FORMULATION AND EVALUATION OF NIOSOMAL GEL LOADED WITH PERMETHRIN FOR THE TREATMENT OF SCABIES

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Abstract:

In the present research work Niosomal gel was developed for an effective treatment of skin infection using Permethrin as model drug. Niosomes play an important role owing to their nonionic properties, in such drug delivery system. Design and development of novel drug delivery system (NDDS) has two prerequisites. First, it should deliver the drug in accordance with a predetermined rate and second it should release therapeutically effective amount of drug at the site of action. Conventional dosage forms are unable to meet these requisites. The main aim of development of niosomes is to control the release of drug in a sustained way, modification of distribution profile of drug and for targeting the drug to the specific body site.

Key words : lipid hydration method, film hydration method , nonionic surfactant, novel drug delivery system

Introduction

Human scabies is caused by the mite Sarcoptes scabei var. hominis,[1].The name Sarcoptes scabiei is derived from the Greek word “sarx” (fl esh) and “koptein” (to smite or to cut) and the Latin word “scabere” (to scratch) [2]. In the fall of 2018, oral ivermectin became available in Canada for the off-label treatment of scabies. The use of ivermectin in other jurisdictions has been a huge therapeutic advance for mass populations, institutional outbreaks, crusted scabies, resistant scabies, and those nonadherent to topicals[3]. scabies is under- recognised as a public health problem, despite generating a considerable global disease burden, affectingover 100 million people[4]. which is transmitted by skin-to-skin contact, infested clothing, and infested bedding[5]. Mites in the epidermis are resistant to water and soap, and continue viability even after daily hot baths[6].

Scabies and its complications are often regarded as disorders of resource-poor settings, and particularly affect young children The direct effect of scabies is debilitating itching, leading to scratching, which can result in complications due to bacterial infection of the skin (impetigo), predominantly by Staphylococcus aureus and Streptococcus pyogenes[7].

Niosomes are novel drug delivery systems in which the medication is encapsulated in a vesicle. The vesicle is composed of a bilayer of non-ionic surface active agent and hence the name niosomes. The niosomes are very small, and microscopic in size. Their size lies in the nano metric scale. Although structurally similar to liposomes, they offer several advantages over them. Niosomes have been shown to greatly increase transdermal drug delivery and also can be used in targeted drug delivery. These structures can provide new methods for drug delivery[8]. Niosomes are formations of vesicles by hydrating mixture of cholesterol and nonionic surfactants. These vesicles are called niosomes. These are formed by self-assembly of non-ionic surfactants in aqueous media as spherical, unilamellar, multilamellar system and polyhedral structures in addition to inverse structures which appear only in non-aqueous solvent. Niosomes and liposomes are active in drug delivery potential and both increase drug efficacy as compared with that of free drug. Niosomes are preferred over liposomes because the former exhibit high chemical stability and economy. These types of vesicles were first reported in the cosmetic industries. Nonionic surfactants used in formation of niosomes are polyglyceryl alkyl ether, glucosyl dialkyl ether, crown ether, polyoxyethylenealkyl ether, ester-linked surfactants, and steroid-linked surfactants and spans, and tweens series. Niosomes preparation is affected by processes variables, nature of surfactants, and presence of membrane additives and nature of drug to be encapsulated[9].

Types of niosomal systems

Small unilamellar vesicles (SUV, size 0.025-0.05 μm) are commonly produced by sonication and French Press procedures. Ultrasonic electro capillary emulsification or solvent dilution techniques can be used to prepare SUVs[11].

Multilamellar vesicles (MLV, size >0.05 μm) exhibit increased-trapped volume and equilibrium solute distribution, and require hand-shaking method. They show variations in lipid compositions.[12]

Large unilamellar vesicles (LUV, size >0.10 μm), the injections of lipids solubilized in an organic solvent into an aqueous buffer, can result in spontaneous formation of LUV. But the better method of preparation of LUV is Reverse phase evaporation, or by Detergent solubilization method[13]

Materials and Method

List of chemical used

Table 1 : List of chemicals

Sr. no	Name	Type
	Permethrin	Loba Chemie, Mumbai
	Span 60	Otto Chemie, Mumbai
	Cholesterol	Zeiss Pharma Ltd
	Chloroform	Shree Pharma International
	Dimethyl Formamide	Wagle Industrial Estate, Thane, Maharashtra
	Glycerol	Alpha chemika
	Carbopol 934	Hexon Laboratories Private Ltd., Nashik
	DMSO	Nice Chemicals Pvt Ltd., Cochin
	Phosphate buffer	Matangi Industries,Gujarat
.	Triethanolamine	Thermo Fisher Scientific India Pvt.Ltd., Mumbai
.	Methanol	Zeiss Pharma Ltd
.	Ethanol	Zeiss Pharma Ltd

List of Equipments used

Table 2 : List of equipments

S.No	**Instruments**	**Manufacturer**
	Digital Weighing Balance	Shimadzu, Japan
	UV/VIS Spectrophotometer	Shimadzu, Japan
	Magnetic Stirrer	Remi Equipments, Mumbai
	Melting Point Apparatus	Remi Equipments, Mumbai
	pH Meter	Ohaus, USA
	Infrared Spectrophotometer (FTIR)	Perkin Elmer, Germany
	Franz Diffusion cell assembly	Orchid Scientific, Mumbai
	Water bath	Sunshine Scientific Equipments
	Brookfield Digital Viscometer	Dolphi0n Pharmacy Instruments Pvt.Ltd., Mumbai

Formulation

Formulation of niosomes:

Niosomes were prepared by a thin film hydration method using a lipid mixture consisting of surfactant (span 40, span 60 and tween 60) and CHO, at different specified ratios. Surfactant, CHO and drug were dissolved in 10 ml of chloroform. The lipid mixture was then transferred to a 100 ml round bottom flask, and the solvent was evaporated under reduced pressure at a temperature of 55-65°C, using a rotary flash evaporator until the formation of a thin lipid film. The formed film was hydrated with 20 ml of Phosphate buffer saline pH 7.4. The hydration was continued for 1 h, while the flask was kept rotating at 55-65°C in the rotary evaporator. The hydrated niosomes were sonicated for 20 min using a bath sonicator to obtain niosomal dispersion containing both free and entrapped drugs of varying size[14]

Formulation of Niosomal gel

Promising niosomal gel (formulation prepared by thin hydration film method containing span 60 as surfactant (TNS_4) Formulations of niosomes prepared using span 60 containing Permethrin equivalent to 2 % w/w was incorporated into the gel base composed of Carbopol 934 (150 mg), glycerol (250 mg) Triethanolamine (quantity sufficient) and distilled water up to 15 g.

EVALUATION

Evaluation of parameters of Niosome formulations

Drug entrapment efficiency:

The drug entrapment efficiency of formulated niosomes was estimated by separating the niosomes by ultracentrifugation at 10000 rpm for 30 min. the sum of free permethrin in the supernatant was calculated by UV spectrophotometer at 232nm. The drug loading efficiency in the prepared niosomes was calculated by the following formula:

Entrapment efficiency (%) = Tp-Tf/Tp x100

Where, Tp = Total amount drug, Tf =free drug

Particle size:

The niosomes samples were suspended in Milli-Q water and screened for particle size at 25ºC by Zetasizer (Nano-ZS90, Malvern Instruments, UK). The disposable cuvettes were used for sample analysis. The results were reported as the mean ± standard deviation for tree replicates[15]

Polydispersity Index:

The niosomes samples were suspended in Milli-Q water and screened for PDI at 25ºC by Zetasizer (Nano-ZS90, Malvern Instruments, UK). The disposable cuvettes were used for sample analysis. The results were reported as the mean ± standard deviation for tree replicates[16]

Zeta Potential:

The niosomes samples were suspended in Milli-Q water and screened for zeta potential at 25ºC by Zetasizer (Nano-ZS90, Malvern Instruments, UK). The disposable cuvettes were used for sample analysis. The results were reported as the mean ± standard deviation for tree replicates[17]

Scanning Electron Microscope(SEM) :

Scanning electron microscope is used to attain scanning electron micrographs of permethrin containing niosomes. The instrument used for this purpose is Hitachi S-4800scanning electron microscope. The microsphere were assembled directly on the SEM sample stub, using double sided sticking tape, and coated with gold film (thickness 200nm) under reduced pressure (0.001 torr)[18]

Evaluation parameters of niosomal Gel formulations

Physical appearance

The prepared niosomal gel formulations were inspected visually for their color, homogeneity, consistency, grittiness and phase separation.

Determination

1g of gel was accurately weighed and dispersed in 100ml of distilled water. The pH of dispersion was measured by using digital pH meter.

Rheological studies

Brookfield digital viscometer was used to measure the viscosity (in cps) of the prepared niosomal gel formulation. The spindle number 62 was rotated at 50rpm for the viscosity measurement. The viscosity of the formulated batches was determined using a cone and plate viscometer with spindle 7(Brookfield engineering Laboratories). The assembly was connected to a thermostatically controlled circulating water bath maintained at 25^{o} C. The formulation whose viscosity was to be determined was added to a beaker covered with thermometer jacket. Spindle was allowed to move freely into the niosomal gel. And reading was noted[19].

