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Research Article

FORMULATIONAND EVALUATION OF TRANSDERMAL GEL PREPARATION OF PIROXICAM NIOSOMES

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ABSTRACT

The objective of the study was an attempt to formulate and evaluate transdermal gel preparation of Piroxicamniosome. Piroxicam is a class of drug called NSAIDS (non-steroidal anti-inflammatory drugs) which works by reducing hormones that cause inflammation and pain in the body. It blocks the COX-1 enzyme resulting into disruption of production of prostaglandins. The drug and excipient compatibility study was performed by FT-IR and study revealed that there was no interaction between drug and excipient. The various parameters of evaluation like drug content, entrapment efficiency, vesicle physical analysis, in-vitro drug release studies was performed. The concept of formulating targeted drug delivery of Piroxicamniosome offers a suitable and practical approach in serving desirably to target site.

KEYWORDS: *Piroxicam, Noisome, Transdermal gel.*

INTODUCTION

In recent years, vesicles have become the vehicle of choice in drug delivery. Lipid vesicles were found to be of value in immunology, membrane biology, diagnostic techniques, and most recently, genetic engineering. Vesicles can play a major role in modeling biological membranes, and in the transport and targeting of active agents. Encapsulation of a drug in vesicular structures can be predicted to prolong the existence of the drug in systemic circulation and perhaps, reduces the toxicity if selective uptake can be achieved. The phagocytic uptake of the systemic delivery of the drug loaded vesicular delivery system provides an efficient method for delivery of drug directly to the site of infection, leading to reduction of drug toxicity with no adverse effects. Vesicular drug delivery reduces the cost of therapy by improved bioavailability of medication, especially in case of poorly soluble drugs. They can incorporate both hydrophilic and lipophilic drugs. These systems delay drug elimination of rapidly metabolizing drugs and function as sustained release systems and solve the problems of drug insolubility, instability and rapid degradation. Consequently, a number of vesicular delivery systems such as liposomes, transferosomes, pharmacosomes, niosomes/proniosomes etc, were developed [1-3].

From early 1980s, niosomes have gained wide attention by researchers for their use as drug targeting agents, drug carriers to have variety of merits while avoiding demerits associated with the conventional form of drugs. Niosomes were studied as better alternatives to liposomes for entrapping both hydrophilic and hydrophobic drugs. From a technical point of view, niosomes are promising drug carriers as they possess greater chemical stability and lack of many disadvantages associated with liposomessuch as high cost and the variable purity problems of phospholipids. The additional merits with niosomes are low toxicity due to non-ionic nature, no requirement of special precautions and conditions for formulation and preparation. Moreover it is the simple method for the routine and large-scale production of niosomes without the use of unacceptable solvents. However, stability is a prime concern in the development of any formulation and even though, niosomes have shown advantages as drug carriers, such as being low cost and chemically stable as compared to liposomes. They too, are associated with problems related to physical stability, such as fusion, aggregation, sedimentation, and leakage on storage. Proniosomal concept minimizes these problems [4, 5].

Proniosomes are dry formulation of water-soluble carrier particles that are coated with surfactant and can be measured out as needed and dehydrated to form niosomal dispersion immediately before use on brief agitation in hot aqueous media within minutes the resulting niosomes are very similar to conventional niosomes and more uniform in size. The proniosome approach minimizes these problems by using dry, free-flowing product, which is more stable during sterilization and storage. Ease of transfer, distribution, measuring, and storage make proniosomes a versatile delivery system with potential for use with a wide range of active compounds. In general a limited number of studies are available which deal with the preparation and evaluation of proniosomes. Proniosomes are dry formulations of surfactant-coated carrier, which can be measured out as needed and rehydrated by brief agitation in hot water. These "proniosomes" minimize problems of niosomes physical stability such as aggregation, fusion and leaking and provided additional convenience in transportation, distribution, storage and dosing. Proniosome-derived niosomes are superior to conventional niosomes in convenience of storage, transport and dosing. Stability of dry proniosomes is expected to be more stable than a pre-manufactured niosomal formulation. In release studies proniosomes appear to be equivalent to conventional niosomes. Size distributions of proniosome-derived niosomes are somewhat better that those of conventional niosomes so the release performance in more critical cases turns out to be superior. Proniosomes are dry powder, which makes further processing and packaging possible. The powder form provides optimal flexibility, unit dosing, in which the proniosome powder is provided in capsule could be beneficial. A proniosome formulation based on maltodextrin was recently developed that has potential applications in deliver of hydrophobic or amphiphilic drugs. The better of these formulations used a hollow particle with exceptionally high surface area. The principal advantage with this formulation was the amount of

