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Research Article

Development Of Spanlastics: Nanovesicular Drug Delivery Of Oxiconazole Nitrate

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ABSTRACT

Oxiconazole nitrate is used to treat fungal infections. It has a restrictive pharmaceutical role because of its poor aqueous solubility, which reduces the bioavailability of the drug. The present investigation was carried out to formulate and evaluate the Oxiconazole nitrate loaded spanlastic. Spanlastic was prepared by Ethanol injection method using Span 60 and Tween 80 as non-ionic surfactant and edge activator. The formulation was evaluated for various parameters like, particle size, transmittance, entrapment efficiency, surface morphology, surface charge and in vitro release studies. Out of eight formulations, F8 having minimum particle size of 452.56nm, transmittance of 79.23±0.23%, higher entrapment efficiency of 94.67±0.89% and dissolution of 82.74±1.34%. The vesicles were found to be spherical and tiny in size. The surface charge of spanlastic was -5.74 mV. Thus it can be concluded that the developed Spanlastic formulation would be a promising delivery system with improved efficacy, controlled release and patient compliance.

INTRODUCTION

Drug delivery refers to approaches, technologies and systems for transporting a pharmaceutical compound in the body as required to safely achieving its desired therapeutic effect, in the past few decades, considerable attention has been focusing on the development of novel drug delivery system (NDDS). The novel drug delivery system is referred as a rebirth system as it is the most suitable and approachable in developing the delivery system which improves the therapeutic efficacy of new as well as pre-existing drugs thus provides controlled and sustained drug delivery to the specific site and meets the real and appropriate drug demand of the body.1 Pharmaceutical nanotechnology, the most recent addition to the pharmaceutical sciences, offers new capabilities, chances, and instruments that are anticipated to

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have a big impact on treatment and disease diagnostics.2 In the field of nanotechnology, novel vesicular drug delivery systems have advanced significantly. Spanlastics are novel surfactant based elastic vesicular drug delivery system, which entraps the drug in the core cavity in the form of the bilayer. These are amphiphilic in nature, in which the drug is encapsulated in a vesicle which is made by non-ionic surfactant. They are shown to be chemically more stable.3 These Spanlastics can be incorporated onto topical formulations for prolonged release and enhanced skin retention, thus reducing the variability of drug absorption, improving the patient compliance and have improved several drawbacks of the conventional dosage form.4 The Oxiconazole nitrate is a broad -spectrum imidazole antifungal agent. Its antifungal activity is due to the inhibition of the ergosterol biosynthesis, which is critical for cellular membrane integrity. Oxiconazole has also been shown inhibition of DNA synthesis and suppresses intracellular concentrations of ATP.5 It belongs to BCS class II having low aqueous solubility and high permeability. Due to its poor solubility in water it leads to low dissolution rate and thus poor therapeutic efficacy if given orally. Low systemic absorption can be overcome by its topical delivery by incorporating drug in spanlastic based gel or ointment. Spanlastic will deliver drug by enhancing the solubility of the drug and entrapment increases skin permeability, and incorporation into gel provides prolong retention time due to viscosity of the formulation and better patient compliance.

MATERIALS AND METHODS

MATERIALS:

Oxiconazole nitrate was supplied from Yarrow Chem Products, Mumbai .All other excipients and solvents used were of the analytical pharmaceutical grade.

METHODS

Preformulation studies of drug:

6-7 Organolepetic properties like melting point, solubility Oxiconazole nitrate was evaluated.

Determination of Standard calibration curve of oxiconazole nitrate8

The solution containing 10 µg/ml concentrationof oxiconazole was prepared and scanned over range of 200-400nm against phosphate buffer of pH 6.8 as blank using double beam U V spectrophotometer. The calibration curve was plotted against concentration versus absorbance.

Drug- excipient compatibility study9

FT-IR spectra of pure oxiconazole nitrate, surfactant, edge activator, and prepared spanlastic formulation were obtained using FT-IR spectrometer. FT-IR spectra were recorded within the spectral region of 4000 and 400 cm−1 using the instrument Perkin Elmer FTIR.