Spreadability

Spreadabilty of the formulation was determined by using an apparatus designed and developed in the laboratory especially for the project and diagram of the apparatus. Two rectangular glass plates of standard dimension were selected. 500mg of the sample was placed on one of the glass plate. Second plate was placed over the other one to sandwich sample between plates. A 20gm weight was placed on the top of upper plate to provide a uniform thin film of the sample between the plates. Weight was removed excess of the of the gel sample was scrapped off from the edges. The top plate was then subjected to pull by using string to which 50gm weight was applied. The time required by the upper plate to travel a distance of 6cm and separate from the lower plate was noted. A shorter interval indicated better spreadability. Experiment was repeated and averages of three attempts were calculated for each formulation using formula[20]

Spreadability= (M×L) /T

M= weight tied to upper side

L = length of the glass slide

T= time in second

Extrudability

The development formulations were filled in collapsible metal tubes and crimped at one end. After removing the cap tube is pressed to extrude the product from the tube[21]

Drug content

Drug content of the niosomal gel was determined by dissolving an accurately weighed quantity of 1 g gel in about 100ml of methanol. 2ml of this solution was diluted to 10ml with

methanol solutions were then filtered and spectrophotometrically analyzed for drug content at 285nm. Drug content was determined from the standard curve of permethrin[22]

In Vitro drug release of nioosomal gel formulations loaded with permethrin

The in Vitro drug release studies were carried out using a modified Franz diffusion (FD) cell. The formulation was applied on dialysis membrane which was placed between donor and receptor compartment of the FD cell. Phosphate buffer pH 7.4 was used as a dissolution media. The temperature of the cell was maintained at 37º C by circulating water jacket. This whole assembly was kept on a magnetic stirrer and the solution was stirred continuously using a magnetic bead. A similar blank set was run simultaneously as a control. Sample (5ml) was withdrawn at suitable time intervals and replaced with equal amount of fresh dissolution media. Samples were analyzed spectrophotometrically at 285nm and the cumulative % drug release was calculated. The difference between the reading of drug release and control was used as the actual reading in each case

In vitro release kinetics of niosomal gel formulations

Zero- order kinetics

Following this profile, prescription dosage formulation emits the same volume of medication per unit of time, rendering it the perfect type of drug release for achieving pharmacologically extended operation. This model can be represented in a simple way using the following relation:

$$\boxed{Qt = Qo + Kot}$$

Where Q_t is the amount of drug dissolved in time t, Q_o is the initial amount of drug in the solution (most time, $Q_o = 0$) and K_o is the zero order release constant.

First- order kinetics

The following relation expresses this model:

$$\boxed{\log Qt = \log Qo + \frac{k1t}{2.303}}$$

Where Q_o is the amount of drug dissolved in time t, Q_o is the initial amount of drug in the solution and K1 is the zero order release constant.

A graph of the decimal logarithm of the drug's published number Vs time would be linear as a result. Pharmaceutical dosage formulations that adopt this dissolution profile, such as those containing water- soluble drugs in porous matrices, release medication proportionally to the amount of drug remaining in their interior, resulting in a reduction in the amount of drug released per unit of time.

Higuchi model

Higuchi devised a number of experimental models to investigate the release of water- soluble and low- soluble drugs in semi-solid and solid matrixes. For drug particles scattered in a uniform matrix acting as diffusion media, mathematical expressions were obtained.

The simplified Higuchi model is expressed as:

$$\boxed{Q = KH.t1/2}$$

The amount of drug release in time t is Q, and Higuchi dissolution constant is KH. The Higuchi model depicts drug release as a square root time dependent diffusion mechanism

based on Fick's law. This association can be used to explain the degradation of water- soluble medications from a number a modified released prescription dosage formulation, such as transdermal systems and matrix tablets.

Korsmeyer- Peppas model

Korsmeyer et al. used a simple empirical equation to describe general solute release behavior from controlled release polymer matrixes:

$$\frac{Mt}{M\infty} = at^n$$

Where, $M_t/M\infty$ is fraction of drug released is a kinetic constant, t is release time and n is the diffusional exponent for drug release. 'n' is the slope value of log $M_t/M\infty$ versus log time curve. Regardless of the release process, Peppas stated that the above equation could accurately explain the release of solutes from slabs, spheres cylinders and disks. Peppas used this n value in order to characterize different release mechanism, concluding for values for slab, of n= 0.5 for Fickian diffusion and higher values of n, between 0.5 and 0.1, or n= 1.0, for mass transfer following a non- Fickian model. In case of a cylinder n= 0.45 instead of 0.5 and 0.89 instead of 0.1. this equation can only be used in systems with a drug diffusion coefficient fairly concentration independent. To the determination of the exponent n the portion of the release curve where $M_t/M\infty < 0.6$ should only be used. To use this equation, the release must be one- dimensional and the device width – thickness or length- thickness relationship must be at least ten. To account for the lag time (1) at the start of drug release from the pharmaceutical dosage type, a modified version of this equation was developed:

$$\frac{Mt}{M\infty} = a(t-l)n$$

When there is the possibility of a burst effect, b, this equation become:

$$\frac{Mt}{M\infty} = at^n + b$$

The 1 and b values would be zero if there was no lag time or burst effect, and only atn would be used. This statistical model, also known as power Law has been used to explain the release of a number of prescription adjusted release dosage types on a daily basis[23]

Stability studies

The main objective of stability testing is to give evidence on the changes of quality of drug product with respect to time under the influence of various environmental factors such as temperature, humidity, and light and enables recommended storage conditions; re-test periods and shelf lives to be accomplished. According to the ICH guidelines the formulation was kept for accelerated stability for six months. Microspheres were kept in stability chamber maintained at temperature of $40^oC \pm 2^oC$/75% RH$\pm$5% RH. During the study period, the formulation was monitored at prearranged time intervals of 0, 15, 30, 45, 60, 75, 90, 180 days for change in physical appearance, drug content, in vitro studies[24].

RESULT AND DISCUSSION

FORMULATION

Table 3 : Composition of Permethrin loaded Niosomes formulations.

S.no	Formulation code	Drug (g)	Span 60 (g)	Cholestrol (g)	Methanol (ml)
1	N1	40	640	40	80
2	N2	40	600	80	80
3	N3	40	560	120	80
4	N4	40	520	160	80
5	N5	40	480	200	80
6	N6	40	440	240	80

Formulation of niosomal gel

Table 4 : Composition of Niosomal gel Loaded with Permethrin formulations

S no	Formulation code	Carbopol 934 (g)	Distilled water (ml)	Triethanolamine (ml)
1	NG1	8	800	q.s
2	NG2	12	800	q.s
3	NG3	16	800	q.s
4	NG4	20	800	q.s
5	NG5	24	800	q.s
6	NG6	28	800	q.s

Evaluation of Niosomal formulations

Vesicle size

Table 5 : Vesicle Size of Different Niosomal formulations

S.No.	FormulationCode	Vesicle Size(nm)
1	N1	467.4±1.74
2	N2	295.0±.1.50
3	N3	398.5±2.21
4	N4	259.0±1.94
5	N5	480.4±1.18
6	N6	318.4±2.32

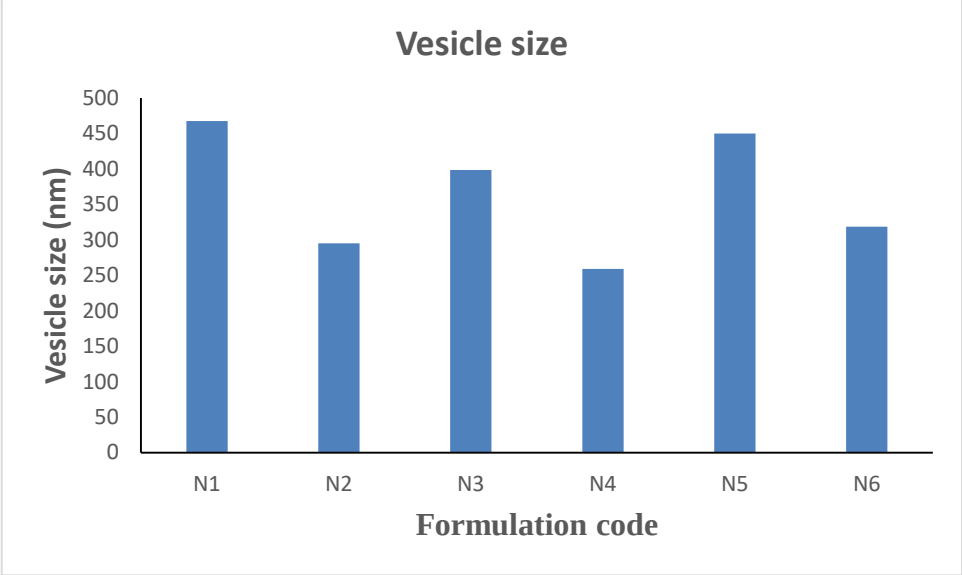

Fig 1 : vesicle size of different niosomal formulations

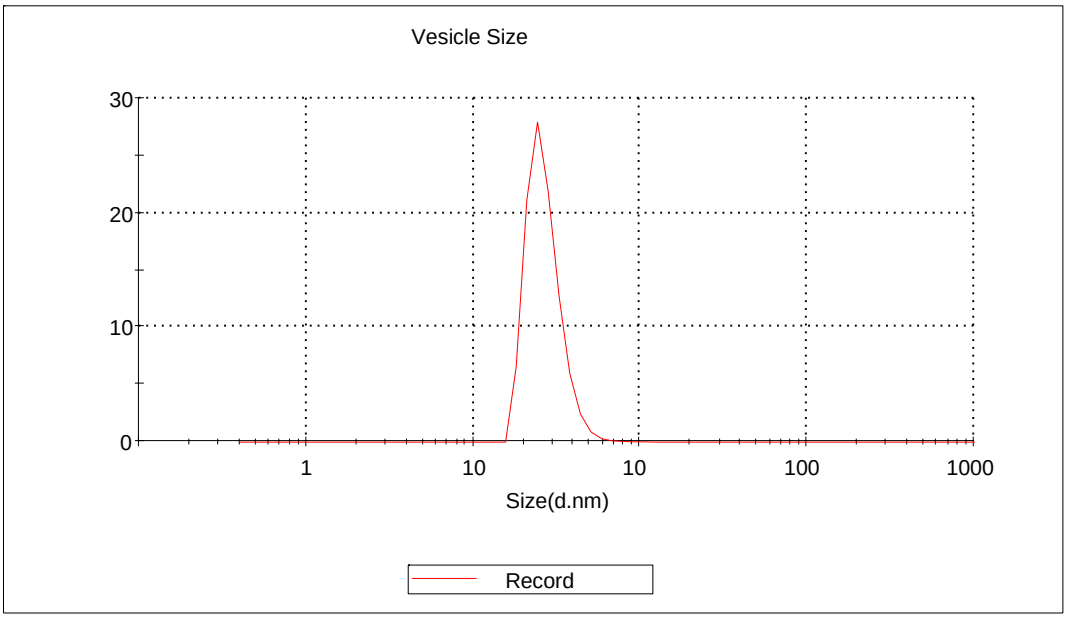

Figure 2 : Vesicle size distribution of N-4 formulation

Discussion:

The smaller vesicle size in N4 259.0±1.94 could be due to optimal preparation condition, such as prolonged or adequate sonication time ensures the breakdown of larger vesicles smaller ones. Were shown in table 5.22 and figure 5.16and The use of unsaturated fatty acids or a lower concentration of lipids can helps form smaller vesicles. Optimal hydration conditions can produce more uniform and smaller vesicles. In contrast, the larger vesicles size in N1 467.4±1.74 and N5 480.4 ±1.18 could of be due to suboptimal preparation condition, such as unappropriate sonication time, higher concentration of lipids can result in the formation of larger vesicles. Suboptimal hydration conditions can affect vesicle size, leading to larger vesicles.

The best Vesicle size was found in N4 259±1.94 smaller vesicle sizes can enhances drug delivery efficiency, cellular uptake, and stability. Smaller vesicles tend to be more stable, reducing the likelihood of aggregation

Entrapment Efficiency

Table 6: Percentage Entrapment efficiency of Niosomes

S.No.	Formulation Code	(%)Entrapment efficiency
1	**N1**	46.32±0.27
2	**N2**	63.81±0.32
3	**N3**	54.55±0.48
4	**N4**	83.59±0.78
5	**N5**	45.20±0.67
6	**N6**	69.56±0.71

Mean±SD,n=3

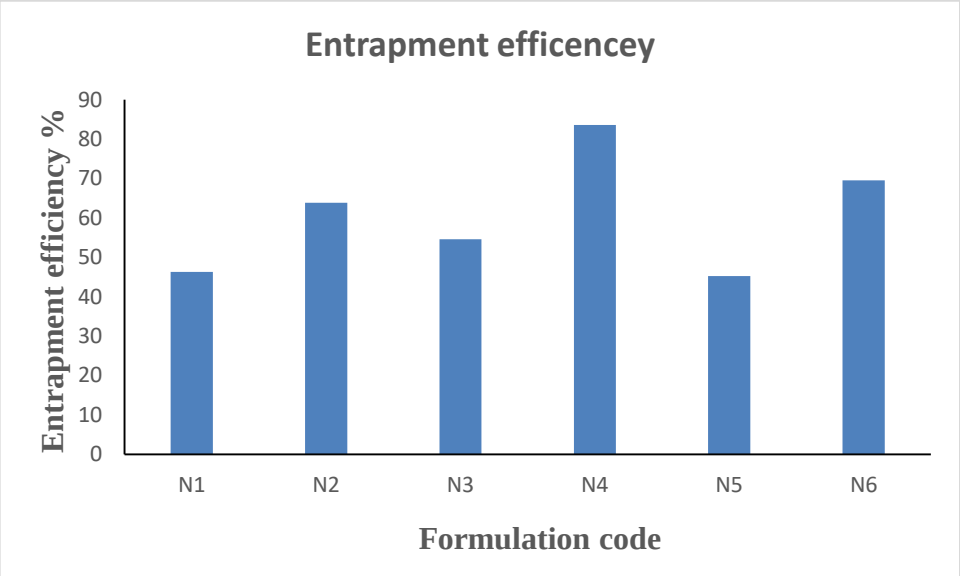

Figure 3 : Entrapment efficiency of different niosomal formulations

Discussion:

The Entrapment efficiency of all formulations N1, N2, N3, N4, N5, N6 was found to 46.32±0.27, 63.81±0.32, 54.55±0.48, 83.59±0.78, 45.20±0.67, 69.56±0.71 were shown in Table 5.23 and figure 5.18 The higher efficiencies observed in formulation like N-4 83.59±0.78 and could be attributed to ideal lipid composition and preparation method that promote effective drug encapsulation. Due to low stirring speed, high drug polymer interaction, low solubility of drug in continous phase, low concentration of emulsifier leads to high entrapment efficiencies. Conversely, formulation N-1 46.32±0.27 and N-5 45.20.56±0.67 shows lower efficiencies because of high stirring speed, low drug polymer interaction, high solubility of drug in continous phase, high concentration of emulsifier leads to low entrapment efficiencies.

The best entrapment efficiency of N-4 shows best result in entrapment efficiency with range of 83.59±0.78 .

Polydispersity Index:

Table 7 : Polydispersity Index of Niosomes

S.No	Formulation code	Polydispersity Index
	N1	0.22±0.01
	N2	0.24±0.23
	N3	0.20±0.33
	N4	0.18±0.34
	N5	0.21±0.25
	N6	0.27±0.54

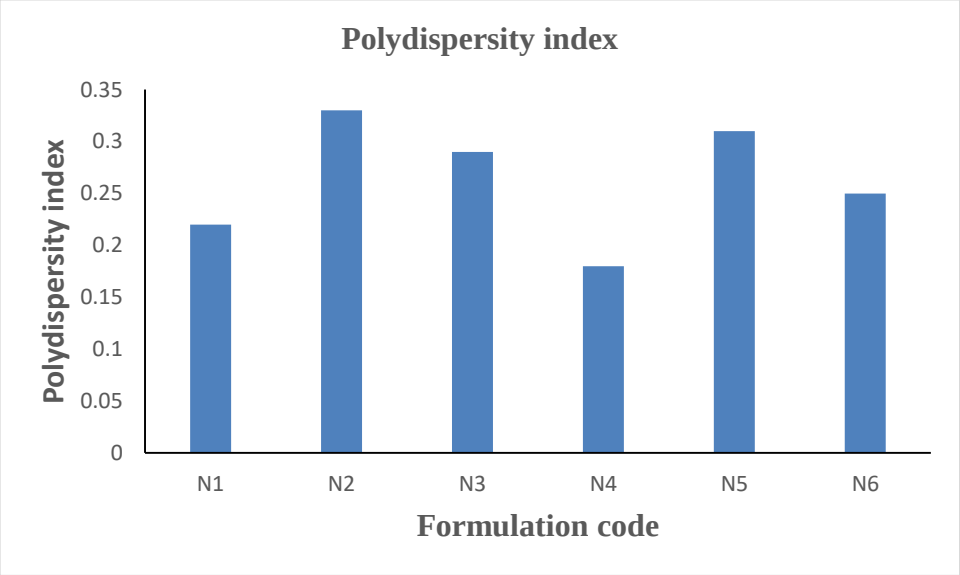

Fig : Polydispersity index of different niosomal formulations

Discussion:

The PDI value of all N1, N2, N3, N4, N5, and N6 was found to be 0.22, 0.33, 0.29, 0.18, 0.31, 0.25 were shown in Table 5.24 and Figure 5.19. The PDI of N 2 0.33±0.02 and N 5 0.31±0.04 indicates wider size disrtibution, suggesting more variability in particles size. Potentially less stable and reproducible. The polydispersity index of N 4 0.18±0.01 is due to ideal method by controlled mixing methods can leads to a more uniform distribution of vesicles size, using high-purity and consistent raw materials can reduce variability in particle formation, concentration of surfactants used can impact the uniformity of vesicle formation leads to lowering the PDI.

The best PDI was found in N 4 0.18±0.01 due to its more uniform particle size distribution, which contributes to better stability and reproducibility**.**

Zeta Potential

Table 8 : Zeta Potential of Niosomes

S.No.	FormulationCode	Zeta Potential(mV)
1	N1	-29.2±1.8
2	N2	-27.6±0.7
3	N3	-29.5±0.4
4	N4	-32.8±1.5
5	N5	-30.5±0.4
6	N6	-28.7±0.5

