FORMULATION AND EVALUATION OF AJWAIN OIL AND WINTERGREEN OIL OF NIOSOMAL GEL DRUG DELIVERY SYSTEM

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ABSTRACT

The aim of the study was to formulate and evaluate the ajwain oil and wintergreen oil loaded niosomal gel. Span 40 and span 60 used as SAA, Carbopol 934 as gelling agent, cholesterol as membrane stabilizer(lipid), phosphate buffer saline as hydration medium. All the formulation were passed various evaluatoryparameters and found within limits. Among all formulation highest % entrapment efficiency shown in F8 formulation i.e. 89.65% . It contains increase amount of span 60 concentration and hence showed better and desired drug release pattern.

Keywords: Ajwain oil, Wintergreen oil, Carbopol 934, Cholesterol, Gel, Niosome, TDDS, % Entrapment efficiency.

INTRODUCTION :

Transdermal Drug Delivery System (TDDS)

Transdermal drug delivery system(TDDS) is a method of developing drug via the skin to generate local as well systemic therapeutic effects. Drug administration method of TDDS is convenient, simple to use, non- invasive as well as improving patient compliance.It also decreases drug concentration fluctuations in the blood, maintains stable plasma levels, reduces the risk of overdosing, and facilitates drug detection. At the same time, it avoids the effects of the

gastrointestinal environment, such as pH, enzymatic activity, and drug-food interactions on drug efficacy and the liver's "first pass effect" (where active drug molecules might be transformed to inactive molecules or even molecules that cause side effects), prolong the therapeutic impact of medicines with a shorter half-life and improve the drug's long-term stability . After the stimulus has been removed from the location, medication administration can be discontinued at any time. Despite the various benefits of TDDS, the use of medicines in TDDS is currently limited. The SC of the skin provides the highest resistance to drug penetration through the skin. Topical drug delivery system means delivery of API through or in to the skin for direct treatment of cutaneous disorder or the cutaneous manifestation. When a large number of medicines are administered through the skin, achieving an acceptable permeability rate to meet therapeutic needs is challenging. Nanotechnology may be a viable option for overcoming these challenges.[7]

Nanotechnology is the technique of producing or processing macromolecular materials into a substance with a particle size of 1-100 nm utilising a single atom or molecule. Nano-formulationsare an essential aspect of nanotechnology. Nano-formulations have a higher effect on drug retention, specificity, and targeting because of their tiny particle size, making them an excellent TDDS. They offer a number of benefits, including painlessness, little skin damage (does not affect the overall structure of the skin's SC or impair the skin barrier function), and the ability to enhance macromolecular drug penetration, which has been a prominent area of TDDS research. Vesicles, such as liposomes, transfersomes, ethosomes, niosomes, and invasomes, and nanoparticles, such as lipid nanoparticles, polymeric nanoparticles, and nano-emulsions, are two types of nano-formulation.The categorization, components, features, transdermal mechanism, and application of nano-formulations are the subject of this study, which is based on recent developments in research on passive TDDS nano-formulations. We want to provide the groundwork for future study in nano-formulations for TDDS, as well as improve our understanding of clinical and therapeutic implications.[10,11]

Advantages of Transdermal Drug Delivery Systems

1. Transdermal medication delivers a steady infusion of a drug over an extended period of time. Adverse effects or therapeutic failures frequently associated with intermittent dosing can also be avoided.[8]

2. Transdermal delivery can increase the therapeutic value of many drugs by avoiding specific problems associated with the drug e.g., gastro-intestinal irritation, low absorption, decomposition due to hepatic "first- pass" effect, formation of metabolites that cause side effects, short half - life necessitating frequent dosing etc.

3. Due to the above advantage, it is possible that an equivalent therapeutic effect can be elicited via transdermal drug input with a lower daily dose of the drug than is necessary, if, for example,the drug is given orally.[10]

4. The simplified medication regimen leads to improved patient compliance and reduced inter & intra- patient variability.

6. Self administration is possible with these systems.

Disadvantages of Topical Drug Delivery System

1. Skin irritation of contact dermatitis may occur due to the drug and/or excipients.[8]

2. Poor permeability of some drugs through the skin.

3. Possibility of allergenic reactions.

4. Can be used only for drugs which require very small plasma concentration for action.[10]

5. Enzyme in epidermis may denature the drugs.

6. Drugs of larger particle size not easy to absorb through the skin.

MATERIALS AND METHODS :

Materials and Suppliers:

The following materials were used with AR/LR grade or the best possible grades available were used.

