WORLD JOURNAL OF PHARMACEUTICAL RESEARCH
SJIF Impact Factor 8.084
Volume 9, Issue 3, 674-690. Research Article ISSN 2277– 7105

FORMULATION AND EVALUATION OF LINEZOLID NIOSOMAL GEL FOR TOPICAL DRUG DELIVERY

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Article Received on
26 Dec. 2019,

Revised on 16 Jan. 2020,
Accepted on 06 Feb. 2020,

DOI: 10.20959/wjpr20203-16644

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ABSTRACT

Background: In the current study Linezolid niosomes were formulated and incorporated into the gel base for topical drug delivery as the conventional dosage forms of Linezolid undergo first-pass metabolism. Thereby when given topically it shall provide local action and improve the patient compliance. **Materials and methods:** Niosomes were formulated using surfactant (span 40 and 60, tween 60 and 80) and cholesterol with different ratios (1:1, 1.5:1, 1:2) by thin film hydration method and evaluated for vesicle size, entrapment efficiency, zeta potential, drug release study. Physical parameters of niosomes were found to be within the acceptable limits. **Results and discussion:** The niosomes were found to be spherical in shape. FV4 and FV5 formulations showed better result for % EE of 78.8% and 87.5% respectively. The particle size of FV4 was found to be 170 nm and FV5 showed the particle size of 125 nm, the percentage drug release of FV4 formulation was found to be 76.25% and FV5 showed the release of 80.5%. FV4 and FV5 were selected as optimized formulation and incorporated into the gels with different ratios of gelling agents and evaluated for pH, viscosity, spreadability, drug release, antibacterial test, skin irritation test and stability studies. Formulation FG5 showed better results in terms of pH (6.35), viscosity (11872cps), spreadability (9.61 g.cm/sec) and percentage drug release of 73.74% in 8 h. Formulation FG5 was selected as the optimized formulation. **Conclusion:** The above results indicated that the niosomal gels of Linezolid could be the better formulation in the future.

KEYWORDS: Linezolid, Niosomes, Cholesterol, Topical Drug Delivery.

INTRODUCTION

Delivery of drug via a particular system is a planned procedure which are used so that drugs get into the body and reach their desired site of action. Transdermal drug release system involves absorption of drug from the formulation which is present onto the body surface. Transdermal drug delivery system aims at delivering of drugs into systemic circulation.[1] In order to achieve transdermal membrane permeation, most of the drug candidates have to overcome the barrier of stratum corneum.[2,3] This has been attractive as well as challenging area for research having several advantages such as they are non-protruding, convenient and less expensive and can be self administered. Further plasma concentration profile can be maintained for prolonged period of time. Methicillin-resistant *Staphylococcus aureus* (MRSA) is resistant to several antibiotics, certain individual are at the risk of developing skin infections like, those who have diabetes, human immunodeficiency virus (HIV), AIDS or other immune disorders.[4]

Niosomes are novel drug delivery system which serves as drug depots in the body as they release the drug through the bilayer that helps to control the release of the enclosed drug.[5] Niosomes are self-assembling vesicle systems formed from non-ionic in an aqueous environment.[6] Niosomes enhance the solubility, bioavailability and stability of certain BCS class II drugs along with an ability to provide sustained release for prolonged drug effects.[7]

Linezolid is an antibiotic which is useful for the treatment of MRSA skin infections which inhibits bacterial protein synthesis by acting at an early step and a site different from that of other anti-microbial agents (AMAs) and acts by binding to the 23S fraction (P site) of the 50S ribosome that interferes with formation of the ternary N-formylmethionine tRNA 70S initiation complex.[4,8,9] Currently, about 40% of the drug candidates are related to transdermal system which are under clinical assessment. Transdermal drug delivery offers many benefits over oral or intravenous administration such as better regulation of blood levels, decreased systemic toxicity, preventing hepatic firstpass metabolism, reduced side effects and dosing frequency with improved bioavailability.[10]

Commercially available marketed formulations of Linezolid in the form of tablets and injections are found to have adverse side effects such as headache, nausea, vomiting, abdominal discomfort and diarrhea. Since Linezolid cannot be taken in combination with a number of medications orally, a novel dosage form has been proposed as topical application by incorporating the drug in niosomal gel formulations.[11] Transdermal drug delivery gels are

prepared with organic polymers like carbomers as they impart an asthetic pleasing as well as help in reducing the doses as compared to oral forms and deliver the drug in controlled and sustained manner.