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carrier required to support the surfactant could be easily adjusted and proniosomes with very high mass ratios of surfactant to carrier could be prepared. Because of the ease of production of proniosomes using the maltodextrin by slurry method, hydration of surfactant from proniosomes of a wide range of compositions can be studied [6].

Advantages of proniosomes over the niosomes:

1. Avoiding problem of physical stability like aggregation, fusion, leaking.
2. Avoiding hydrolysis of encapsulated drugs which limiting the shelf life of the dispersion.

Disadvantages of Niosomes:

1. Physical instability
2. Aggregation
3. Fusion
4. Leaking of entrapped drug
5. Hydrolysis of encapsulated drugs which limiting the shelf life of the dispersion

To overcome these Disadvantages, proniosomes are prepared and reconstituted into niosomes**.**

Proniosomes:

Proniosomes are dry formulation of water soluble carrier particles that are coated with surfactant and can be measured out as needed and dehydrated to form niosomal dispersion immediately before use on brief agitation in hot aqueous media within minutes. The resulting niosomes are very similar to conventional niosomes and more uniform in size. The proniosome approach minimizes problems associated with the liposome and niosomes by using dry, free-flowing product, which is more stable during sterilization and storage. Ease of transfer, distribution, measuring, and storage make proniosomes a versatile delivery system with potential for use with a wide range of active compounds. In general a limited number of studies are available which deal with the preparation and evaluation of proniosomes [7, 8].

Preparation of Proniosomes:

There are number of components present in proniosomes with non-ionic surfactants and cholesterol, lecithin being the main ingredient. Desirable characteristics of the selected carrier that could be used in the preparation of proniosomes includes safety and non-toxicity, free flow ability, poor solubility in the loaded mixture solution and good water solubility for ease of hydration. Different carriers and non-ionic surfactants and membrane stabilizers used for the proniosome preparation are shown in table 1. Three different methods were reported for the preparation of proniosomes.

Slurry method:

Carrier material 10 g is added to a 250-ml round-bottom flask and the entire volume of surfactant solution (14.5 ml) was added directly to the flask to form slurry. If the surfactant solution volume is less, then additional amount of organic solvent can be added to get slurry. The flask was attached to the rotary evaporator and vacuum was applied until the powder appeared to be dry and free flowing. The flask was removed from the evaporator and kept under vacuum overnight. Proniosome powder was stored in sealed containers at 4°C. The time required to produce proniosomes is independent of the ratio of surfactant solution to carrier material and appears to be scalable [9].

Coacervation phase separation method:

This method is widely adopted to prepare proniosomal gel. Precisely weighed amounts of surfactant, lipid and drug are taken in a clean and dry wide mouthed glass vial of 5.0 ml capacity and alcohol (0.5 ml) is added to it. After warming, all the ingredients are mixed well with a glass rod; the open end of the glass bottle is covered with a lid to prevent the loss of solvent from it and warmed over water bath at 60-70°C for about 5 min until the surfactant mixture is dissolved completely. Then the aqueous phase (0.1% glycerol solution) is added and warmed on a water bath till a clear solution was formed which is then converted into proniosomal gel on cooling.

Slow spray-coating method:

This method involves preparation of proniosomes by spraying surfactant in organic solvent onto carrier material and then evaporating the solvent. Because the carrier is soluble in the organic solvent, it is necessary to repeat the process until the desired surfactant loading has been achieved. The surfactant coating on the carrier is very thin and hydration of this coating allows multilamellar vesicles to form as the carrier dissolves. The resulting niosomes are very similar to those produced by conventional methods and the size distribution is more uniform. It is suggested that this formulation could provide a suitable method for formulating hydrophobic drugs in a lipid suspension without concerns over instability of the suspension or susceptibility of the active ingredient to hydrolysis [10, 11].