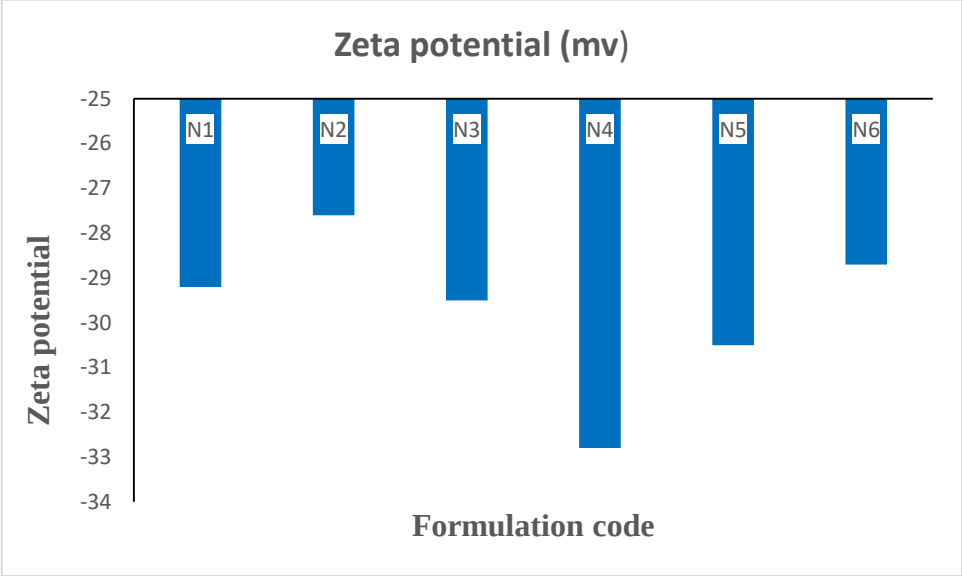

Fig 4 : Zeta potential of different niosomal formulation

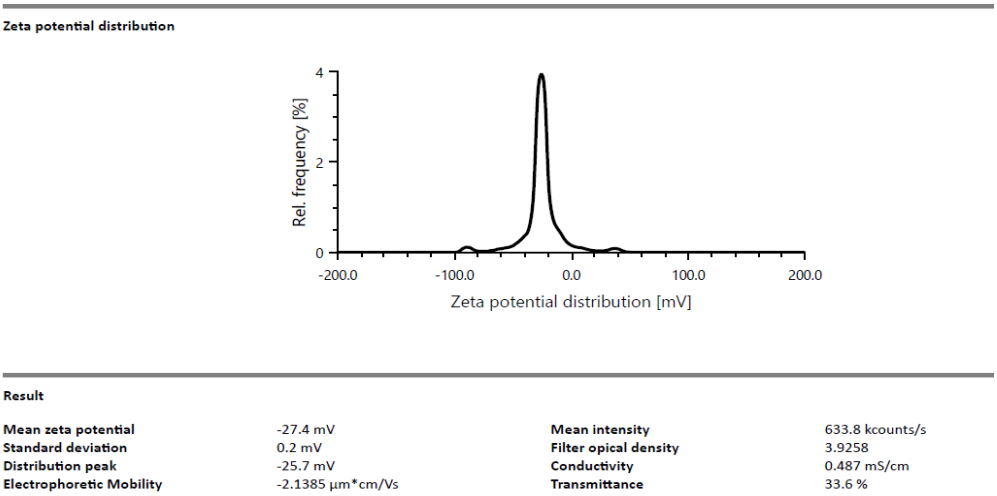

Figure 5 : Graph represents the zeta potential of the N-4 formulation

Discussion: Table5.25 , Figure 5.20 demonstrated high zeta potential of N4 -32.8±1.5 is likely due to a optimal values such as lipid composition, inclusion of charged molecules, the pH and iconic strength of the dispersion medium, presence of stabilizing agent, and the preparation methods used. The type and concentration of lipids used in N5 might leads to a higher surface charge density. In contrast, while other formulations shows low zeta potential such as in is likely due to suboptimal values such as N1-29.2±1.8, N2 -27.6±0.7, N3 -29.5±0.4, N4-32.8±1.5, N5 -30.5±0.4 N6 -28.7±0.5 lipid composition, use of weakly charged lipids, presence of impurities, particle aggregations and suboptimal preparation methods.

The best zeta potential was in the N4 -32.8±1.5 ensures better colloidal stability, reduces risk of aggregation, and contributes to improved performance and longer shelf life of the formulation.

Morphological Characterization of Niosomes

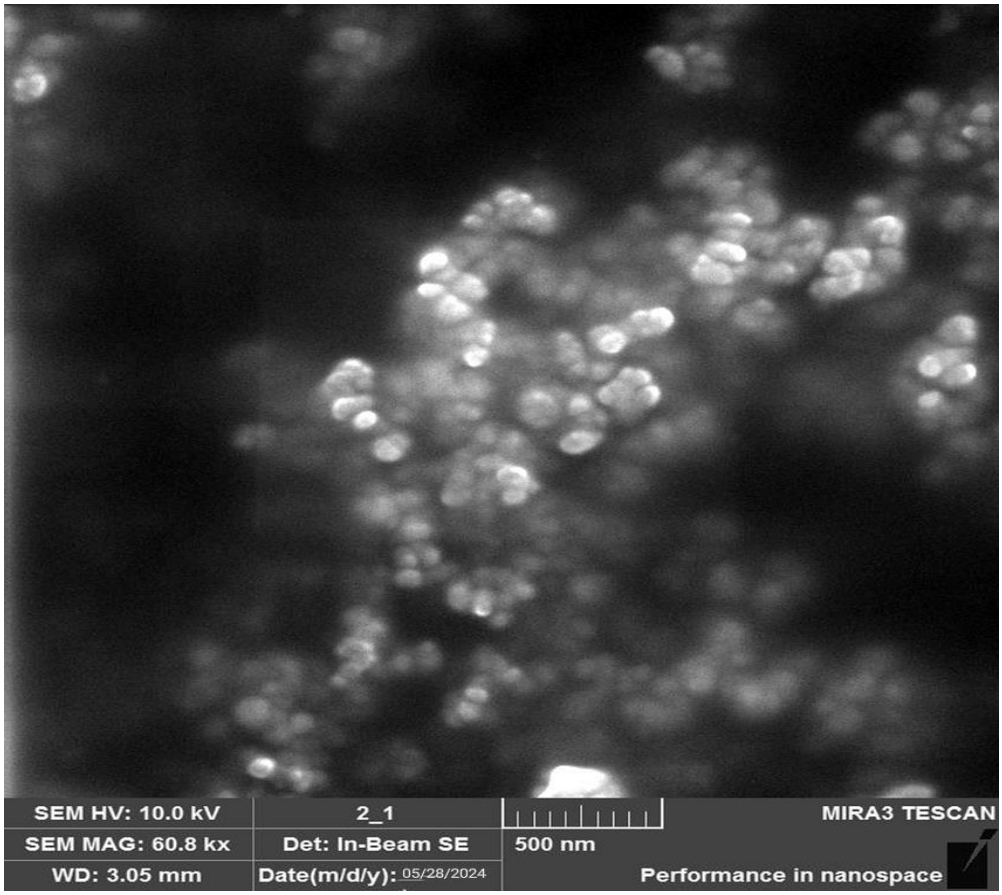

Figure 6 : Scanning electron microscopy photograph of N2

Discussion:

The N 4 likely contain an ideal mix of lipids that favors the formation of spherical vesicles. The preparation methods for N 6 is probably designed to produce and maintain spherical shape were shown in Figure 522 . The high zeta potential of N 4 results in strong repulsive force, reducing aggregation and helping maintain a spherical shape. While, the other formulations like N 1, N 3, N 5 likely contain an inferior mix of lipids that favors rod like structures. Variation in preparation conditions such as temperature, hydration rate, or lack of sufficient shear forces could lead to rod like structures. Lower zeta potential results in weak

repulsive forces , leading to more aggregation and less control over shapes. Hence, The Best Representation of scanning electron microcopy was found in N 4 which shows proper spherical shape and less aggregation of particles.

EVALUATION OF NIOSOMAL GEL

PHSICAL APPEARANCE

Table 9 : Physical appearance of Niosomal gel formulations

S.no	Formulation code	Color	Homogeneity	Consistency	Grittiness
1	NG-1	Pale brown	Satisfactory	Satisfactory	Gritty particles
2	NG-2	Pale brown	Excellent	Excellent	Smooth
3	NG-3	Opaque	Good	Good	Smooth
4	NG-4	Pale brown	Good	Good	Smooth
5	NG-5	Pale brown	Good	Good	Smooth
6	NG-6	Pale brown	Good	Good	Smooth

Discussion: The NG 1, shows gritty particles is due to insufficient mixing during the formulation process can lead to incomplete dispersion of ingredients, results in the formations of aggregates or clumps that appears as gritty particles. Were shown in table 5.26 The use of excipients that do not fully dissolve or disperse in the gel matrix cause grittiness. In contrasts, the NG2 maintain Pale brown color with better overall properties, like homogeneity of NG 2 ensuring the uniform distribution of the active ingredients throughout the gel and have smooth texture without any gritty particles**.**

The physical appearance of **NG2** was selected as the optimal formulation due to their superior physical characteristics.

pH determination

Table 10: pH determination formulations

Formulation Code	pH
NG1	7.4±0.47
NG2	6.7±1.98
NG3	7.1±1.14
NG4	7.3±0.25
NG5	7.9±0.37
NG6	7.8±0.42

All values are average of three determination (n=3)

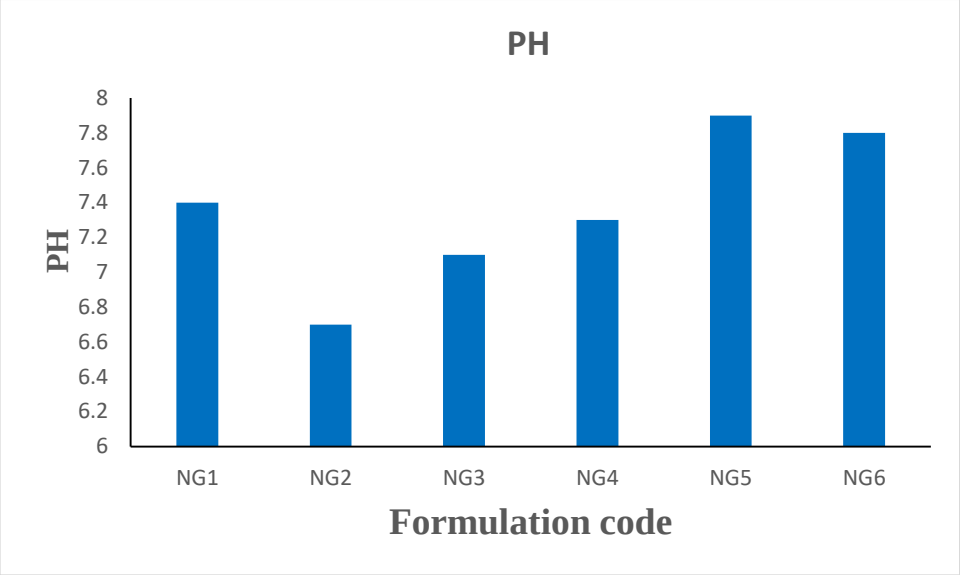

Fig 7 : pH determination formulations

Discussion: The NG2 shows low pH range 6.7±1.98 were shown in table 5.13 and figure 5.23 because active ingredients in gel formulation are more stable and effective at lower pH levels. Acidic pH can enhance the penetration of active ingredient through the stratum corneum, making formulation more effective. Lower pH can help in reducing skin irritation and sensitivity, making the formulation suitable for sensitive skin types. Lower pH environments can inhibit the growth of harmful bacteria and fungi, contributing to the preservation and safety of the product. While, other formulations shows higher pH can influence the lipophilic drug like permethrin tend to have lower solubility in alkaline conditions. This can lead to in adequate drug dissolution, reducing the effectiveness of the formulation. Formulations with a high pH can disrupt the skin's acid mantle, leading to irritation, dryness and increased susceptibility to infections.