The purpose of the present study is to prepare and evaluate niosomal gel of Linezolid as effective topical drug delivery system which will minimize the side effects associated with excessive dose of Linezolid and improve the patient compliance.

MATERIALS AND METHODS

Materials

Linezolid was obtained as gift sample from Apotex research Pvt. Ltd., (Bangalore, India). Cholesterol was obtained from Sigma Aldrich (Bangalore, India). Span 40 and span 60 was obtained from S.D. Fine-Chem Ltd., (Mumbai, India). Tween 60 and Tween 80 were procured from M/s Hi-media Pvt. LtSd., (Mumbai). Carbopol 934 was obtained from Himedia Pvt Ltd., (India) and Triethanolamine was obtained from Merck Pvt Ltd., (Mumbai, India).

Formulation of Linezolid niosomal suspension

Niosomes containing Linezolid were prepared by thin film hydration method using non-ionic surfactants (span 40, 60 and Tween 60, 80) and cholesterol in the ratios of (1:1, 1:1.5, 1:2). Suitable modifications have been done to the method which has been previously employed by Shirsand SB *et al.*[12] Accurately weighed quantities of drug, surfactant and cholesterol were dissolved in 10 ml of methanol in a round-bottomed flask. The solvent mixture was evaporated in a rotary evaporator under reduced pressure of 250 psi with 190 rpm at 60-65°C. A thin dry film was formed which is further hydrated with 10ml of phosphate buffer 6.8 pH in rotary evaporator for 30 min. A white milky fluid was formed containing Linezolid encapsulated niosomes. In total 12 formulations of niosomes were prepared having different concentrations of cholesterol and surfactant, which were stored in amber colored bottle for further analysis. The formulation of niosomal suspension is given in Table 1.

Table 1: Formulation table of Linezolid niosomal suspension.

Ingredients	FV1	FV2	FV3	FV4	FV5	FV6	FV7	FV8	FV9	FV10	FV11	FV12
Drug (mg)	120	120	120	120	120	120	120	120	120	120	120	120
Cholesterol: surfactant Ratio	1:1	1:1.5	1:2	1:1	1:1.5	1:2	1:1	1:1.5	1:2	1:1	1:1.5	1:2
Cholesterol (mg)	100	100	100	100	100	100	100	100	100	100	100	100
Span 40 (mg)	100	150	200	-	-	-	-	-	-	-	-	-
Span 60 (mg)	-	-	-	100	150	200	-	-	-	-	-	-
Tween 60 (mg)	-	-	-	-	-	-	100	150	200	-	-	-
Tween 80 (mg)	-	-	-	-	-	-	-	-	-	100	150	200
PBS (ml)	10	10	10	10	10	10	10	10	10	10	10	10
Methanol (ml)	10	10	10	10	10	10	10	10	10	10	10	10

Evaluation of niosomal suspension

Particle size

The particle size and polydispersity index of the prepared niosomes was measured using nanotrac where niosomal suspensions were diluted appropriately with millipore water and analysed.

Entrapment efficiency

Percentage Entrapment efficiency of niosomal formulations was carried out by using ultra centrifugation method.[13] 1 ml of niosomal suspension was taken and ultra-centrifuged at 14,000 rpm, 4°C for 1 h (Sorval MX 150, Thermo scientific Ultracentrifuge, US). The supernatant liquid was separated and was analysed for un-entrapped drug at λ_{max} of 251nm by UV spectrophotometer (Shimadzu -1800, Japan). % EE was calculated by using formula.

$$\% EE = \frac{\text{Total drug content} - \text{unentrapped drug}}{\text{Total drug content}} \times 100$$

Transmission electron microscopy (TEM) and Scanning electron microscopy (SEM)

The morphology of Linezolid niosomes was analyzed by transmission electron microscopy (JEM-2100, JEOL. Japan). Niosomal Suspension was diluted with water; a drop of the diluted suspension was then directly deposited on a carbon coated grid for 2 min, negatively stained with 1% aqueous solution of phosphotungestic acid. Then air dried sample was visualized under Transmission electron microscope.