Ajwain oil and wintergreen oil purchased from Sci Tech. Pune ; Carbopol 934, Chloroform, Glycerine and Methanol purchased from LOBA Chemie Pvt. Ltd. Mumbai ; Cholesterol purchased from SDFCL-SD Fine-Chem Ltd. ; Span 40 and Span 60 purchased from Pure Chemie Lab. Pune.

METHOD :

Formulation of niosomal gel by Thin Film Hydration Method:

Adjust temp. of water bath to desired temp.

Weigh span 40 and span 60 and cholesterol in RBF

Add organic solvents (chloroform /methanol/triethanolamine) to dissolve the contents

Attach the flask to rotary evaporator and allow to evaporate for at least 30 min.

Detached RBF and add aqueous solution of drug (Ajwain oil and Wintergreen oil along with Phosphate Buffer Saline as a hydration medium)

Re-attach RBF and allow to run for at least 60 min.

Sonicate for at least 1 – 2 min.

Centrifugation for 30 min. and then niosomes formed

Table no. 1. Formulation Composition For Niosomal Gel :

Ingredients	F1	F2	F3	F4	F5	F6	F7	F8	F9
Ajwain oil	1%	1%	1%	1%	1%	1%	1%	1%	1%
Wintergreen oil	10%	10%	10%	10%	10%	10%	10%	10%	10%
Span 40	1	1	2	-	-	-	1	1	2
Span 60	-	-	-	1	1	2	1	2	1
Cholesterol	1	2	1	1	2	1	1	2	2
Chloroform	10 ml	10 ml	10 ml	10 ml	10 ml	10 ml	10 ml	10 ml	10ml
PBS 7.4	6ml	6ml	6ml	6ml	6ml	6ml	6ml	6ml	6ml

Evaluation and Characterization of optimize batch of Niosomes :

1. FTIR:

FTIR spectra of pure drug and physical mixture of pure drug with excipients were carried out.The FTIR studies are perform for characterization of drug and to observe the any interaction between drug and excipients in the formulation.

The FTIR spectrum of Ajwain oil and Wintergreen oil loaded Niosomes formulation batch was recorded in the wavelength range of 4000 to 400 cm-1 The characteristics IR absorption peaks of were studied.

2. Particle size ,Zeta potential and PDI value:

The particle size and zeta potential are two important parameters that characterize colloidal drug delivery systems and their effects on the stability of the carriers is a well established relationship. In order to prevent the aggregation of systems it is necessary to provide some barrier between the particles or introducing a charge on the surface of the vesicles. Zeta potential is an indicator for the size of this barrier. If all of the particles have large enough zeta potential the particles may repel each other strong enough to so that they will not have the tendency of coming together. However, this phenomenon is an assumption and there are several other parameters that affect the stability such as particle size, viscosity, chemical interactions within the system, storage conditions etc. As the ratio of gravitational forces to Brownian forces increase the particle size of the niosomes becomes more dominant on the stability of the systems because the electrostatic interactions do not provide sufficient protection against precipitation. The mean particle size analysis and PDI value was done. Zeta potential determines stability of formulation by measuring change of the drug loaded droplet surface. Zeta potential for optimized batch was measured using HORIBA scientific.

3. TEM:

Shape and surface morphology of Niosomes was observed by Transmission electron microscope. TEM study was carried out using ZEISS Apparatus.

4. Accelerated stability study of F8 batch :

The leakage was relatively low at low temperature and this was expected because the drug leakage increases with temperature due to enhanced fluidity of the niosome membrane. Under the stability test conditions drug leakage was observed for all of the niosomal formulations. Although the niosome formulations contain cholesterol which increase the rigidity of niosomes and form less leaky niosomes. Accelerated stability was carried out for 3 month. Particle size and entrapment efficiency was determine.

RESULT AND DISCUSSION

Table no. 2.PREFORMULATION STUDY OF DRUG:

Preformulation parameters		
I. Organoleptic properties	Ajwain Oil	Wintergreen oil
Appearance	Mobile liquid	Mobile liquid
Colour	Reddish brown	Colourless liquid
Odour	Peppery aroma	Sweet, rooty
II. Boiling point	232℃	222℃
III. Solubility	mg/ml	mg/ml
Water	0.1191	0.8071
Phosphate buffer	8.146	0.8821
Chloroform	8.775	2.7142
Ethanol	8.932	3.2107

Drug-Excipient Compatibility Studies

The FTIR spectroscopy used as supplementarytechnique in order to investigate possible chemical interactions. The figure no. 1 presents the IRspectra of API and APIwith different excipients.