The best formulation of NG2 6.7±1.98 with low pH is generally more favorable for gel formulations, especially when dealing with lipophilic drug like Permethrin, due to improved solubility, skin compatibility and overall formulation effectiveness.

Rheological Studies:

Table 11 : Viscosity of the formulations

Formulation Code	Spindle no.	Revolutions per minute(rpm)	Torque (%)	Viscosity(cps)
NG1	S63	50	88.2	1574±33.4
NG2	S63	50	88.5	1399±22.50
NG3	S63	50	82.8	1434±26.51
NG4	S63	50	81.5	1525±31.1
NG5	S63	50	86.3	1681±31.39
NG6	S63	50	88.1	1512±33.4

All values are average of three determination (n=3)

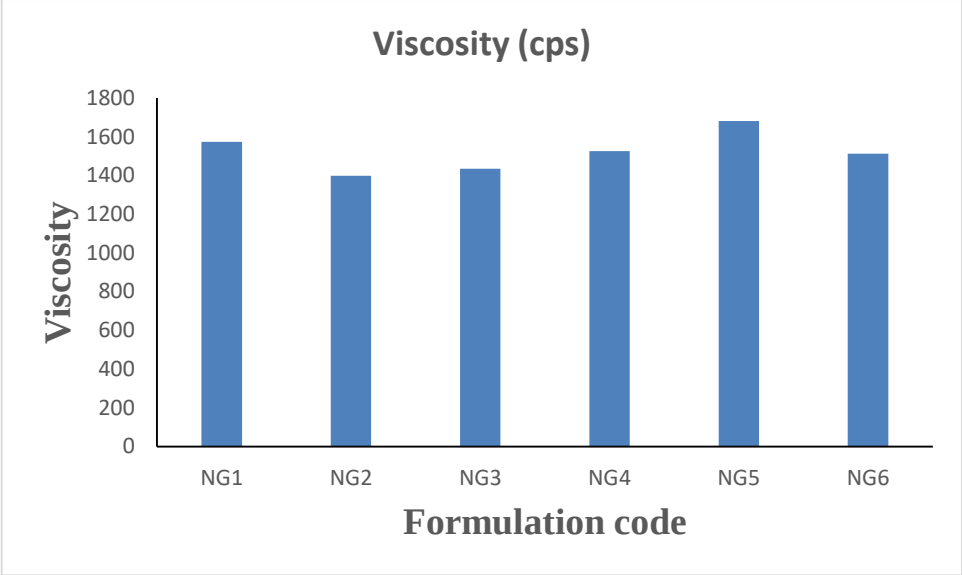

Fig 8: Viscosity of the formulations

Discussion:

The rheological behavior of all formulated Niosomal gel was studies using Brookfield viscometer at a speed of 50rpm and spindle no.63 was used . were shown in table 5.14 anfd figure 5.24. The NG 2 shows low viscosity 1399±22.50 cps because the smaller particles or more uniform distribution within the gel can reduce overall viscosity. Higher temperature can reduce the viscosity of a gel as the molecular motion increases, making gel less viscous. Gelling agents inherently produce gel with lower viscosity. The choice of the gelling agent cam significantly affects the viscosity of the final formulation. While, NG4 and NG5 shows high viscosity because using of higher concentration of gelling agents are designed to produce more viscous gels. Lower temperatures generally increase the vicosity of gel as molecular motion decreases.

Thus, the best viscosity profiles of NG2 1399±22.50 shows low viscosity is typically better; because it offers good spreadability, absorption, and ease of application and ensure the effective delivery of the active ingredient.

Spreadability

Table 12 : Spreadability coefficient of formulations

Sr. No	Formulation Code	M(gm)	L(cm)	T(sec)	Spreadability
	NG1	50	6	10	26.4±0.54
	NG2	50	6	11	35.5 ±0.46
	NG3	50	6	15	20.2± 0.34
	NG4	50	6	10	22.07±0.47
	NG5	50	6	11	25.27 ± 0.65
	NG6	50	6	16	20.42± 0.24

All values are average of three determination (n=3)

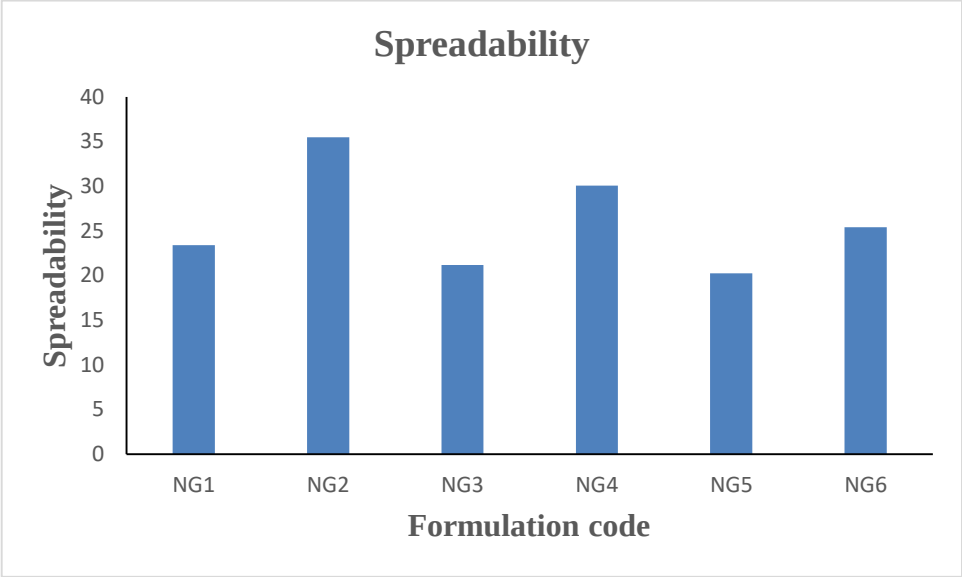

Fig 9: Spreadability coefficient of formulations

Discussion:

The NG 3 shows low spread ability 20.2± 0.34 were shown in table 5.15 and figure 5.25 because larger particle size or unevenly distribution particles can increases resistance to spreading. Higher concentration of gelling agents can lead to lower spread ability. Higher viscosity of NG 3 which can make the gel thicker and less easy to spread. While, the NG2 35.5 ±0.46 shows high Spread ability because smaller or uniformly distributed particles in gel can lead to better spread ability. Gel with lower viscosity can easily spread over the skin.

Thus, the best result shown in NG2 35.5 ±0.46 with higher spreadability is more suitable for gel formulation. Its lower viscosity and potentially better rheological properties contribute to easier and more effective application, enhancing the overall performance of the gel formulation.

Extrudability

Table 13 : Extrudability of formulations

Sr. No.	Formulation code	Weight extruded from the tube(gm)
	NG1	72.65±0.23
	NG2	84.87±0.33
	NG3	73.45±0.43
	NG4	76.88±0.24
	NG5	82.34±0.23
	NG6	83.14±0.56

All values are average of three determination (n=3)

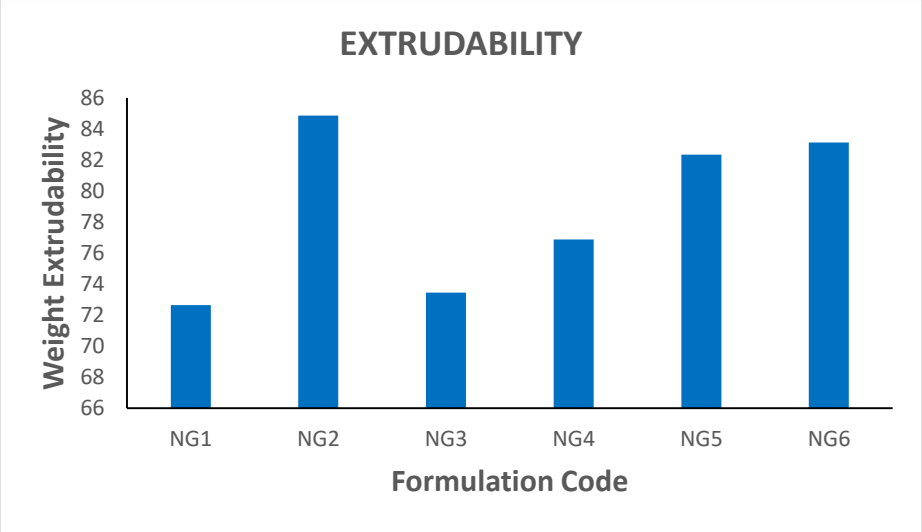

Fig 10 : Extrudability of formulations

Discussion:

All the niosomal gel had good extruding property. Comparatively NG2 has good extruding property than others formulations.The NG 1 shows low extrudability, because higher viscosity making it thicker and more resistant to flow. This requires more force to extrude the gel. Larger or unevenly distributed particles can increase internal friction, making it harder to extrude the gel. While, the formulation NG 2 shows high extrudability because NG 2 has a low viscosity making it easier to push through the nozzle of the container. Lower viscosity gels require less force to extrude. Smaller and more uniformly distributed particles can reduce internal friction, allowing the gel to flow more easily.

