage (%) drug release from optimized formulation was found to be 58.645% in 720 min.

Table no. 3: Evaluation parameters for Niosomal gel of Piroxicam

Formula	**Clarity**	**Homogeneity**	**Spreadability**	**Extrudability**	**pH**	**Viscosity (cPs)**
F1	good	Very Good	8.9±0.21	92.37±1.31	6.77±0.16	6667
F2	good	Very Good	9.5±0.28	93.77±0.59	5.70±0.12	7239
F3	Very clear	Excellent	10.3±0.3	97.56±1.56	5.56±0.14	8470
F4	turbid	Good	8.2±0.31	87.18±0.22	5.90±0.17	5556

***In-vitro* permeation study of Piroxicam gels:**

In-vitro permeation study of niosomal gel of Piroxicam was performed using Franz's diffusion cell. A cellophane membrane was placed between donor and receiver compartment. About 0.5 % Piroxicam gel was placed on top membrane. At predetermined time interval, 5 ml sample withdrawn from receptor compartment and replenished with fresh medium. The absorbance of withdrawn samples was measured after suitable dilution at 356 nm for drug content.

Table no. 4: In-vitro diffusion profile of Piroxicam Niosomes (batch A1-C3) in pH 7.4 Phosphate buffer

S. No.	Formulation code	Particle size	Drug content	%Entrapment Efficiency
1	A1	51.4	88.08±1.2	90.042
2	A2	62.4	92.90±3.4	92.975
3	A3	90.5	96.33±2.7	89.025
4	B1	126.2	89.84±3.2	98.708
5	B2	129.4	99.9±1.5	99.680
6	B3	131.7	97.14±3.1	95.541
7	C1	65.7	89.22±1.09	80.371
8	C2	95.1	94.56±3.21	86.739
9	C3	98.3	93.57±0.27	84.603

Table no. 5: Percentage (%) drug release profile of Niosomes of Piroxicam (batch A1-C3) in pH 7.4 phosphate buffer

Time (min.)	A1	A2	A3	B1	B2	B3	C1	C2	C3
0	0	0	0	0	0	0	0	0	0
60	7.444	8.667	6.664	9.444	10.667	9.222	5.444	8.244	6.115
120	12.189	13.2	11.231	14.189	15.2	12.956	9.189	12.956	10.178
180	15.093	16.316	14.314	17.093	18.316	16.854	13.093	16.124	15.092
240	18.277	19.51	17.511	19.277	22.567	19.043	18.277	21.262	19.261
300	23.203	24.437	22.436	24.203	26.437	23.969	22.203	26.204	24.211
360	27.955	28.188	26.188	28.955	30.188	27.621	26.955	29.944	28.922
420	32.648	33.882	31.881	33.648	34.882	32.409	31.648	33.648	32.648
480	36.838	37.072	35.072	38.838	40.072	37.704	35.838	39.822	36.811
540	41.614	42.848	40.848	43.614	44.848	42.335	40.614	44.611	42.612
600	46.32	48.554	45.554	47.32	49.554	46.083	44.32	48.311	46.312
660	52.46	53.699	51.699	53.46	55.699	53.926	51.46	54.441	53.433
720	57.706	58.607	55.607	58.706	61.018	57.361	56.706	59.711	58.666