MATERIALS AND METHODS

Piroxicam, Tween 20,40 & 80, Span 20,40,60 & 80, Cholesterol, Soya Lecithin, Absolute Ethanol, Methanol, Ultra-Pure Water.

Development of UV spectroscopic method:

Determination of absorption maxima:

Absorption maxima are the wavelength at which maximum absorption takes place. For accurate analytical work, it is important to determine the absorption maxima of the substance under study.

Procedure: For the preparation of calibration curve stock solution was prepared by dissolving 10mg of pure drug in volumetric flask containing 25ml of methanol and sonicated for 5 minutes and the volume was made up to 100ml with methanol. The working standard solution of Piroxicamwas prepared with suitable dilution of the stock solution as 10µg/ml solution .From this stock solution, pipette out 5 ml and subject for UV scanning in the range of 200 – 400 nm using double beam UV-VIS spectrophotometer, (Shimadzu double beam 3200, model Japan withwith UV probe software version-2.33). The absorption maxima were obtained at 334 nm with a characteristic peak (figure 1). The results are shown in table 4.

Preparation of calibration curve:

Using absorption maxima a standard curve was prepared in the concentration range of 50-300 µg/ml. Different volumes of standard stock solutions, containing 50-300 µg mL^{-1} of drug were transferred to 10ml volumetric flasks and volume was made up with methanol. The absorbance was measured at 334 nm against the corresponding reagent blank. The drug concentrations of Piroxicam were analyzed by UV-spectrophotometer at 334 nm (fig. 2).

Experimental Methods:

Preparation of Niosomes:

Niosomes were prepared by a method modified from Perrett et al., 1991. 0.1%w/w of Piroxicam with surfactant, lecithin, and cholesterol were mixed with 2.5ml absolute Ethanol in a wide mouth glass tube. The composition of additives is listed in Table 5. Then the open end of the glass tube was covered with aluminium foil and warmed in a water bath at 65 ± 3°C for 15 min. A 1.6ml; pH 7.4 phosphate buffer was added and still warmed on the water bath for about 5 min till the clear solution was observed. The mixture was allowed to cool down at room temperature till the dispersion was converted to niosomes gel. In case of formulations in which drug was not properly dissolved, the drug and formulation surfactants were dissolved in chloroform, followed by evaporation of solvent.

Table No. 1: Composition of various Niosome Formulations

Sl.No	Niosomes Code	Span 20 (mg)	Span 40 (mg)	Span 80 (mg)	Tween 60 (mg)	Tween 80 (mg)	Cholesterol (mg)	Lecithin (mg)	Absolute Ethanol (ml)	7.4pH Phosphate Buffer (ml)
1	PNG F1	180					20	180	2.5	1.6
2	PNG F2		180				20	180	2.5	1.6
3	PNG F3			180			20	180	2.5	1.6
4	PNG F4				180		20	180	2.5	1.6
5	PNG F5					180	20	180	2.5	1.6

Note: Drug Dose in all formulations is 10 mg

Preparation of Gel:

For the preparation of gels, Carbopol 941 was selected in various concentrations ranging from 0.5 %, 1% and 1.5% and after adding triethanolamine to the prepared carbopol dispersions, the carbopol gel with 1% concentration was found to be clear and good in appearance, hence it was optimized for loading the niosomes.

Characterization of Niosome:

FTIR studies:

The compatibility between pure drug and surfactants, cholesterol, lecithin was detected by FTIR spectra obtained on Bruker FTIR (Alpha T). The potassium bromide pellets were prepared on KBr press. To prepare the pellets the solid powder sample were ground together in a mortar with 100 times quantity of Kbr, the finely grounded powder was introduced into a stainless steel die. The powder was pressed in the die between polished steel anvils at a pressure of about 10t/in2. For liquid samples thin film of sample liquid is made on pellet. The spectra's were recorded over the wave number of 8000-1 to 500 cm -1.