Thus, the best result shown in NG 2 with higher extrudability value 84.87 is more suitable for gel formulations. Its low viscosity and potentially better flow properties contribute to easier and ensuring effective application of the gel**.**

Drug Content:

Table 14 : Drug Content

Sr. No	Formulation Code	Drug Content (%)
	NG1	74.21±0.35
	NG2	84.29±1.98
	NG3	72.21±1.16
	NG4	82.45±0.87
	NG5	75.88±1.31
	NG6	74.88±1.10

All values are average of three determination (n=3)

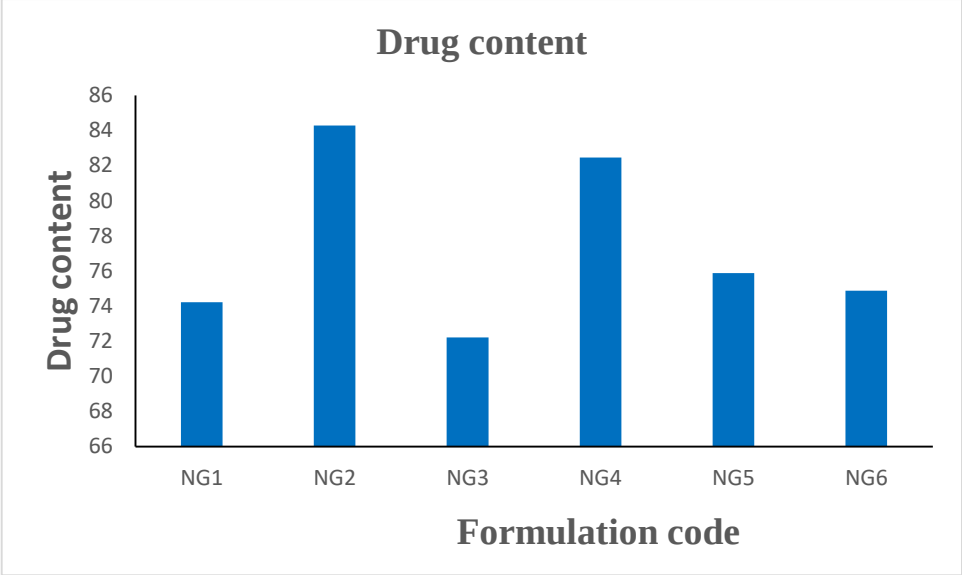

Fig 11: Drug Content of formulations

Discussion: The NG1 and NG3 shows low drug content there is many factors leading to low drug contents, like suboptimal formulation process (inefficient mixing, encapsulation or stabilization) can lead to lower drug content. Larger particles or unevenly distributed particles may have smaller surface area for drug encapsulation, resulting in lower drug content. In contrast, the NG2 shows high drug content due to optimized formulation process include efficient formulation techniques, such as proper mixing , encapsulation can enhances the drug loading capacity of the ufasomes leads to high drug content. Smaller and uniformly distributed particles can provide a larger surface area for drug absorption, increasing drug content.

Thus, the best result shown in NG2 with its higher drug content 84% is more suitable for gel formulations. Higher drug content ensures greater efficacy, consistent dosing, and cost effectiveness. The formulation process, particle size, and drug – excipients compatibility play critical role in achieving high drug content in gel formulations.

IN –vitro Drug Release of niosomal gel formulations

Table 15 : Percentage drug release of ufasomal gel formulations for N1 to N6

Time (hrs)	**Cumulative (%) Drug Release**					
	NG1	**NG2**	**NG3**	**NG4**	**NG5**	**NG6**
0	0	0	0	0	0	0
0.5	18.10±0.23	20.89±0.21	17.09±0.20	19.89±0.19	16.15±0.18	18.43±0.17
1	27.90±0.25	30.9±0.24	26.09±0.23	27.89±0.22	23.05±0.21	24.89±0.20
2	40.80±0	46.89±0.2	39.09±0.2	41.82±0.2	40.12±0.	42.89±0.2

	.27	6	5	4	23	2
4	50.78±0.17	54.8±0.16	51.98±0.15	47.01±0.14	45.9±0.13	58.93±0.12
6	56.90±0.19	60.01±0.18	58.09±0.17	55.78±0.16	54.34±0.15	59.34±0.14
8	64.90±0.24	74.9±0.23	65.34±0.22	65.9±0.21	67.65±0.20	64.64±0.19
10	77.90±0.28	89.98±0.27	74.67±0.26	69.08±0.25	74.67±0.24	69.9±0.23

Mean±SD, n=3

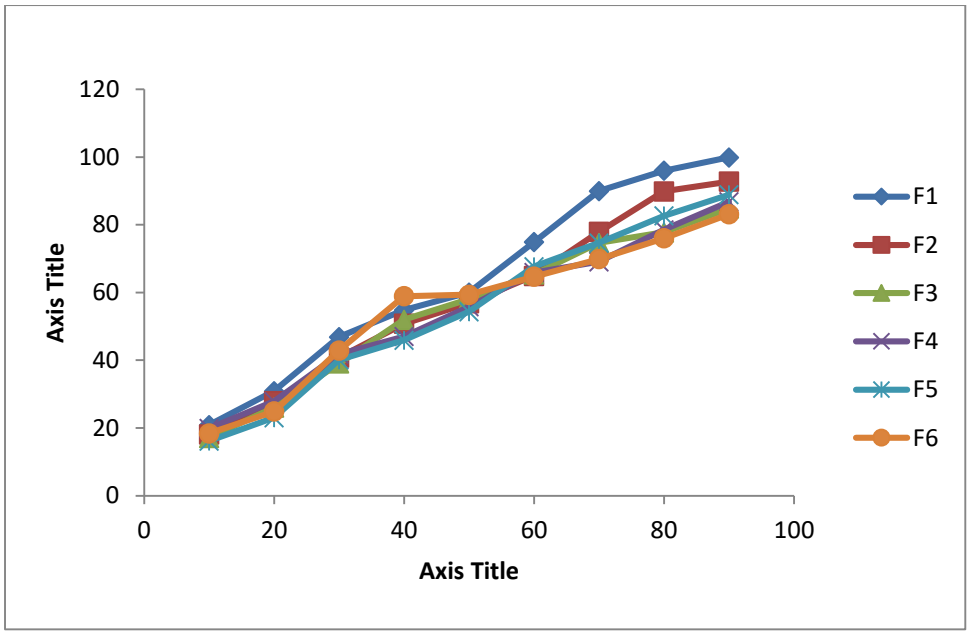

Fig 12 : Representative of In-vitro drug release of gel formulation NG1 to NG6

Discussion :

From Table 5.32 and Figure 5.28 the in-vitro drug release pattern of initial burst release of surface adsorbed drug was observed followed by slow and sustained release of entrapped drug from the NGs the initial burst effect on the release of Permethrin may be due to the loosely associated Permethrin on the surface of niosomal gel formulations. The burst release is clinically significant to achieve initial high drug concentrations in the target tissue. The slow release of the drug is controlled by the speed of the degradation of niosomes. Thus, NG 3 show a slow and sustained release of drug which found to be the best formulation. These indicate to the growing body evidence supporting the use of niosomes as a promising delivery system for prolonged drug release.

5In- vitro drug release kinetic

Table 16 : In- vitro drug release kinetic for NG2 formulation

Time (hrs)	Square root of time (h) 1/2	Log time	Cumulative % drug release	Log cumulative % log release	Cumulative% drug remaining	Log cumulative % drug remaining
0.5	1	0	20.89	1.432	71.34	1.854
1	1.41	0.301	30.9	1.554	65.67	1.814
2	1.73	0.477	46.86	1.578	60.56	1.779
4	2.23	0.602	54.8	1.634	55.43	1.74
6	2.23	0.698	60.01	1.745	49.65	1.79
8	2.24	0.778	74.9	1.756	45.21	1.69
10	2.82	0.903	89.98	1.734	38.45	1.58