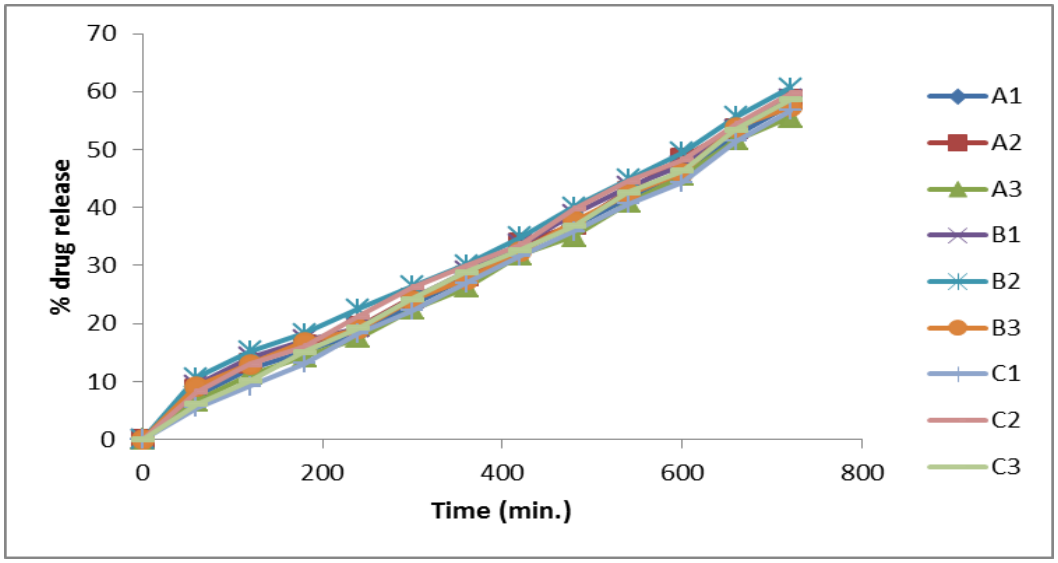

Figure no. 1: Percentage (%) drug release vs. time profile graph of Niosomes of Piroxicam (batch A1-C3) in pH 7.4 phosphate buffer

Based on the results, obtained from evaluation parameters of Piroxicam niosomes revealed that batch B2 was considered as optimized formulation as it showed maximum drug content, entrapment efficiency and drug release. Optimized batch thus selected was subjected to release kinetic study and then formulated as niosomal gel using different gelling agents i.e. sodium alginate, methyl cellulose, HPMC and CMC.

Table no. 6: Evaluation parameters for optimized batch (B2)

S. No.	Parameter	Results
1	**Vesicle diameter**	129.4 µm
2	**Drug content**	99.9±1.5
3	**Drug Entrapment efficiency**	99.680
4	***In-vitro* diffusion study**	% drug release- 61.018% in 720 min.
5	**Release kinetic model**	Korsemeyer- peppas
6	**Surface morphology**	Almost spherical in shape

Table no. 7: Percentage (%) drug release profile of Niosomal gels of Piroxicam (batches F1-F4) in pH 7.4 phosphate buffer:

S. No.	Time (min.)	% Drug release			
		F1	F2	F3	F4
1	0	0	0	0	0
2	60	8.458	7.458	9.542	6.551
3	120	12.375	11.312	13.311	10.327
4	180	14.771	15.772	16.66	13.663
5	240	19.798	18.795	20.795	17.699
6	300	24.946	23.921	25.899	22.495
7	360	27.132	26.132	29.133	25.135
8	420	32.976	31.133	34.145	30.147
9	480	38.727	36.611	39.522	34.542
10	540	41.628	40.611	43.613	38.613
11	600	46.976	45.973	47.963	43.964
12	660	52.455	51.897	53.651	50.352
13	720	56.98	55.641	58.645	54.655