Drug content:

Niosomes equivalent to 50 mg were taken into a standard volumetric flask. They were lysed with 25 ml of methanol by shaking for 15 min. The clear solution was diluted to 100 ml with methanol. Then 10 ml of this solution was diluted to 100 ml with saline phosphate buffer 7.4. Aliquots were withdrawn and the absorbance was measured at 267 nm and drug content was calculated from the calibration curve.

Entrapment efficiency:

Niosomes gel (0.5g) was reconstituted with 10 ml of pH 7.4 phosphate buffer in a glass tube. The aqueous suspension was sonicated in a sonicator bath (CITIZEN Digital Ultrasonicator CD-4820) for 30 min. The Piroxicam containing niosomes were separated from untrapped drug by centrifuging at 20,000 rpm at 20°C for 30 min (REMI Cooling Centrifuge TR-01). The supernatant was taken and diluted with methanol, and the Piroxicam concentration in the resulting solution was assayed by UV spectrophotometric method at 334 nm. The percentage of drug encapsulation was calculated by the following equation:

$$\text{Encapsulation Percentage (\%)} = [(Ct - Cf)/ Ct] \times 100$$

Where Ct is the concentration of total Piroxicam, and Cf is the concentration of free Piroxicam.

Vesicle physical analysis:

Particle size of Niosomes is very important characteristic. The surface morphology roundness, smoothness, and formation of aggregates and the size distribution of Niosomes were studied by Scanning Electron Microscopy (SEM). 1g of the proniosome gel in a glass tube was diluted with 10ml of ph 7.4 phosphate buffer. The niosomes were mounted on an aluminium stub using double-sided carbon adhesive tape. Then the vesicles were sputter-coated with gold palladium(Au/Pd) using a vacuum evaporator(Edwards) and examined using a scanning electron microscope JSM-5510(Jeol Ltd, Tokyo, Japan) equipped with digital camera, at 20kV accelerating voltage.

In vitro drug release studies:

The release of Piroxicam from niosomes formulations were determined using membrane diffusion technique. The niosomes formulation equivalent to 10 mg of Piroxicam was converted to niosomal suspension and taken on egg membrane and mounted on receptor compartment of franz diffusion cell which is filled with phosphate buffer pH 6.8 and the donor compartment was kept above the receptor compartment and the diffusion cell was placed on magnetic stirrer and intermittent sampling was done and the samples were analyzed in UV. The temperature of receptor medium maintained at 37±0.5^{0}C and the medium was agitated at 100 rpm speed using magnetic stirrer. Aliquots of 5ml sample were withdrawn periodically and after each withdrawal same volume of medium was replaced. The collected samples were analyzed at 334 nm in Double beam UV-VIS spectrophotometer using phosphate buffer 6.8 as blank. The in vitrodrug release was studied by using UV probe software version-2.33.

Release Kinetics:

The mathematical models are used to evaluate the kinetics and mechanism of drug release from the formulation. The model that best fits the release data is selected based on the correlation coefficient (r) value in various models. The model that gives high 'r' value is considered as the best fit of the release data.

The various mathematical models are as follows:

1) Zero order release model
2) First order release model
3) Hixson-Crowell release model
4) Weibull release model
5) Higuchi release model
6) Korsmeyer – Peppas release model

The mechanism of release for the optimized formulations was determined by finding the R^2 value for each kinetic model viz. Zero-order, First-order, Higuchi, and Korsmeyer-Peppas corresponding to the release data of formulations. For most of the formulations the R^2 value of Korsmeyer-Peppas and zero-order model is very near to 1 than the R^2 values of other kinetic models. Thus it can be said that the drug release follows Korsmeyer-Peppas and zero-order model mechanism.

The n values of Korsmeyer-Peppas model of the best formulations are in between 0.50-0.88. Therefore the most probable mechanism that the release patterns of the formulations followed was non-fickian diffusion or anomalous diffusion.

RESULTS AND DISCUSSION

Development of UV spectroscopic method:

Determination of absorption maxima:

Absorption maxima are the wavelength at which maximum absorption takes place. For accurate analytical work, it is important to determine the absorption maxima of the substance under study.