Mean±SD, n=3

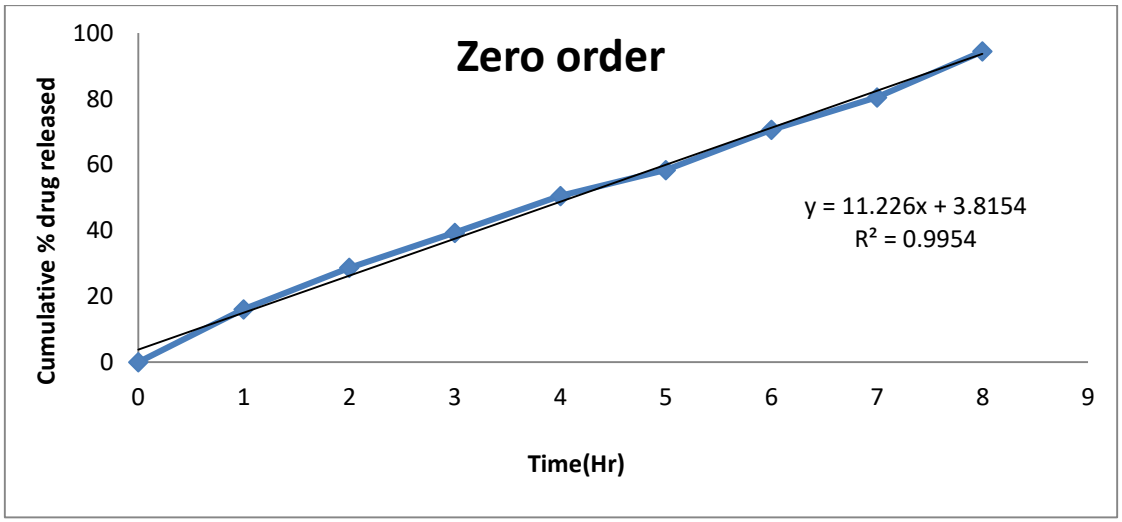

Figure13 : (A) Zero order kinetics

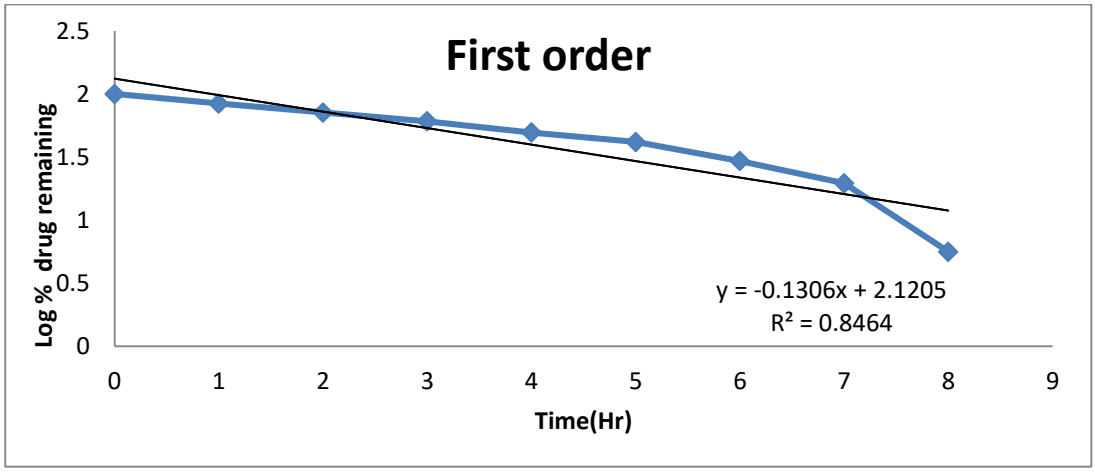

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Figure 14 : (B) First order kinetics

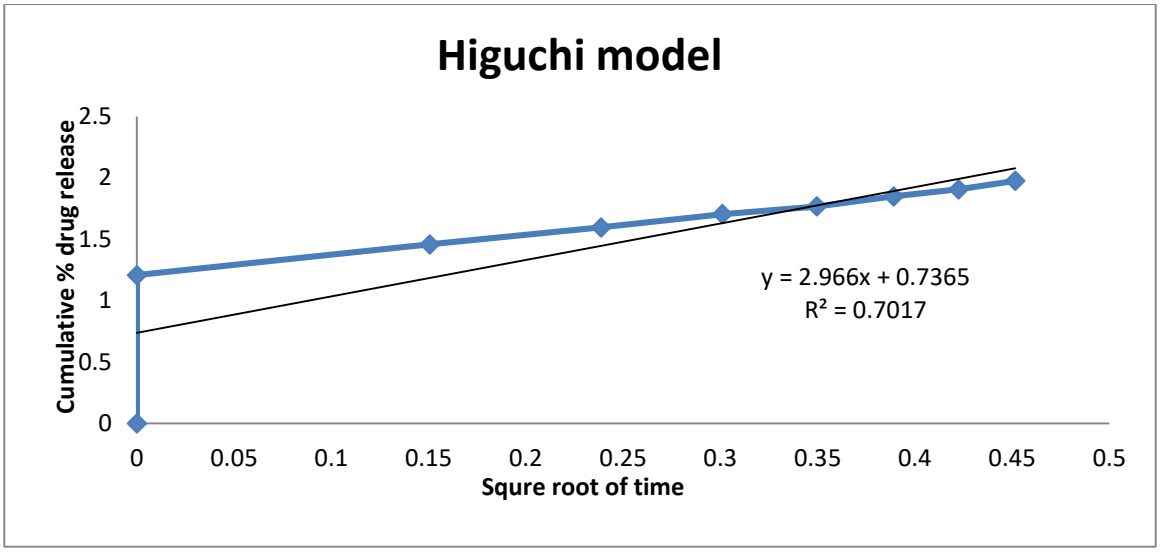

Figure 15 : (C) Higuchi Model

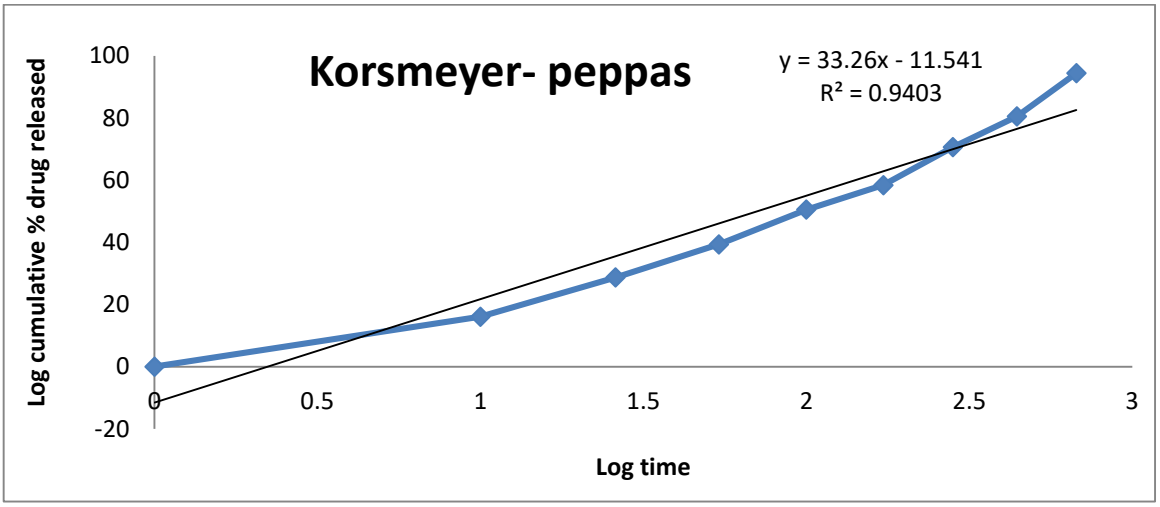

Figure 16 : (D) Korsmeyer peppas model

Table 17 : Correlation coefficient values of kinetic models

S. No.	Kinetic model	Correlation coefficient values (r^2)
1.	Zero-order	0.9954
2.	First-order	0.8464
3.	Higuchi model	0.7017
4.	Korsemeyer-Peppas model	0.9403

Discussion:

The correlation coefficient values of Zero-order was found to be 0.9954, First order was found to be 0.8464, Higuchi model was found to be 0.7017, and Korsemeyer Peppas model was found to be 0.9403. The highest R^2 value was found in the case of Zero-order. So, it was concluded that drug release from NG2 follows Zero-order kinetics. Zero order kinetics was found to be best fit the release data.

The attainment of zero–order kinetics with high coefficient of determination (R^2= 0.995) represents a pivotal achievement in the development of the gel formulation investigated in this study. Zero–order kinetics indicates that the drug release from the formulation occurs at a constant rate over time, independent of its concentration. This characteristics is highly desirable for topical formulations like gels, as it's ensure consistent and sustained delivery of the active ingredient to the target site. The observed high R^2 value underscore the precision drug release, reflecting optimized formulation parameters such as excipients composition, drug loading, and particle characteristics. Such controlled release kinetics not only enhance therapeutics efficacy by maintaining effective drug levels but also signify formulation stability and robustness. Moreover, achieving zero- order kinetics holds implications for regulatory compliances and clinical applicability, demonstrating the formulation ability to meet stringent safety and efficacy standards.

Hence, the NG6 shows zero order kinetics, which shows the optimal formulation and has high coefficient of determination which is best achievement in the development of the gel formulation.

Stability studies:

Table 18: Stability study appearance of Niosomal gel NG 2 formulation for 6 month

Duration (days)	**Appearance at 4±2˚C**	**Appearance at 25±2˚C/65˚%±5%RH**	**Appearance at40±2˚C/75%±5%RH**
0	Light brown in color	Light brown in color	Light brown in color
30	No change	No change	No change
60	No change	No change	No change
90	No change	No change	No change
120	No change	No change	No change
150	No change	No change	No change
180	No change	No change	No change

Table 19 : Stability study of drug content of Niosomal gel NG2 formulation for 6 month

Duration(days)	**Percentage of drug content at 4±2ºC**	**Percentage of drug content at 25±2ºC/65%±5%RH**	**Percentage of drug content at 40±2ºC/75%±5%RH**
0	97.18±0.543	97.15±0.545	97.09±0.119
30	97.17±0.528	97.11±0.524	97.03±0.111
60	97.16±0.509	97.08±0.498	97.01±0.108
90	97.13±0.501	97.06±0.477	97.00±0.102
120	97.11±0.490	97.03±0.465	96.70±0.098
150	97.09±0.461	97.01±0.432	96.56±0.083
180	97.05±0.446	97.00±0.405	96.20±0.072

Table 20: Stability studies of an in vitro drug release of niosomal gel formulation NG2 at 4±2ºC