Preparation of oxiconazole nitrate spanlastic by ethanol injection method10-11

Tween 80 was accurately weighed and dissolved in 40mL of distilled water heated to the temperature of 70ºC. Span 60 were accurately weighed and dissolved in 10 mL of ethanol and Oxiconazole nitrate was weighed and added to the span solution. Span solution was then injected using a 30- gauze syringe at a fixed rate of 1 mL/min to the pre-heated tween solution which was continuously being stirrer on a magnetic stirrer at 500 rpm, Stirring was continued for 30 minutes at 70ºC. The solvent was evaporated by heating to obtain drug-loaded spanlastic vesicles. It will be subjected to probe sonication by transferring the colloidal suspension into a beaker and stored at 2-4°C

Table 1: Formulation chart of Oxiconazole Nitrate spanlastic

Ingredients	F1	F2	F3	F4	F5	F6	F7	F8	F9
Oxiconazole nitrate (mg)	200	200	200	200	200	200	200	200	200
Span 60 (mg)	1000	925	1000	925	850	1000	850	850	925
Tween 80 (mg)	250	250	200	300	300	300	200	250	200
Ethanol (ml)	10	10	10	10	10	10	10	10	10
Distilled water (ml)	40	40	40	40	40	40	40	40	40

Characterization of oxiconazole nitrate loaded spanlastic:

Particle size analysis12

Particle size was measured using Zeta sizer (Malvern Instruments, UK) based on the dynamic light scattering principle. Each sample was suitably diluted with water and measured at 25 °C.

Determination of Transmittance13

To analyze transparency, 1ml of spanlastic dispersion was diluted to 10ml and % transmittance was measured at 600 nm using UV - Vis Spectrophotometer.

Determination of Entrapment efficiency12

10 ml of the spanlastic dispersion was taken in a centrifuge tube and the supernatant was collected after cooling centrifuge at 17,000 rpm for 15min. Then, the supernatant was filtered through a 0.45 µm filter. 1 ml of the above supernatant was taken in a 10ml of volumetric flask and the volume makeup is done by methanol. The amount of drug present in the supernatant was determined by ultraviolet (UV) spectrophotometrically.

The EE% of the drug was calculated using this equation:

$$\%DEE = \frac{\text{Total amount of drug} - \text{Free drug in supernatant}}{\text{Total amount of drug}} \times 100$$

Surface morphology study14

The optimized oxiconazole nitrate loaded spanlastic was characterized using optical microscope for structural attributes such as uniformity of size, lamillarity and shape.

Determination of zeta potential15

The zeta potential of optimized oxiconazole nitrate loaded spanlastic was measured using Zeta sizer (Malvern Instruments, UK), which functions based on the electrophoretic mobility principle under an electric field.

In-vitro release Studies16

In-vitro drug release from prepared Spanlastic formulation was evaluated by dialysis bag membrane diffusion technique. The formulation was added to the dialysis bag immersed in phosphate buffer solution maintained at 37°C. Suitable volumes of the sample were withdrawn at regular time intervals and equivalent volume was replaced with phosphate buffer solution. The samples were analyzed spectrophotometrically using UV-Visible Spectroscopy to determine amount of drug released over a period of time.

RESULTS AND DISCUSSION

Preformulation studies of drug:

Table 2: Organoleptic properties and melting point

Properties		Reported	Observed
Organoleptic properties	Color	White powder	White powder
	Nature	White crystalline powder	White crystalline powder
	Odor	odorless	Odorless
Melting point		137-139^{0}C	138^{0}C

Table 3: Solubility of pure drug in different solvents

Propertied	Reported				Observed		
Solubility	Water	Phosphate buffer pH 6.8	Methanol	Ethanol	Water	Phosphate buffer pH 6.8	Methanol
	0.00192mg/ml	0.078 mg/ml	35 mg/ml	15.2 mg/ml	0.00190	0.072 mg/ml	30 mg/ml