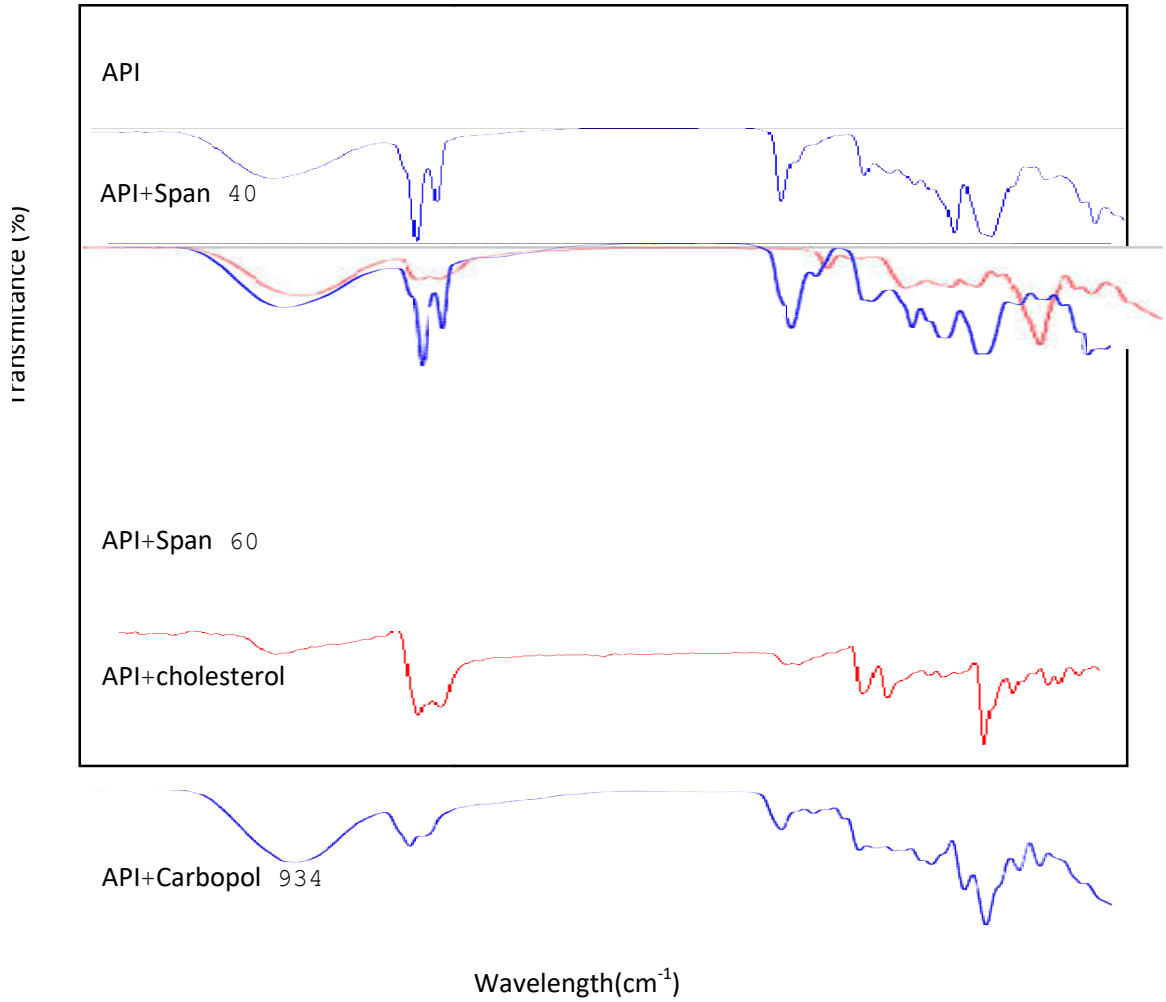


Fig.No. 1 IRspectra of API and APIwith different excipients.

EVALUATION OF NIOSOME BASED GEL :

1. **Appearance, pH, drug content, spreadability:**

Homogenecity and clarity of niosomes were observed. The appearance of F8 formulation gel was found to be translucent and clear. The pH of the gel was measured using digital ph meter and found to be suitable with skin pH (between 3 - 9). The spreadability of gel formulation was

determined by using sliding plate apparatus and by measuring the diameter of 1 gm of gel between horizontal plates after 1 min. The standardized weight tied on the upper plate of 125 gm . The bottom slide is anchored to the apparatus and weights are placed in the pan. The time in seconds needed to separate the two slides is taken as measure of spreadability. A shorter time interval indicates better spreadability and determined by using formula :

$S=M\times L/T$

Where, S= spreadability

M= weight tie to upper slide

L= length of glass slide

T= time taken to separate two slides in sec.