The surface morphology of Linezolid niosomes was analysed by scanning electron microscopy. The dried NLCs were mounted on metal stubs and coated with Platinum using a

Sputter Coater JFC-1600 (JEOL, Japan) and were then observed under JSM-6360LV Scanning Electron Microscope (JEOL, Japan).

***In vitro* drug release**

In vitro release studies were performed using modified Franz diffusion cell.[14] Dialysis membrane (Himedia laboratories Pvt Ltd) having pore size 2.4 nm, molecular weight cut off 12,000–14,000 was used. 100 ml of Phosphate Buffer pH 6.8 was taken in receptor compartment. 1ml equivalent to 6mg of niosomal suspension was taken in donor compartment. The temperature was set at 37°C with continuous stirring. Aliquots were collected at predetermined interval and replaced with equal amounts of fresh buffer. Aliquots were diluted with phosphate buffer pH 6.8 and analyzed at 251 nm by UV-1800 (Shimadzu, Japan).

Preparation of gel

Gel was prepared by soaking 1g of Carbopol 934 in distilled water overnight to get 1% concentration. Magnetic stirrer was used to form homogeneous base. Optimized niosomal suspensions were dispersed in the gel base to get 0.5% w/v of gel. Triethanolamine (TEA) 0.05% was slowly added to adjust the pH of the gel and mixing was continued to obtain clear homogenized gel. The pure drug gel is also prepared by incorporating pure drug in gel base and is then stored in air tight bottle till further analysis.

Evaluation of gel

pH and viscosity of gel

The pH of the gel was determined by digital pH meter. Viscosity was determined by Brookfield viscometer CAP 2000+. The spindle 1 was rotated at 50 rpm. Samples of gel were allowed to settle over 5 min at room temperature (25 ± 2°C) before measurements.

Drug content

A specific quantity of prepared gel was taken and dissolved in 100 ml of methanol and it was set aside for sonication for 30 min. The solution of 1 ml was diluted to 10 ml with methanol. After suitable dilution drug absorbance was recorded by UV-spectrophotometer at 251 nm.

***In vitro* drug release of niosomes**

Appropriate medium was developed that can maintain sink conditions so as to provide sufficient solubility for the drug during diffusion studies. The release of Linezolid from

niosomes was analyzed by using the membrane diffusion technique. 1ml of niosomal suspension was located in a diffusion cell (glass tube) of diameter 2.5 cm, the lower open end of the glass tube was enclosed with cellulose membrane-150. This cell suspended in beaker containing 100 ml of phosphate buffer solution of pH 6.8. This was continuously stirred at speed of 50 rpm at 37ºC on magnetic stirrer with a thermostat. Aliquots were withdrawn at the intervals of 0, ½, 1, 2, 3, 4, 5, 6, 7 and 8 h and substituted with equivalent volume of fresh phosphate buffer solution. The samples were diluted and estimated for concentration of Linezolid by spectrophotometer at λ_{max} 251 nm.

***Ex vivo* skin permeation study**

The study was carried out using male Wistar rat abdominal skin. Animal was sacrificed by inhalation of diethyl ether. Hair on abdominal area of rat was removed using electric clipper. Abdominal skin was excised and washed with phosphate buffer pH 6.8 and fat was removed. The skin samples were mounted onto Franz diffusion cells (Perme Gear, Inc., PA, and USA) with the effective diffusion area of 1.77 cm^2. The epidermal side of the skin was exposed to ambient conditions while the dermal side was bathed with receptor compartment containing phosphate buffer of pH 6.8, 100 ml to maintain the sink conditions. The receptor compartment was adjusted at 37°C. Continuous stirring was maintained to simulate *in vivo* condition. After equilibration for 30 min, equivalent to 0.5% w/w of F-2 optimized niosomal gel and pure gel were applied to the skin surface. Aliquots from each cell receptor medium was withdrawn at predetermined intervals and replaced by equal volume of fresh buffer. Aliquots were diluted with buffer and analyzed at 251 nm by UV spectrophotometer (UV-1800, Shimadzu, Japan). After 12 h, the skin samples were carefully wiped off to discard the rest of formulations. The flux (J_{max}) at 12 h was calculated by

$$J_{max} = \frac{\text{Amount of permeated drug}}{\text{Time x effective area of skin}}$$