Determination of Standard calibration curve of oxiconazole nitrate:

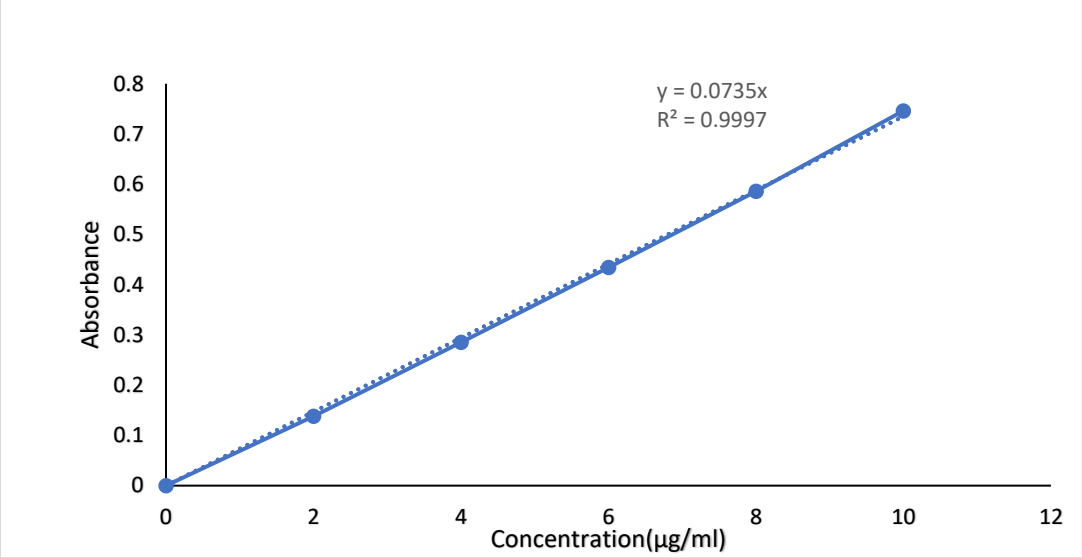

Fig 1:Standard calibration curve of oxiconazole nitrate in phosphate buffer pH6.8

The calibration curve of Oxiconazole nitrate with slope, intercept and regression co-efficient was determined the absorbance value remained linear and obeyed Beer's Lamberts Law in the range of 0-10µg/ml with the R2 value of 0.9991.

Drug – excipient compatibility studies:

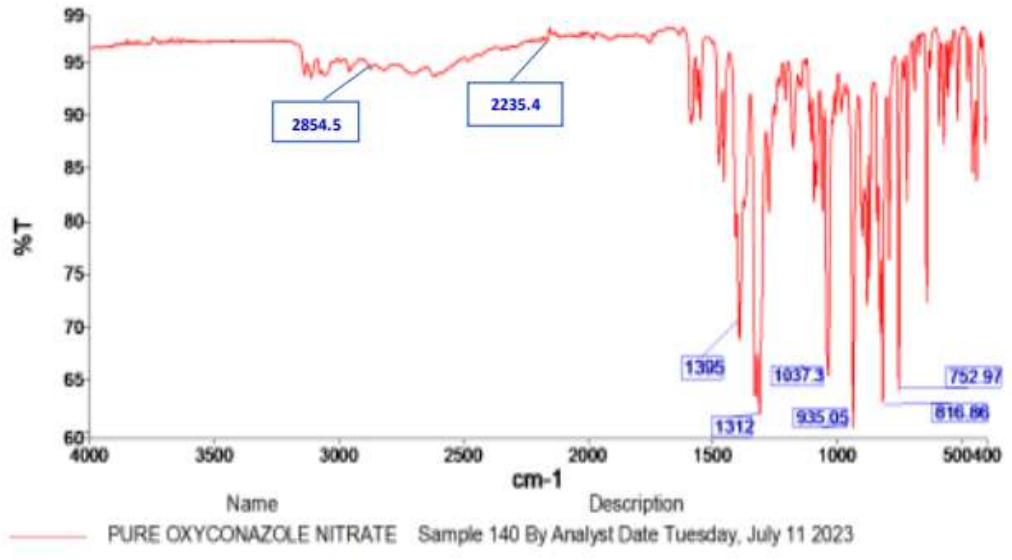

Fig 2:FTIR spectra of pure oxiconazole nitrate

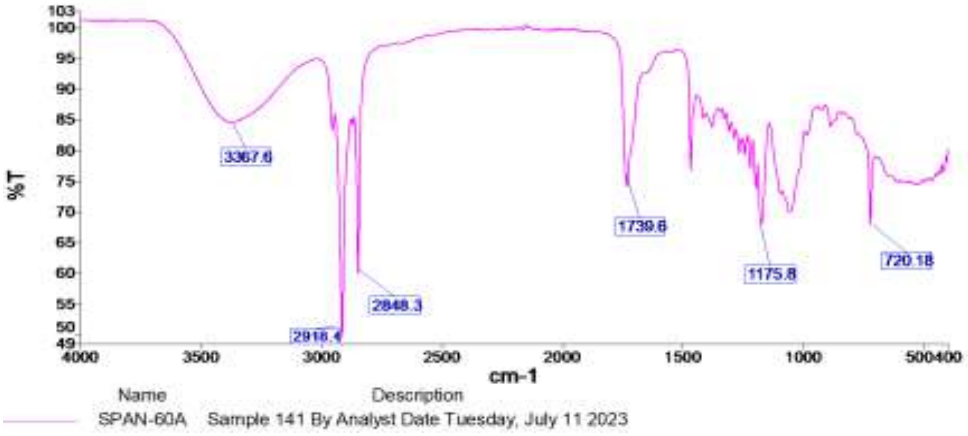

Fig 3:FTIR spectra of span 60

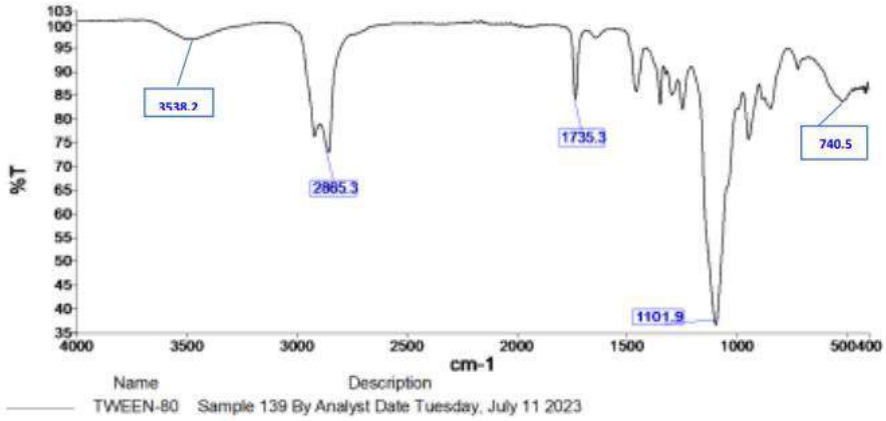

Fig 4 :FTIR spectra of tween 80

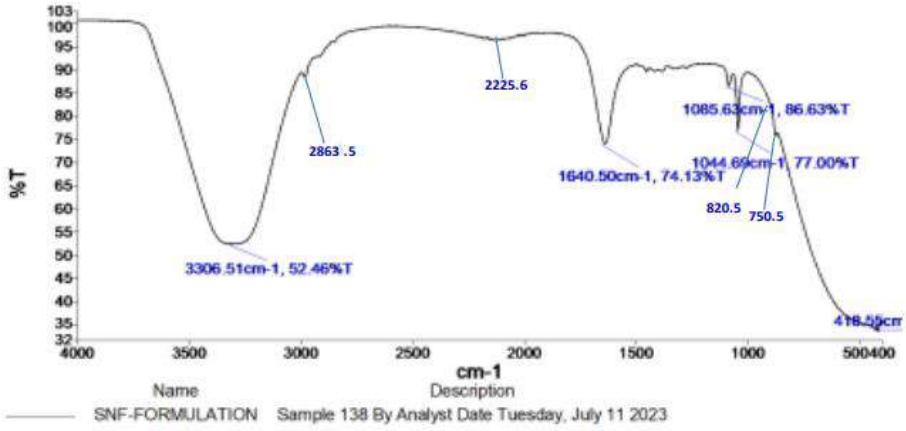

Fig 5: FTIR spectra of spanlastic formulation

All the characteristics of IR peaks related to pure drug Oxiconazole, Span 60, and Tween 80 have also appeared in the FT-IR spectrum of optimized spanlastic formulation. This result could infer that there was no chemical incompatibility between the drug and excipients.

Characterization of Oxiconazole nitrate spanlastic:

Table 3: Determination of particle size, transmittance and entrapment efficiency

Formulation code	Particle size (nm)	Transmittance (%)	Entrapment efficiency (%)
F1	945.9	66.8±0.05	74.3±0.41
F2	446.2	76.8±0.03	88.45±0.75
F3	798.9	61.3±0.09	71.90±0.23
F4	561.8	68.3±0.02	78.67±0.89
F5	582.8	73.5±0.03	79.90±0.45
F6	921.3	75.7±0.06	84.12±0.78
F7	495.6	78.2±0.01	90.78±0.56
F8	452.2	82.4±0.04	94.67±0.89
F9	760.3	72.3±0.01	85.90±0.67

The results of study indicated that particle size was influenced by the concentration of span 60 and tween 80. Out of all nine formulation F8 (452.2nm) shows lesser particle size.The % transmittance of spanlastic formulation ranged from 61.3 to 82.4%.The results of the study indicated that as the concentration of Span 60 decreases and tween 80 increases % transmittance increases. The results of % entrapment of spanlastic formulation indicated that formulation F8 with 94.67% have higher entrapment efficiency.