Table No. 3. Evaluation Parameters

Sr.no.	Parameters	Observations
1.	Appearance	Translucent
2.	pH	6.7 ± 0.6
3.	Drug content (%)	84.50 ± 0.51
4.	Spreadability (cm)	2.5 ±0.37

2. **Viscosity measurement** :

Viscocity of prepared gel was measured using Brookfield viscometer. From below figure it was concluded that as shear rate increases the viscosity decreases upto certain point and then viscosity remains constant.

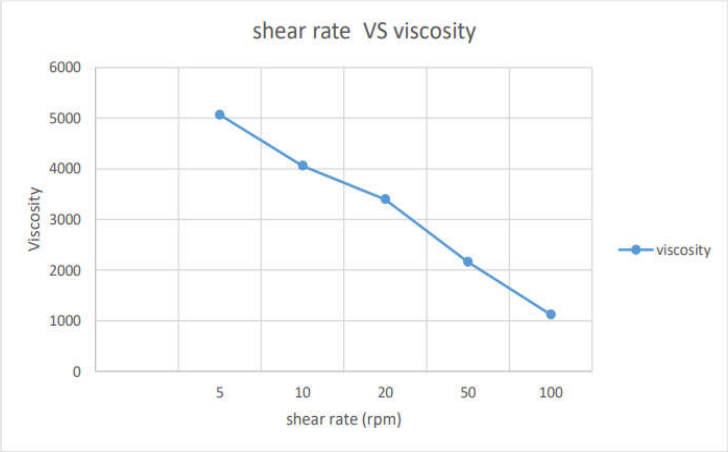


Fig. No.2. Viscosity measurement of F8 batch

3. UV Spectrophotometric analysis of Ajwainoil and Wintergreen oil in Ethanol:

λmax of Ajwain oil was found to be 274 nmand that of Wintergreen oil was found to be 305 nm.

Construction of Beer lamberts plot of Ajwain oil in ethanol –

The Beer's lamberts plot for Ajawain oil in ethanol was constructed. The regression coefficient of the lines obtained in ethanol was found to be 0.999 which is shown in Figure No.3. The linearity ofdrug in ethanol was found in the concentration range of 0-25µg/ml.

Table No.4. Reading of construction of Beer's lamberts plot in ethanol

Sr. no.	Concentration ($\mu g/ml$)	Absorbance
1	5	0.148
2	10	0.317
3	15	0.467
4	20	0.65
5	25	0.789

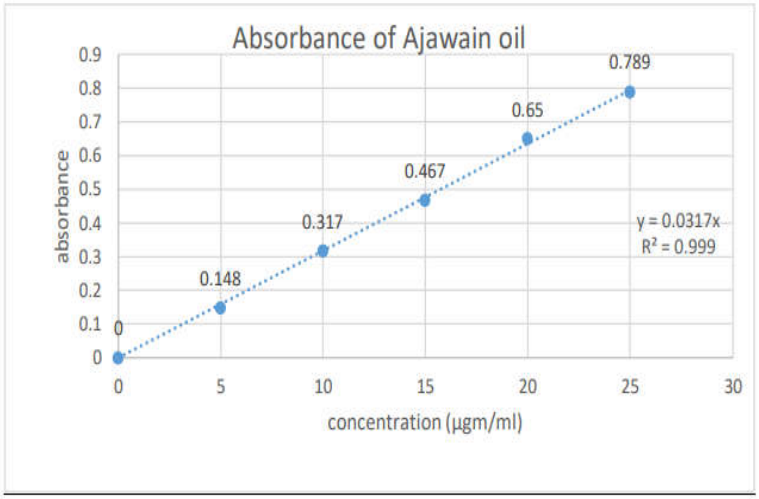


Fig.No. 3. Beer Lamberts plot of Ajwain oil in ethanol

Construction of Beer lamberts plot of Wintergreen oil in ethanol –

The Beer's lamberts plot for Wintergreen oil in ethanol was constructed. The regression coefficient of the lines obtained in ethanol was found to be 0.999 which is shown in Figure No.4. The linearity drug in ethanol was found in the concentration range of 0-25µg/ml.