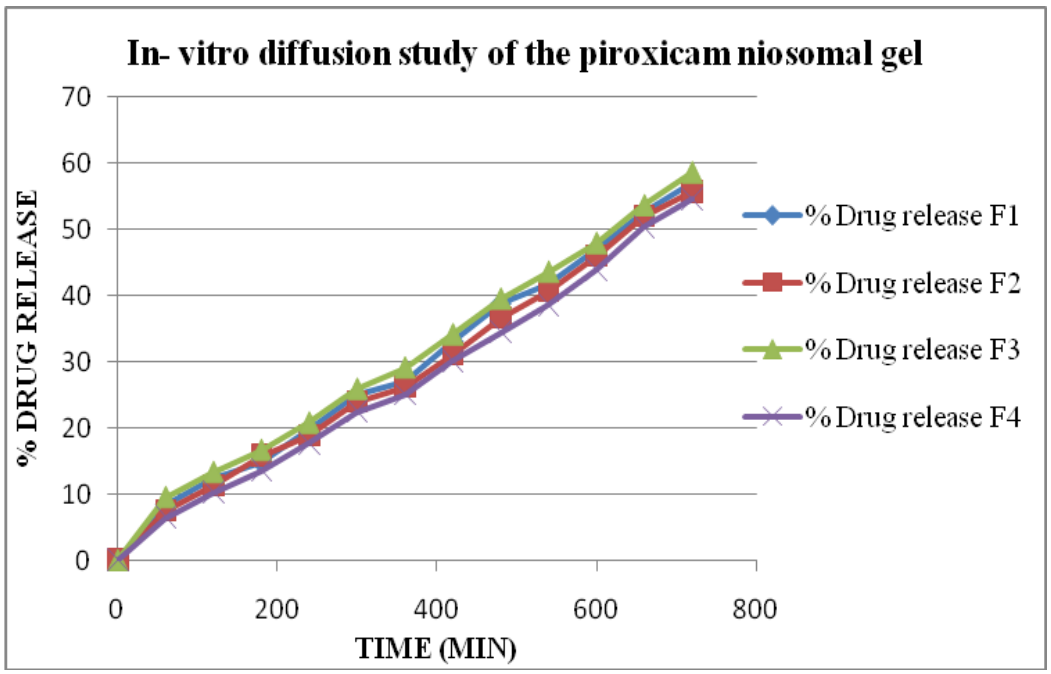

Figure no. 2: In-vitro dissolution of Niosomal gels (batch F1-F4) in pH 7.4 phosphate buffer

III. RESULTS AND DISCUSSION

The selected drug (Piroxicam) was studied for physicochemical characteristics and run on U.V-Visible Spectrophotometer (in different concentrations) to determine wavelength maxima which was further confirmed from overlain spectra thus obtained. Standard calibration curves were also prepared using different solvent media i.e. distilled water, pH 7.4 phosphate buffer. FTIR & densitometry, TLC studies were carried out for testing the compatibility of drug with selected surfactant and other excipients.

In this research work initially nine formulations of niosomes were prepared after selecting appropriate ratio of surfactant and co-surfactant by thin film hydration method. Prepared niosomes formulations were evaluated for Vesicle diameter, Drug content, Drug entrapment efficiency & in-vitro drug release. Vesicle diameter (51.4-500), drug content (88.08±1.2 – 98.9±1.5), Drug entrapment efficiency (80.37 – 99.68)

Percent drug release of Piroxicam varies from 87.70 – 694.607% at the end of 720 min. Maximum drug release was found to be 94.607% in 7.4 phosphate buffer in 720 min and B2 considered as optimized batch [(16)].

The best batch (B2) containing Span 60 and cholesterol in 0.5:1.0 ratios was selected for formulating as Niosomal gel using different gelling agents that is HPMC, CMC, MC, Sodium alginate. Prepared gels evaluated for various physicochemical parameters Clarity, Homogeneity, Spreadability, Extrudability, pH, Drug content, Viscosity & in-vitro drug release results inferred.

Similarly Niosomes gels thus prepared were evaluated an results were Clarity, Homogeneity **(**all formulation were found clear and vesicle were uniformly dispersion medium which was confirmed by homogeneity**),** Spreadability **(**7.2±0.25-10.3±0.3**),** Extrudability **(**75.67±0.67-97.56±1.56**),** pH **(**5.56-6.77**),** Drug content **(**96.44±3.1-99.9±1.9**),** viscosity (5556-8470**).**

Based on the results obtained from evaluation F3 formulation was considered as optimized batch as it showed maximum drug release than other batches. *In-vitro* release of the optimized formulation (F3) in pH 7.4 Phosphate buffer was found to be 58.645% in 720 min.

IV. CONCLUSION

The present work suggested that such a formulation design could be extrapolated to many potential therapeutic candidates causing gastric irritation and targeting overwhelming demands of better permeability encompassing utmost economic relevance. The purpose of this research was to prepare piroxicam loaded niosomes for controlled release of drug and incorporate it into topical gel delivery system to reduce the side effects.

The prolonged release of the drug from the niosomes suggests that the frequency of administration and adverse effects significantly thereby improving the patient compliance. The administration of drug as gel type formulation enhances its penetration and release.

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CONFLICT OF INTEREST: Nil

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