***In vitro* antibacterial activity**

The *in vitro* antibacterial activity was carried out to find the efficacy of the formulated gel. Linezolid is active against methicillin-resistant *staphylococcus aureus* which is responsible for bacterial skin infections. Mac-conkey nutrient agar was placed into petri-dish and kept to set for 30min. 5mm wells were made and the MRSA bacteria was spread on petri-dish by spreading technique. The optimized gel and pure gel were added into the wells and was kept at 30°C for 24 h and zone of inhibition was recorded.

Skin irritation test

Male wistar rats were used as the test animals for skin irritation study. They were separated into two groups i.e., control and test groups. The back skin of the rat of 5 cm^2 was shaven a day before the beginning of the examination. After 24 h of shaving the skin of rat, the control group was treated with pure gel and the test group was treated with the optimized niosomal gel and the rates were noticed for any aggravation towards the finish of 24 h. The animals were observed for any skin irritation like erythema or edema and score were given as needed.

RESULTS AND DISCUSSION

The present study was focused on the preparation of niosomes. Preliminary studies were performed to optimize the concentrations cholesterol and surfactant. Niosomal formulations FV1-FV12 were successfully prepared and subjected to various evaluation parameters. Based on the best obtained results one formulation was optimized and subjected for the preparation of gel.

Particle size and vesicle morphology

Particle size measurement was required to confirm the production of the particles in required range. Particle size data for the niosomes by using different ratios of cholesterol and surfactant are shown in Table 2. The mean particle size of Linezolid niosomal formulations were found in the range of 126.03 ± 0.85 nm to 474 ± 0.56 nm. The vesicles with the tween 60 and tween 80 showed larger vesicle size whereas the span 40 and span 60 showed smaller vesicle size. It is due to the fact that spans are sorbitan fatty acid esters which have low HLB values in the range of 1.8 – 8.6 and tweens are polyoxyethylene derivatives of spans which have high HLB values in the range of 9.6 – 16.7.[15] Higher the HLB value of surfactants larger the size of the vesicles as reported by Yoshioka *et al.*[16] The scanning electron miscrosopic and transmission electron microscopic images showed that the vesicles are spherical in shape with sharp boundaries having large internal aqueous space. The FV5 formulation containing span 60 showed smallest vesicle size of 126 nm and poly dispersibility index (PDI) of 0.388. Small vesicle size was due to the fact that span 60 has the lowest HLB value of 4.7 unlike span 40 and tween 60 which are having HLB value of 6.7 and 14.9 respectively.[17] The FV12 formulation containing tween 80 showed largest vesicle size of 474 nm with PDI of 1.15. Large vesicle is attributed to the fact that tween 80 has higher HLB value of 15 as compared to other surfactants used.[18] The particle size of vesicles is shown in Table 2 and the microscopic images are shown in Fig. 1 and Fig. 2.

Table 2: Particle size, polydispersibility index, % entrapment efficiency of vesicles.

Formulation Code	Particle size (nm)	PDI	Entrapment Efficiency (%)
FV1	141.9±0.12	0.692± 0.056	80.66±0.88
FV2	149.1±0.39	0.819±0.007	76.3±0.44
FV3	173.6±0.78	0.465±0.021	72.4±0.33
FV4	170.8±0.67	0.395± 0.086	78.8±0.24
FV5	126.0±0.85	0.388±0.021	87.3±0.25
FV6	179.2±0.71	0.338±0.85	81.08±0.63
FV7	357±0.09	0.867±0.007	74.1±0.44
FV8	279±1.12	0.950±0.063	85±0.56
FV9	380±1.21	1.093±0.054	81.1±0.39
FV10	422±0.85	0.699±0.009	67.55±0.25
FV11	466±0.63	1.108±0.040	74.9±0.89
FV12	474±0.56	1.551±0.010	72.3±0.72