Table No.5. Reading of construction of Beer's lamberts plot in ethanol

Sr. No.	Concentration $(\mu g/ml)$	Absorbance
1	5	0.156
2	10	0.278
3	15	0.424
4	20	0.561
5	25	0.693

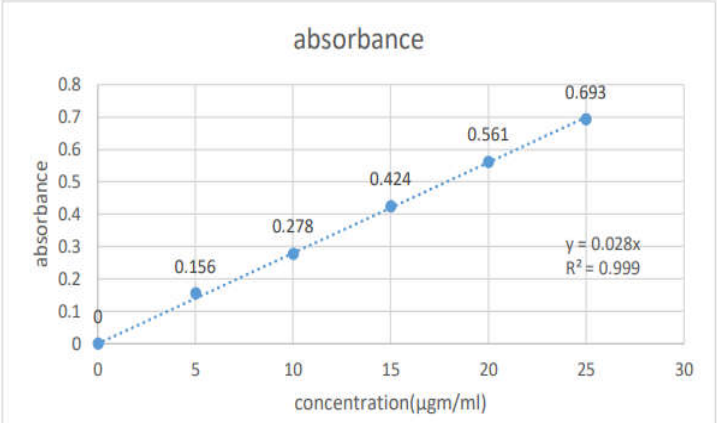


Fig. No. 4. Beer Lamberts plot of Wintergreen oil in ethanol

4. Fourier Transform Infrared Spectroscopy(FTIR) :

The FTIR studies are perform for characterization of drug and to observe the any interaction between drug and Surfactant in the formulation. FTIR study of optimized niosome was carried out. The FTIR spectra of optimized nanoparticle were shown in the following Fig. No. 5.

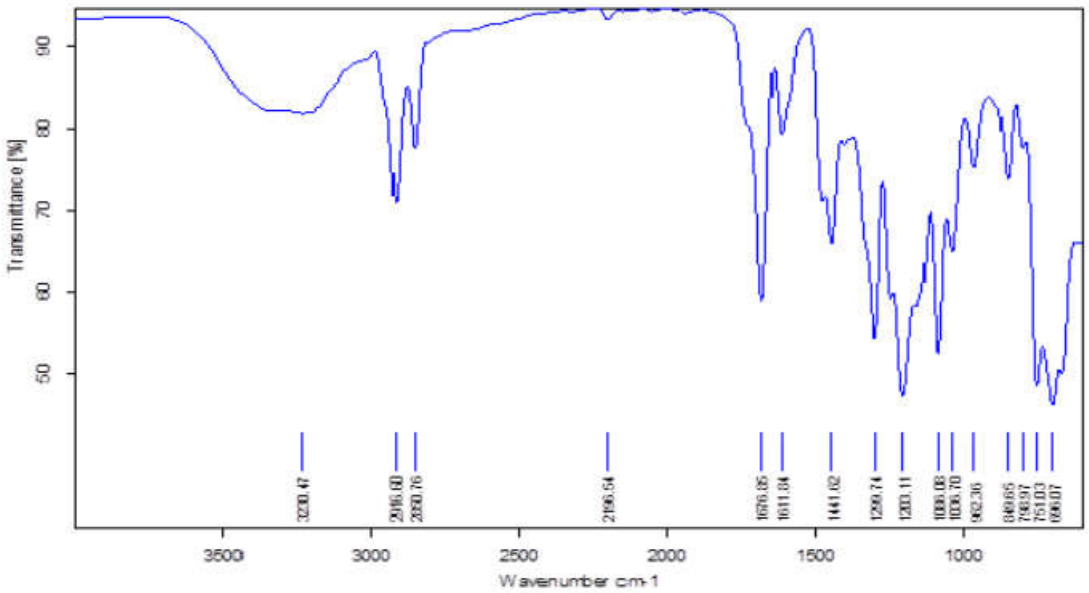


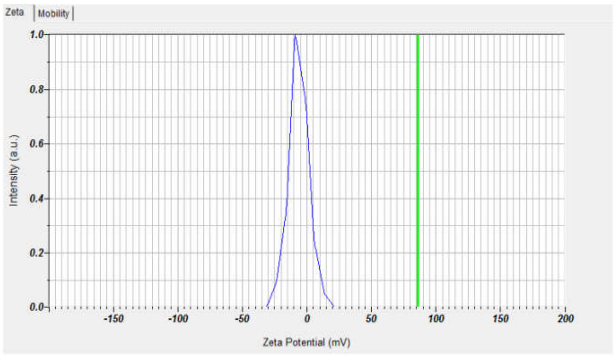
Fig. No. 5. FTIR spectra of F8 batch of noisome

Table No. 6. Interpretation of FTIR spectra of niosome

Functional groups	Observed ranges (cm^{-}) at 0 days	Observed ranges (cm^{-}) at 14 days	Standard ranges (cm^{-})
C=C aromatic	1441.62	1441.62	1600-1430
C-Cl Streching	798.97	798.97	750-900
C-N Streching	1203.11	1203.11	1380-1250
N-H Streching	2916.60	2616.60	3000-2800

5. **Zeta potential** :

Zeta potential give the type of charge present on the surface of the nanoparticle and stability of the prepared formulation. It is used for the quantification of the magnitude of the charge. Zeta potential graph is shown in the Figure No. 6.