Procedure: For the preparation of calibration curve stock solution was prepared by dissolving 10mg of pure drug in volumetric flask containing 25ml of methanol and sonicated for 5 minutes and the volume was made up to 100ml with methanol. The working standard solution of Piroxicam was prepared with suitable dilution of the stock solution as 10µg/ml solution .From this stock solution, pipette out 5 ml and subject for UV scanning in the range of 200 – 400 nm using double beam UV-VIS spectrophotometer, (Shimadzu double beam 3200, model Japan withwith UV probe software version-2.33). The absorption maxima were obtained at 334 nm with a characteristic peak.

Preparation of calibration curve:

Using absorption maxima a standard curve was prepared in the concentration range of 50-300 μg/ml. Different volumes of standard stock solutions, containing 50-300 μg mL^{-1} of drug were transferred to 10ml volumetric flasks and volume was made up with methanol. The absorbance was measured at 334 nm against the corresponding reagent blank. The drug concentrations of Piroxicam were analyzed by UV-spectrophotometer at 334 nm

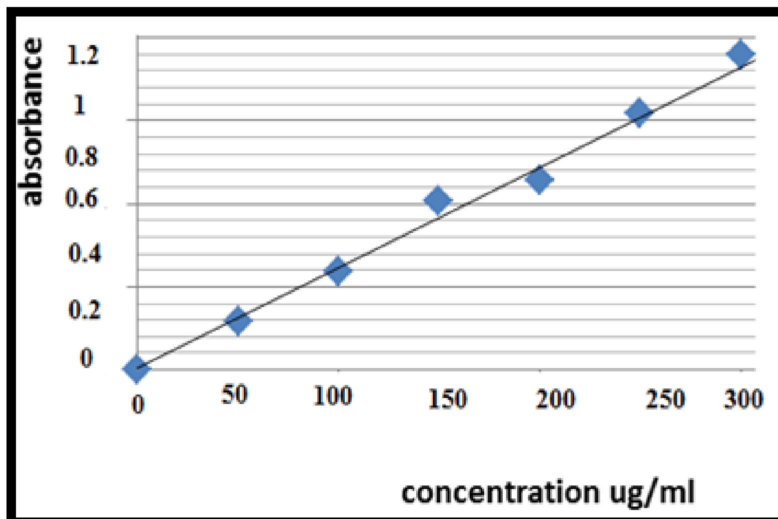

Fig. 1: Calibration curve of Piroxicam

Table No. 2: Optical Parameters

Parameters (Units)	Values of Piroxicam
λ max/ nm	334 nm
Linearity Range (μg/ml)	50-300
Molar Absorptivity(1/mol/cm)	$0.00284x10^3$
Correlation coefficient (r^2)	0.9996
Regression equation (y)	0.120x + 0.0047
Intercept, *c*	0.0047
Slope , *b*	0.120
LOD (μg/ml)	0.106
LOQ (μg/ml)	0.324
Sandell's sensitivity (Mg cm^{-2})	2.34×10^{-4}
Relative standard deviation %	0.169

Entrapment Efficiency:

Niosomes have generated interest as a topical formulation and to achieve the desirable therapeutic effect of niosomesas a drug carriers, they must be loaded with sufficient amount of active compound. Niosomes prepared with non-ionic surfactants of alkyl ester including span (sorbitan esters) and tween (polyoxyethylenesorbitan esters) were utilized to determine the encapsulation of associated Piroxicam and vesicle size. As shown in the Table , encapsulation efficiency of niosomes formed from formulation PNGF1, PNGF3, PNGF4, PNGF5 proniosome gel exhibit lower encapsulation efficiency when compared to PNGF2. The results of entrapment efficiency are shown in 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%, 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 No. 3: Encapsulation percentage of various Niosomal Gel Formulations

Sl. No	Niosomal code	Encapsulation percentage (%)
1.	PNG F1	23.84 ±1.4
2.	PNG F2	59.50 ±2.3
3.	PNG F3	23.84 ±1.6
4.	PNG F4	28.84 ±2.0
5.	PNG F5	17.24 ±1.9