*Data expressed as Mean±SD (n=3)

Entrapment efficiency

The entrapment efficiency percentage of niosomal formulations range obtained from 67.55% to 87.16%. Spans shows higher phase transition temperature than tweens providing higher entrapment efficiency for the drug. Also tween 60 and tween 80 showed lower entrapment efficiency as compared to span 60 and span 40. The maximum entrapment efficiency was found in FV5 formulation containing span 60 which has saturated alkyl chain and high transition temperature. It complies with the previous works reported by Shilpa DJ *et al*[19] and Lavanya SB *et al*.[20] The drug encapsulation efficiency of all formulations is shown in Table 2.

Transmission electron microscopy (TEM) and Scanning electron microscopy (SEM)

The TEM study suggested that the particles had almost round and uniform shape and were in required range of 100 nm as shown in Fig. 1.

SEM study suggested that the particles were round in shape and there was no aggregations of particles were seen due to the presence of surfactant as shown in Fig. 2.

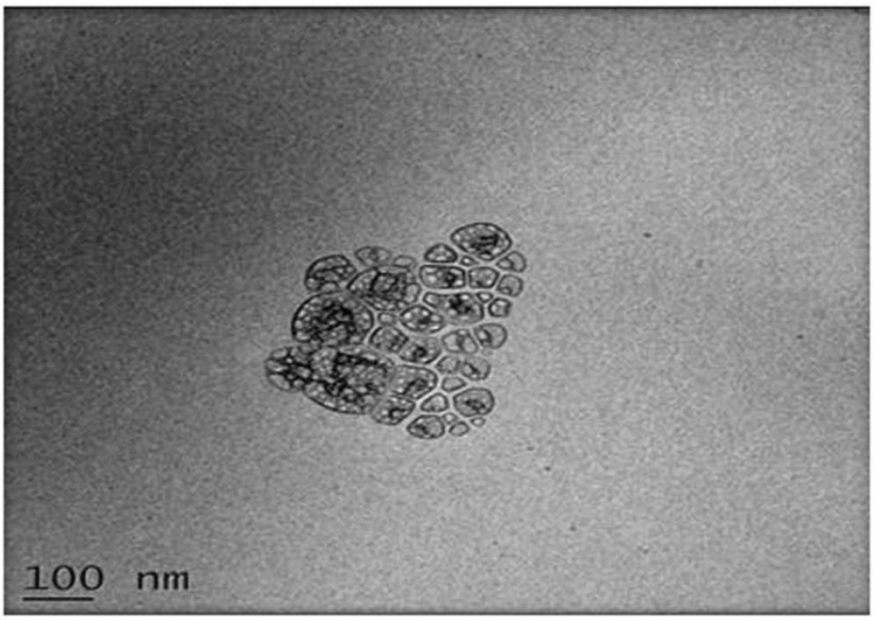

Fig. 1: Transmission electron microscopy of optimized formulation FV5 at 100nm.

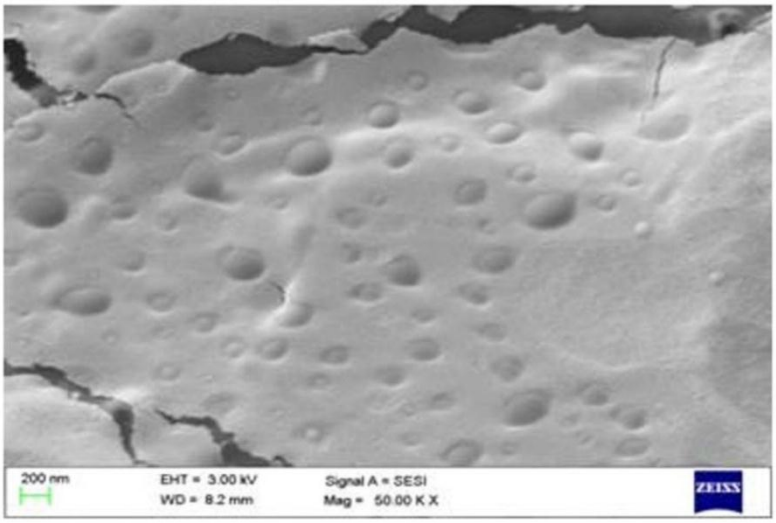

Fig. 2: Scanning electron microscopy of optimized formulation FV5 at 200 nm.