Zeta potential(mV): -35.1 Conductivity(mS/cm): 0.283 Electrophoretic Mobility(cm^2/Vs): -0.000048

Fig. No. 6. Zeta potential

Table No. 7. Zeta potential and conductivity measurement data

Determination of zeta potential (mV) of optimized batch (F8) and Conductivity(mS/cm)	Result Obtained
Zeta potential	-35.1
Conductivity	0.283

6. Particle size and Poly Dispersibility Index (PDI):

Particle size was done by zeta sizer of optimized batch F8.The average particle size of optimized batch F8 was observed 12.3nm. It show that cross-linker has a significant influence on particle size of nanoparticle. The bar graph of particle size for prepared niosome formulation is shown in Fig. 7.

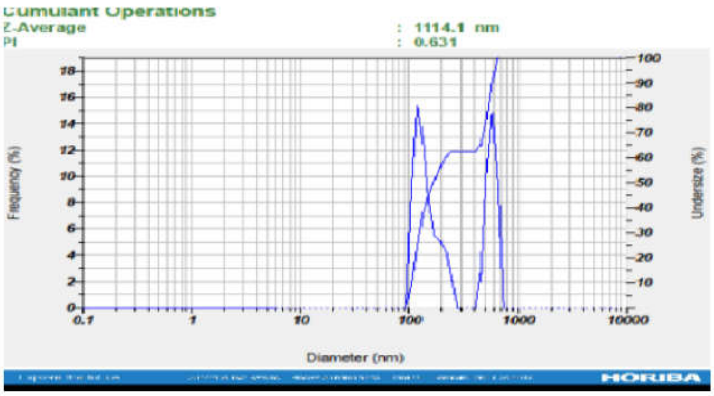


Fig. No. 7. Particle size of optimized F8 formulation

7. **Poly dispersibility index: (PDI)**

PDI is an index of width or spread or variation within the particle size distribution. Monodisperse sample have lower PDI value, whereas PDI of higher value indicates a wider particle size distribution and polydisperse nature of sample. PDI can be calculated by the following equation PDI=Δd/davg.

Where, Δ dis the width of distribution denoted by SD and davg.is the average particle size denoted by MV (nm) in particle size data sheet.

PDI= Δd/davg = 0.4

8. **Transmission electron microscopy (TEM):**

By Transmission electron microscopy TEM the surface morphology of drug particles can be studied. From the TEM photographs of optimized batch F8 the figure confirm that niosomes were spherical in shape, size and surface structure of niosome and also showed the porous surface with no drug crystal on the surface of niosome. The size affected by the encapsulation. The sample was observed under scanning electron microscopy at 5 KX magnetic resonance.

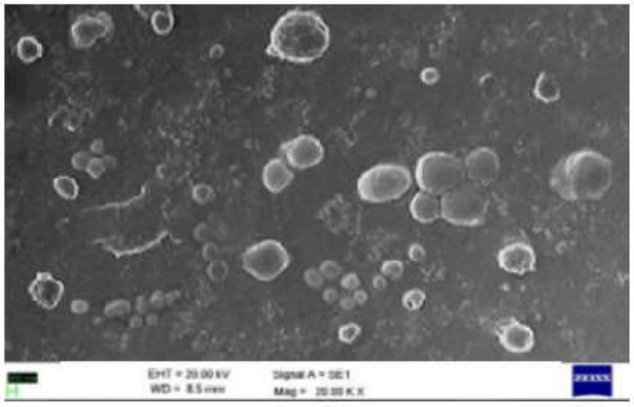


Fig. No. 8. TEM of optimized F8 formulation

9. **Optical Microscopy(F8 batch):**

Optical microscopy of the sample was carried out by using a Digital Microscope (Motic). From the microscopy, it was concluded that F8 batch niosomes were spherical in shape.