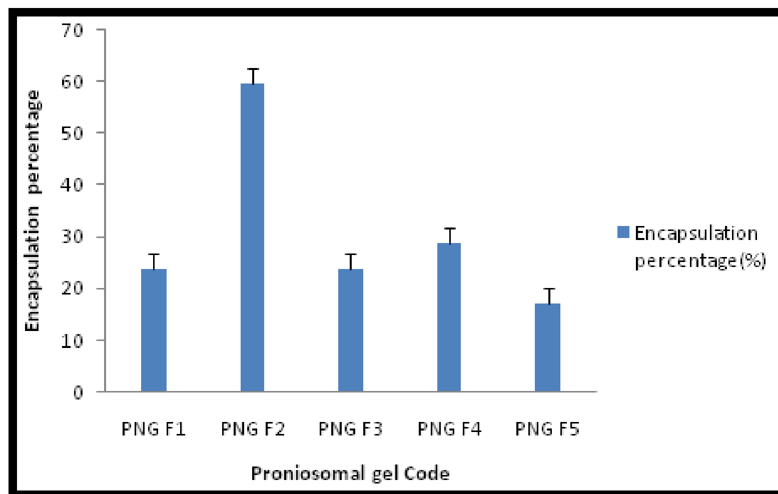

Fig. 2: Encapsulation percentage of various Niosomal Gel Formulations

Table No. 4: 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.	**A2**	2	1	10	20
2.	**A3**	1	2	10	20
3.	**A4**	3	1	10	20
4.	**A5**	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 encapsulation Percentage of different formulations of Span 40 are shown in the Fig. 5.

Table No. 5: Encapsulation percentage of different formulations

Sl. No	Niosomal code	Ratios		Encapsulation percentage (Percentage)
		SPAN 40	Lecithin	
1.	**A2**	2	1	65 ±1.9
2.	**A3**	1	2	57.4 ±1.6
3.	**A4**	3	1	61.2 ±2.1
4.	**A5**	1	3	57.2 ±1.5

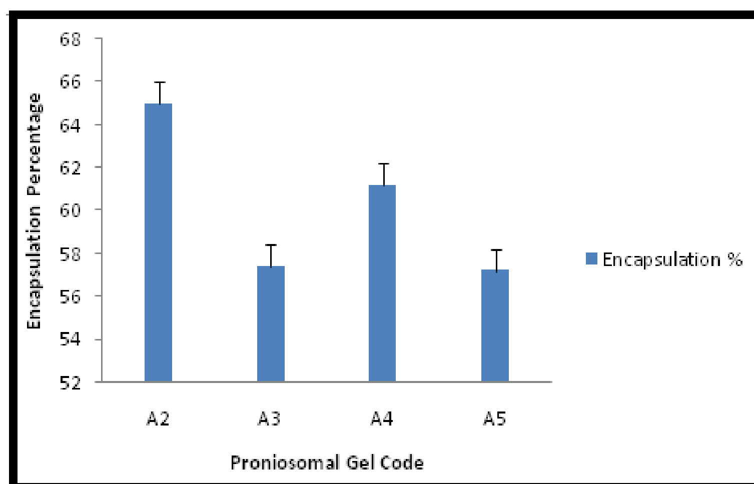

Fig. 3: Encapsulation percentage of different formulations

***In-vitro* Studies:**

Table No. 6: *In-Vitro* Release

S.No	Formulation	Cumulative % drug release
1	F1	76.01
2	F2	55.4
3	F3	55.5
4	F4	80.5
5	F5	69.8
6	F6	74.1
7	F7	60.5