Time (hrs)	Cumulative % drug release at 4±2ºC						
	0days	30days	60days	90days	120days	150days	180days
0	0	0	0	0	0	0	0
0.5	20.89 ±0.09	20.63 ±0.10	20.20 ±0.08	20.08 ±0.84	19.87 ±0.89	19.69 ±0.09	19.54 ±0.89
1	30.9± 0.08	30.1± 0.09	29.9± 0.075	29.01± 0.09	28.9± 0.08	28.05± 0.076	28.00± 0.08
2	46.89± 0.071	45.08± 0.081	45.00± 0.071	44.87± 0.071	44.78± 0.071	44.59± 0.071	46.32± 0.071
4	54.8± 0.065	53.30± 0.075	52.88± 0.062	52.65± 0.065	52.43± 0.060	52.18± 0.065	54.01± 0.065
6	60.01± 0.081	60.00± 0.091	59.51± 0.080	59.21± 0.081	59.01± 0.071	58.81± 0.081	58.21± 0.081
8	74.9± 0.051	73.9± 0.061	73.40± 0.051	73.19± 0.051	73.01± 0.051	72.90± 0.051	72.69± 0.051
10	89.98± 0.078	89.12± 0.058	89.00± 0.088	88.98± 0.078	88.68± 0.079	88.41± 0.078	88.24± 0.078

Table 21 :Stability studies of in vitro drug release of Niosomal gel formulation NG2 Appearance at 25±2˚C/65˚%±5%RH

Time (hrs)	Cumulative % drug release at 4±2ºC						
	0days	30days	60days	90days	120days	150days	180days
0	0	0	0	0	0	0	0
0.5	20.89 ±0.09	20.54 ±0.10	20.35 ±0.08	20.15 ±0.84	19.56 ±0.89	19.29 ±0.09	19.10 ±0.89
1	30.9± 0.08	30.0± 0.09	29.50± 0.075	29.00± 0.09	28.60± 0.08	28.15± 0.076	28.00± 0.08
2	46.89± 0.071	45.34± 0.081	45.07± 0.071	43.87± 0.071	43.78± 0.071	42.59± 0.071	42.32± 0.071
4	54.5± 0.065	53.10± 0.075	52.98± 0.062	52.55± 0.065	52.27± 0.060	52.08± 0.065	51.91± 0.065
6	60.01± 0.081	59.00± 0.091	58.91± 0.080	59.21± 0.081	59.01± 0.071	58.81± 0.081	58.21± 0.081
8	74.9± 0.051	72.90± 0.061	72.40± 0.051	72.19± 0.051	72.01± 0.051	71.90± 0.051	71.69± 0.051
10	89.98± 0.23	88.12± 0.56	88.09± 0.088	87.98± 0.078	87.68± 0.079	87.41± 0.078	87.24± 0.078

Table 22 : Stability studies of in vitro drug release of Niosomal gel formulation NG2 Appearance at40±2˚C/75%±5%RH

Time (hrs)	Cumulative % drug release at 40±2ºC						
	0days	30days	60days	90days	120days	150days	180days
0	0	0	0	0	0	0	0
0.5	19.89 ±0.09	19.54 ±0.10	19.35 ±0.08	19.15 ±0.84	19.01 ±0.89	18.89 ±0.09	18.10 ±0.89
1	29.9± 0.08	29.00± 0.09	28.50± 0.075	28.00± 0.09	27.60± 0.08	27.15± 0.076	26.00± 0.08
2	45.89± 0.071	43.34± 0.081	43.07± 0.071	42.87± 0.071	42.78± 0.071	41.59± 0.071	41.32± 0.071
4	54.5± 0.065	53.10± 0.075	52.98± 0.062	52.55± 0.065	51.27± 0.060	51.08± 0.065	50.91± 0.065
6	59.01± 0.081	57.00± 0.091	56.91± 0.080	56.21± 0.081	56.01± 0.071	55.81± 0.081	55.21± 0.081
8	74.9± 0.051	72.90± 0.061	72.40± 0.051	72.19± 0.051	72.01± 0.051	71.90± 0.051	71.69± 0.051
10	88.98± 0.078	86.12± 0.058	86.09± 0.088	85.98± 0.078	84.68± 0.079	83.41± 0.078	82.24± 0.078

Discussion:

The best formulation of NG 2 shows best result in Stability studies conducted on NG 2 at different temperatures over a period of 180 days revealed robust stability characteristics crucial for its pharmaceutical application. Throughout the study, NG 2 exhibited no significant changes in visual appearance, maintaining its clarity and homogeneity across all storage conditions. Notably, the formulation demonstrated exceptional drug content stability, retaining 87% of its initial drug concentration throughout the entire study period. This consistent drug release is indicative of the formulation's ability to provide reliable therapeutic efficacy over time, which is essential for its intended use in topical gel formulations. Temperature variations did not adversely affect the stability of NG 2, underscoring its resilience to environmental factors. These findings validate the formulation design approach taken and highlight NG 2

REFERENCES:

1. Arora P, Rudnicka L, Sar-Pomian M, Wollina U, Jafferany M, Lotti T, Sadoughifar R, Sitkowska Z, Goldust M. Scabies: a comprehensive review and current perspectives. Dermatologic therapy. 2020 Jul;33(4):e13746.
2. Hengge UR, Currie BJ, Jäger G, Lupi O, Schwartz RA. Scabies: a ubiquitous neglected skin disease. The Lancet infectious diseases. 2006 Dec 1;6(12):769-79.
3. Richards RN. Scabies: diagnostic and therapeutic update. Journal of Cutaneous Medicine and Surgery. 2021 Jan;25(1):95-101.

4. Thompson MJ, Engelman D, Gholam K, Fuller LC, Steer AC. Systematic review of the diagnosis of scabies in therapeutic trials. Clinical and Experimental Dermatology. 2017 Jul 1;42(5):481-7.
5. Raffi J, Suresh R, Butler DC. Review of scabies in the elderly. Dermatology and Therapy. 2019 Dec;9:623-30.
6. Romani L, Steer AC, Whitfeld MJ, Kaldor JM. Prevalence of scabies and impetigo worldwide: a systematic review. The Lancet infectious diseases. 2015 Aug 1;15(8):960-7.
7. Romani L, Steer AC, Whitfeld MJ, Kaldor JM. Prevalence of scabies and impetigo worldwide: a systematic review. The Lancet infectious diseases. 2015 Aug 1;15(8):960-7.
8. Golant AK, Levitt JO. Scabies: a review of diagnosis and management based on mite biology. Pediatrics in review. 2012 Jan 1;33(1):e1-2.
9. Welch E, Romani L, Whitfeld MJ. Recent advances in understanding and treating scabies. Faculty Reviews. 2021;10.
10. Uchegbu IF, Florence AT. Non-ionic surfactant vesicle (niosomes): Physical and pharmaceutical chemistry. Advances in colloid and interface science. 1995; Vol.58(1), pp1-55
11. Yoshioka T, Sternberg B, Florence AT. Preparation and properties of vesicles (niosomes) of sorbitan monoesters (span 20, 40, 60 and 80) and a sorbitan triester (span 85). International journal of pharmaceutics. 1994; 105(1):1-6
12. Rogerson A, Cummings J, Florence AT. Adriamycin-loaded niosomes: Drug entrapment, stability and release. Journal of microencapsulation. 1987; Vol.4(4), pp321-8.
13. Arunothayanun P, Bernard MS, Craig DQM, Uchegbu IF, Florence AT. The effect of processing variables on the physical characteristics of non- ionic surfactant vesicles (niosomes) formed from a hexadecyl diglycerol ether. International journal of pharmaceutics. 2000; Vol.201(1), pp7-14.
14. Carafa M, Santucci E, Lucania G. Lidocaine-loaded non-ionic surfactant vesicles: Characterization and in vitro permeation studies. International journal of pharmaceutics. 2002; Vol.231(1), pp21-32
15. Rajera R, Nagpal K, Singh SK, Mishra DN. Niosomes: A controlled and novel drug delivery system. Biological and Pharmaceutical Bulletin. 2004; Vol. 34(7), pp945-53.
16. Gannu, P.K., Rp, Nonionic surfactant vesicular systems for effective drug delivery- an overreview, acta pharmaceutica sinica B, 2011,Vol.1(4), pp208-219
17. Uchegbu, I.F., Florence, A.T, Nonionic surfactant vesicles; physical and pharmaceutical chemistry. Advances in colloid and interface science, 1995, 2011,58(1), 1-15
18. Saeid Moghassemi, Afra Hadjizadeh, Nano-niosmes as nanoscale drug delivery systems; An illustrated review, Journal of controlled release, 2014; Vol.18(5), pp22-36
19. Kreuter J. Colloidal drug delivery systems: M. Dekker; 1994
20. Manosroi A, Wongtrakul P, Manosroi J, Sakai H, Sugawara F, Yuasa M,. Characterization of vesicles prepared with various non-ionic surfactants mixed with cholesterol. Colloids and Surfaces B: Biointerfaces. 2003; Vol.30(1- 2), pp129-38.

21. Balasubramaniam A, Anil Kumar V, Sadasivan Pillai K. Formulation and in-vivo evaluation of niosome-encapsulated daunorubicin hydrochloride. Drug development and industrial pharmacy. 2002; Vol.28(10), pp1181-93

22. Yoshida H, Lehr CM, Kok W, Junginger HE, Verhoef JC, Bouwstra JA. Niosomes for oral delivery of peptide drugs. Journal of controlled release. 1992; Vol.21(1-3), pp145-53.

23. Gopinath D, Ravi D, Rao BR, Apte SS, Renuka D, Rambhau D. Ascorbyl palmitate vesicles (aspasomes): Formation, characterization and applications. International journal of pharmaceutics. 2004; Vol.271(1), pp95-113.

24. Gandhimathi R. Niosomes: Best Approach for Novel Drug Delivery and Future Aspects. Asian Journal of Pharmaceutics (AJP). 2024 Mar 15;18(01).