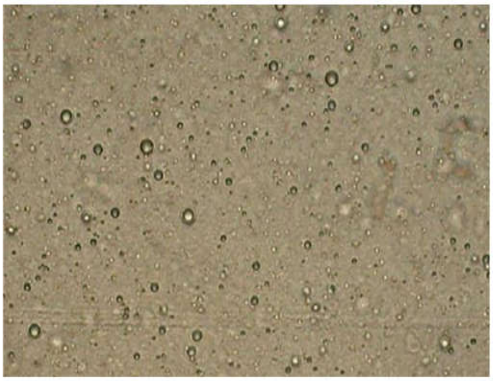


Fig. No. 9. Optical microscopy F8 formulation

10. Entrapment efficiency:

Percentage Entrapment efficiency of batches F1 to F9 was in range from 51.85% to 89.65% of Ajwain oil & Wintergreen oil . Highest % entrapment efficiency shown in F8 batch was 89.65% respectively listed in Table No. 8. from this, it was concluded that, increase in span 60 concentration increases percentage entrapment efficiency.

Batch	Entrapment Efficiency (%) of ajwain oil	Entrapment Efficiency (%) of wintergreen oil	% production yield
Placebo			93.30
F1	55.23 ± 0.65	51.85±0.46	91.65
F2	57.59 ± 0.99	49.65±0.53	92.75
F3	62.89±0.72	64.7± 0.68	93.1
F4	67.86±0.65	69.8 ±0.46	89.7
F5	64.25±0.47	68.8 ±0.78	84.5
F6	72.85 ± 0.62	69.5 ±0.71	95.1
F7	73.65± 0.61	74.44± 0.81	94.5
F8	87.28± 0.24	89.65 ±0.48	96.6
F9	82.19 ± 0.19	85.7 ±0.73	94.25

Table No. 8 Entrapment efficiency of all formulations

11. In vitro drug release study :

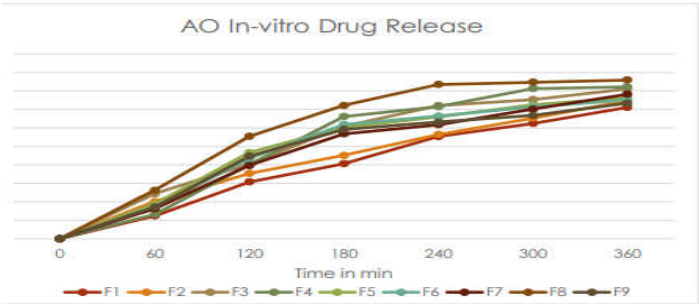


Fig. No. 10. In vitro release of Ajwain oil

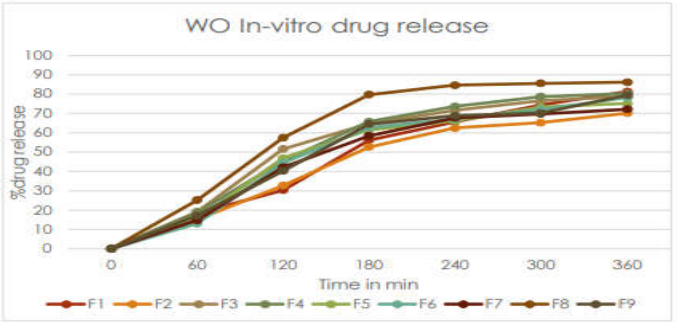


Fig. No. 11. In vitro release of Wintergreen oil

In vitro drug release of niosomal batches was carried out by dialysis bag method. Our main purpose of this study was to sustain the release of drug . Different batches were evaluated , according to the study of F8 batches it is observed that maximum entrapment efficiency was found to be that the surfactants in higher concentrations act as sustained release polymers which cause the drug to release at the controlled rate. Sustained drug permeation and possibly a greater drug deposition and increased drug release where drug containing vesicular systems used, as compared to a pure drug solution.

12. Release kinetic study :

Batch Code	**Zero order model**	**First order model**	**Higuchi/ Matrixm odel**	**Hixson-Crowell model**	**Korsmeyer-Peppas model**		**Best fit kinetic model**
	R	R	R	R	R	n	
F1	0.6550	0.6680	0.9585	0.6550	0.9561	0.6680	First Order model
F2	0.5030	0.6540	0.9684	0.5030	0.9977	0.6540	Korsmeyer-Peppas model
F3	0.7015	0.6220	0.9579	0.7015	0.9970	0.6220	Korsmeyer-Peppas model
F4	0.6370	0.6123	0.9769	0.6370	0.9980	0.6123	Korsmeyer-Peppas model
F5	0.6460	0.5570	0.9458	0.6460	0.9973	0.5570	Korsmeyer-Peppas model
F6	0.7075	0.5630	0.9680	0.7075	0.9870	0.5630	Korsmeyer-Peppas model
F7	0.6020	0.5090	0.9839	0.6223	0.9780	0.5090	Korsmeyer-Peppas model
F8	0.6230	0.5635	0.9723	0.6151	0.9753	0.5635	Higuchi/Matrix model
F9	0.5879	0.5580	0.8072	0.5879	0.9919	0.5580	First Order Model