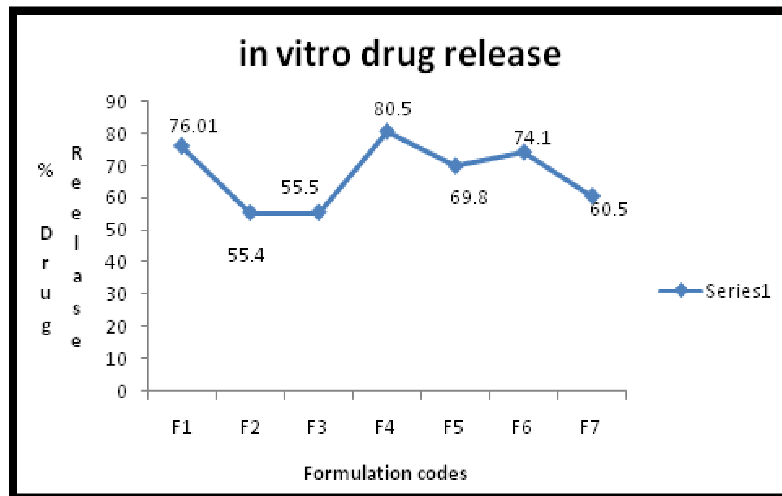

Fig. 4: In vitro drug release profile for Niosomal Gels

Table No. 7: Release kinetics of optimized formulations in *in-vitro* drug release

Sl.No	Formula	Zero Order	First Order	Hixson-Crowell(R^2)	Higuchi (R^2)	Korsmeyer-Peppas	
						(R^2)	N
1	A2	0.9764	0.6821	0.9153	0.7948	0.9762	0.6643
2	A3	0.9737	0.7518	0.9286	0.7878	0.9734	0.5341
3	A4	0.9822	0.6938	0.9262	0.8073	0.9823	0.6572
4	A5	0.9672	0.7736	0.9245	0.7756	0.9677	0.5758

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 A2, A3, A4 and A5 are shown in the Table 7.

Thus it is evident from the study that A3 and A5 formulation of PiroxicamNiosomal 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, KorsemayerPeppas, Hixon-Crowell. The release pattern was found to be Zero Order and the best fit model was found to be Korsemayer-Peppas with 'n' value between 0.45 to 0.89 suggesting that the drug was released by non-fickian release mechanism or anomalous transport.

CONCLUSION

Niosomal formulations can be conveniently prepared by using nonionic surfactants (span 40), cholesterol and lecithin at different concentrations. The Niosomal formulations prepared with span 40 showed a highest encapsulation of 59.50 ±2.3 when compared to formulations with other non-ionic surfactants. The average vesicle size for Niosomal Gel A2, A3, A4 and A5 formulations were found to be 13.70μ, 17.46μ, 18.84μ and 13.28μ respectively. The IR spectral analysis suggested that there is no interaction between the drug and formulation additive, the drug exists in original form and available for the biological action. The skin irritation (erythema) was evaluated after each application according to the scale depicted in Table 13 and it was observed that no erythema was seen in the exposed area of skin showing zero score. The dissolution parameters were studied by using Drug Kinetic Models for formulations and it shows Zero Order rate Reaction. The drug release from vesicles is dependent on concentrations of span 40, lecithin and Volume of Hydration in Niosomal formulations. The cumulative percentage drug release after the completion of *in vitro* drug release for Niosomal Gel A2, A3, A4 and A5 formulations were found to be 75.47%, 66.47%, 75.89% and 61.81% respectively. The cumulative percentage drug release after the completion of in vitro skin permeation for Niosomal Gel A2, A3, A4 and A5 formulations were found to be 56.64%, 57.64%, 55.47% and 59.39%respectively.

The drug release rate of various Niosomal Gel A2, A3, A4 and A5 formulations were found to be 0.1004, 0.0887, 0.1022 and 0.0821ug/cm2/h. The Flux of various Niosomal Gel A2, A3, A4 and A5 formulations were found to be 0.0739, 0.0795, 0.0792 and 0.0741 ug/cm2/h. The Percentage Drug Retained in the skin after completion of in vitro permeation experiments of various Niosomal Gel A2, A3, A4 and A5 formulations were found to be 31.12%, 27.34%, 36.205 and 38.56%.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, Korsemayer Peppas, Hixon-Crowell. The release pattern was found to be Zero Order and the best fit model was found to be Korsemayer-Peppas with 'n' value between 0.45 to 0.89 suggesting that

the drug was released by non-fickian release mechanism or anamolous transport. Thus it is evident from the study that A3 and A5 formulations of Piroxicam Niosomal gel showed good stability characteristics, prolonged release of entrapped drug.

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