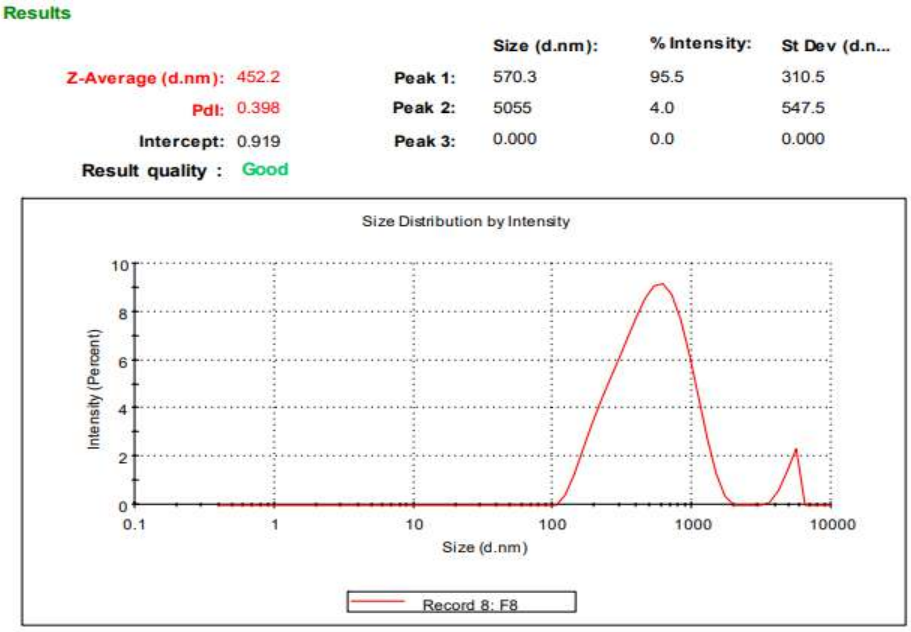

Fig 6: Particle size of F8 by Malvern zeta sizer

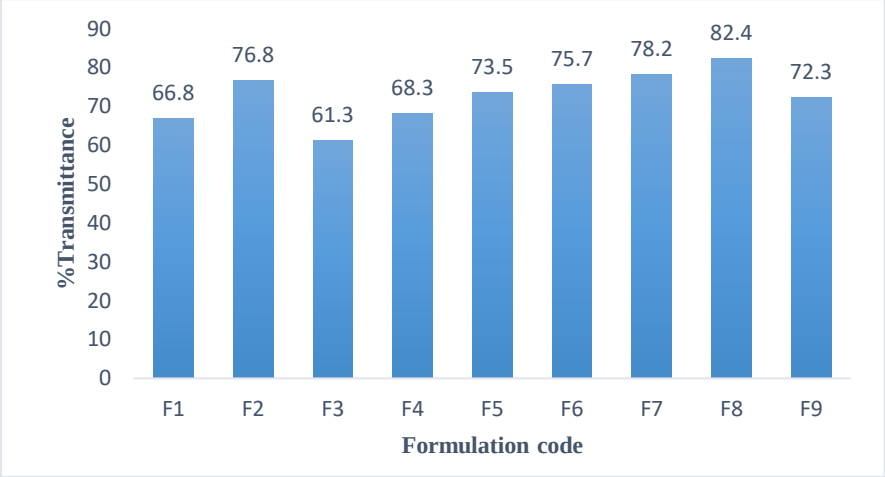

Fig 7: %Transmittance of spanlastic formulation F1-F9

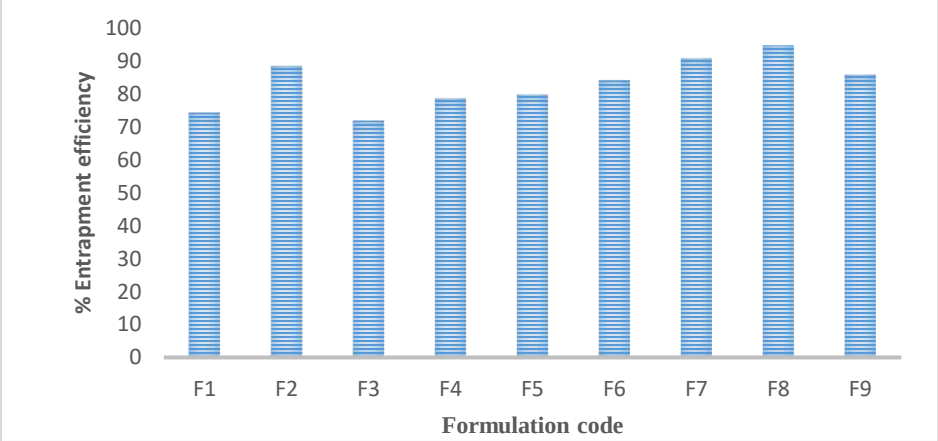

Fig 8: Entrapment efficiency of spanlastic formulation F1-F9

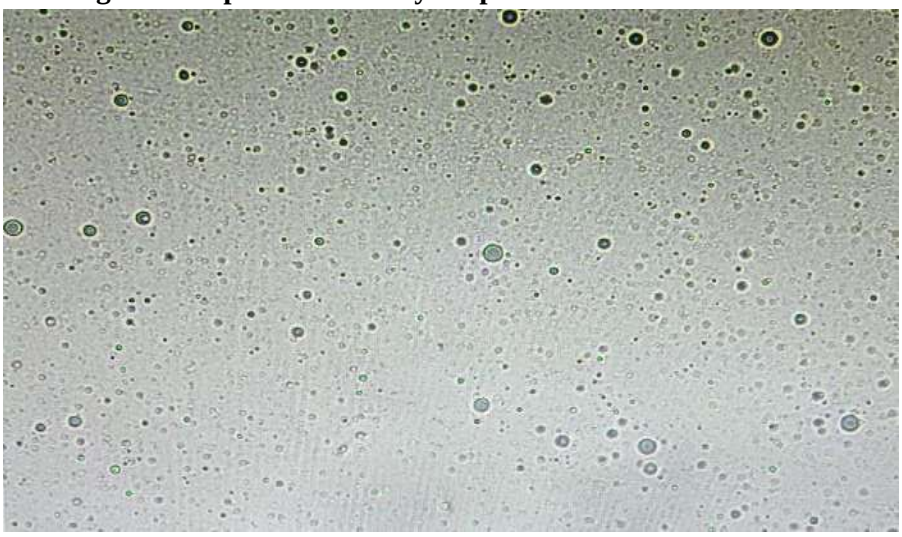

Fig 9: Surface morphology of F8 by optical microscope

The surface morphology of spanlastic was studied by using the optical microscope. Fig 9 demonstrates the surface morphology of optimized oxiconazole nitrate loaded spanlastic which indicated that the vesicles was small in size with round shape.

Zeta potential

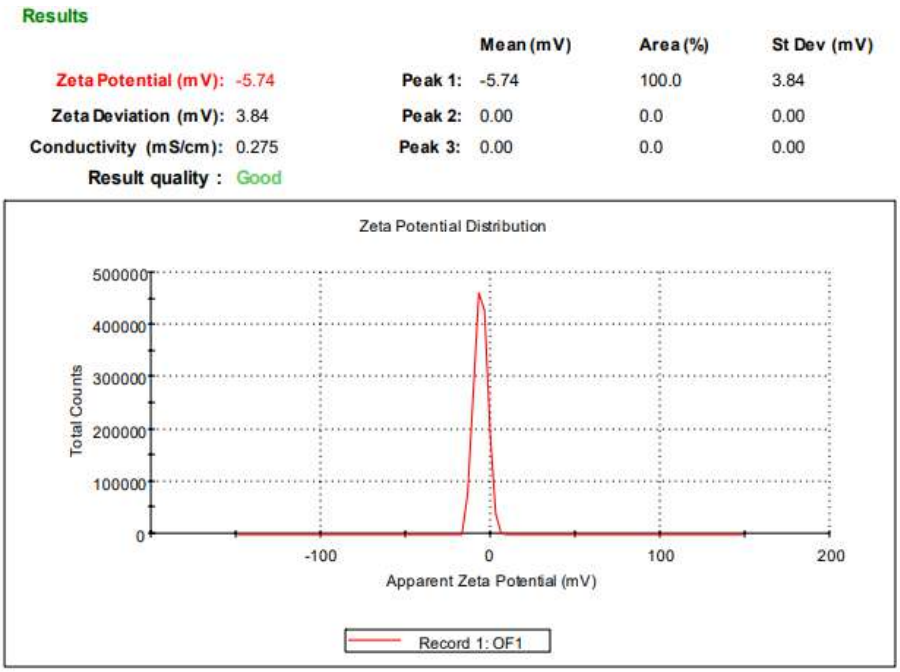

Fig 10: Zeta potential of F8 formulation

The zeta potential of optimized spanlastic formulation was determined by malvern zeta sizer instrument. The Zeta potential of oxiconazole nitrate loaded spanlastic formulation was found to be -5.74 mV (Fig 10) which indicates good stability of spanlastic formulation.

In-vitro release studies:

Table 4: In -vitro release studies of spanlastic

Time (hrs.)	% Cumulative drug release								
	F1	F2	F3	F4	F5	F6	F7	F8	F9
0	0	0	0	0	0	0	0	0	0
1	16.78	18.89	14.56	20.89	19.89	15.90	17.89	20.67	13.78
2	29.56	31.34	27.89	33.67	30.90	29.93	29.78	34.91	27.56
3	37.09	39.89	35.89	40.78	37.56	35.67	36.78	40.89	35.89
4	45.89	47.89	45.89	52.89	49.89	48.90	50.78	55.67	35.89
5	50.78	51.89	49.78	60.45	55.89	50.89	58.98	65.30	49.89
6	55.89	55.67	54.9	66.90	61.91	53.90	64.67	72.56	55.56
7	60.89	59.67	58.90	74.89	65.78	58.67	70.78	78.89	57.89
8	63.08	63.85	61.01	80.27	70.20	63.05	79.20	85.02	60.20