Table No. 9 Release kinetics of Ajwain oil

Batch Code	Zero order model	First order model	Higuchi /Matrix model	Hixson Crowell model	Korsmeyer-Peppas model		Best fit kinetic model
	R	R	R	R	R	n	
F1	0.5738	0.9880	0.9764	0.9880	0.9764	0.5738	First order model
F2	0.6532	0.9770	0.9875	0.9770	0.9875	0.6532	Korsmeyer-Peppas model
F3	0.6627	0.9769	0.9886	0.9769	0.9886	0.6627	Korsmeyer-Peppas model
F4	0.6796	0.9764	0.9866	0.9764	0.9866	0.6796	Korsmeyer-Peppas model
F5	0.4994	0.9770	0.9837	0.9770	0.9837	0.4994	Korsmeyer-Peppas model
F6	0.6333	0.9680	0.9719	0.9680	0.9719	0.6333	Korsmeyer-Peppas model
F7	0.5293	0.9543	0.9864	0.9543	0.9864	0.5293	Korsmeyer-Peppas model
F8	0.7395	0.9455	0.9656	0.9455	0.9656	0.7395	Higuchi/Matrix model
F9	0.5730	0.8420	0.9820	0.8420	0.9820	0.5730	Korsmeyer-Peppas model

Table No. 10 ReleasekineticsofWintergreenoil

13. Stability study :

Time period	Appearance of F8 batch	% Drug content of F8 batch
Initial	Translucent	85.49 ± 0.16
After 1 month	Translucent and stable	83.20 ± 0.15
After 2 months	Translucent and stable	80.25 ± 0.30

After 3 months	Translucent and stable	82.31 ± 0.33

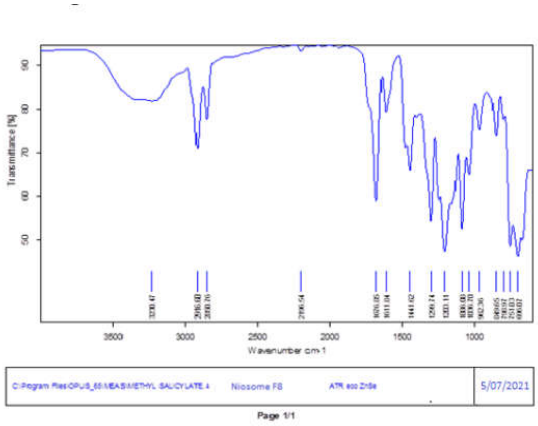


Fig. No. 12. FTIR spectra of F8 batch at 0 days

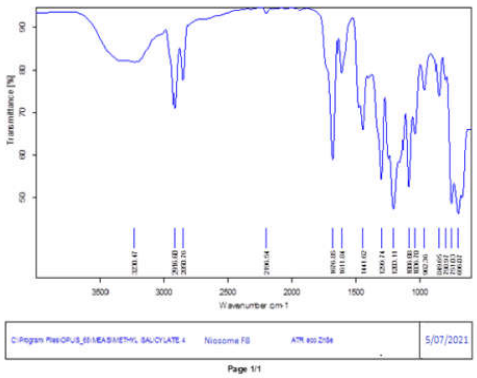


Fig. No. 13 FTIR spectra of F8 batch at 90days

CONCLUSION:

All the formulations show satisfied organoleptic properties. The characterization of drug and excipients was done, all result obtained are compared with the standards and from results obtained it was concluded that drug and excipients are pure and it is of standard quality. From the FTIR study it can concluded that no unaccountable peak was observed. So that developed formulation are pure and no interaction with drug and excipient. From the characterization, it is conform that there was no possible interaction between excipient and drugs. The characterization of optimized niosome under FTIR, SEM, zeta potential and particle size its concluded that the highest drug are entrapped in niosome ,and drug are stable, uniform distribution pattern are achieved for the controlled release of drug. Optimized gel formulation was examined for visual appearance and it was found to be transparent. The pH of the formulation was found to be in between the skin pH range which is in tolerable range for transdermal route. Hence it is concluded that above formulation can be more effective than conventional gel used in treatment of arthritis and back pain.

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