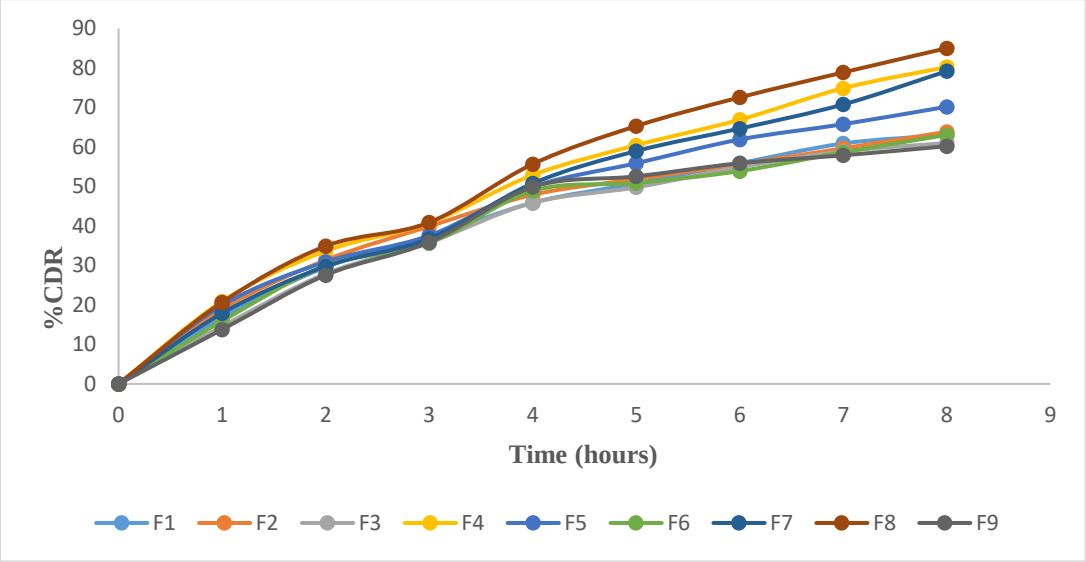

Fig11:In -vitro release studies of spanlastics(F1-F9)

The Drug and excipients composition influences in-vitro release rate of spanlastic. The formulation showed a biphasic release profile, an initial faster release phase up to 3 hrs. Followed by a controlled release over period of 8 hrs. This biphasic release pattern seemed to be a characteristic of bilayered vesicles. Rapid drug leakage was observed during the initial phase due to the presence of drug adsorbed on the surface of the vesicles. After that the entrapped drug would show a controlled release profile. Differences in the in- vitro release profiles might be due to vesicle size, lamella and membrane fluidity as a function of chain length of surfactant.

CONCLUSION

The present study has been satisfactory attempt to formulate spanlastic for the controlled delivery of oxiconazole nitrate using span 60 as a non-ionic surfactant tween 80 as edge activator and ethanol as a solvent. Development of novel surfactant based vesicles of Spanlastics provides a noninvasive tool for delivering the drug to its target site without the need for frequent drug administration. From the reproducible results of the executed experiments, it can be concluded that; The oxiconazole nitrate loaded spanlastic was prepared by ethanol injection method and evaluated for various parameters such as particle size, transmittance, entrapment efficiency Surface morphology, zeta potential and in-vitro release studies. Based on characterization spanlastics formulation with higher entrapment efficiency and transmittance, least particle size and increased drug release (F8) was selected for topical gel formulation. Spanlastics formulation tackle the issue of insolubility, instability, low bioavailability and fast debasement of medications. Thus, it can be concluded that spanlastics can act as a breakthrough in the nano vesicular drug delivery system. This system is being used now for delivering drugs to ocular, oral, and topical routes.

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RELEVANT CONFLICTS OF INTEREST/FINANCIAL DISCLOSURES:

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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