***In vitro* drug release**

The *in vitro* drug release of niosomal suspension was carried out by using phosphate buffer system of pH 6.8. The drug release of the formulated niosomal suspension was found in the range of 57.9% - 80.05%. Higher drug release was found in niosomes prepared with span 60 than the other formulations. The maximum drug release was obtained in the formulation FV5 (Span 60:cholesterol 1.5:1) shown the release of 80.05% in 8 h and formulation FV12 (Tween 80: cholesterol 1:2) showed the drug release of 57.9%. After 8 h, the tween niosomal formulations showed the less drug release as compared to span niosomal formulations. The results are shown in Fig. 3.

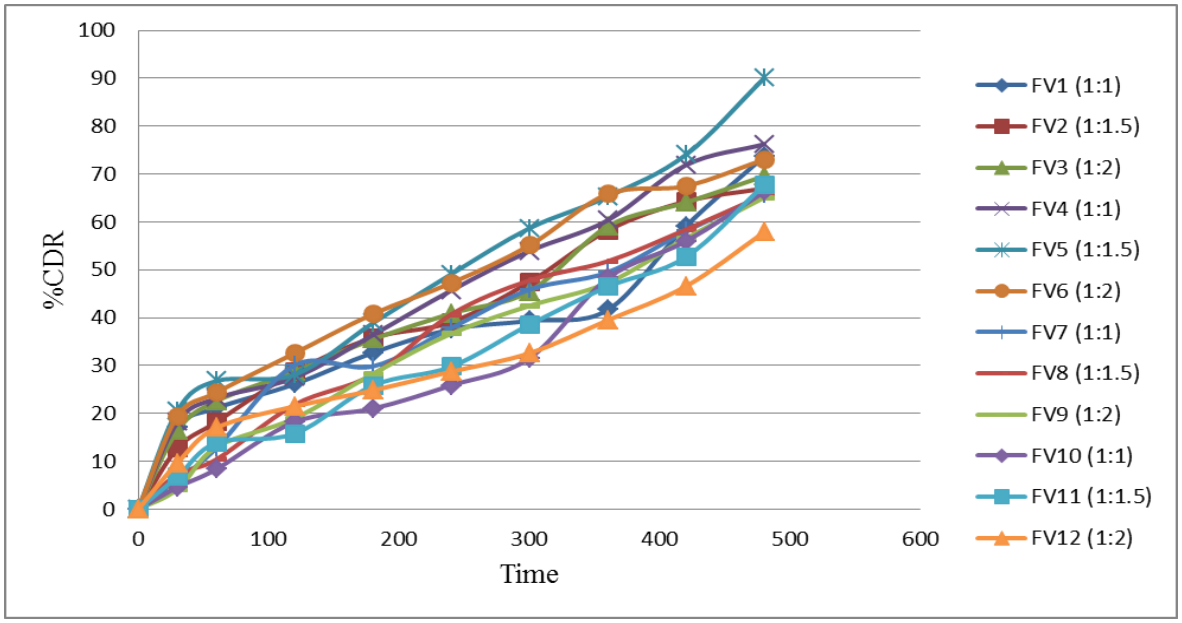

Fig. 3: In vitro drug release studies of niosomal suspension.

Evaluation of niosomal gel

pH and viscosity of gel

The pH of all the FG5 gel formulation was found to be of 6.72 that suit the skin pH indicating the skin compatibility. The viscosity of the FG5 gel was found to be 11872 ± 120 cps.

The percentage drug content of optimized FG5 gel was found to be 91.85% which stated that drug was uniformly distributed in the gel.

Drug content

The percentage drug content of prepared niosomal gel was found in the range of 87.79% to 90.81%. Formulation FG5 showed the maximum drug content of 90.81%. The carbopol 940 gel formulation showed the more drug content as compared to carbopol 934 gel formulations.

Table 3: Drug content, pH and viscosity niosomal gels.

Formulation	Drug content (%)	pH	Viscosity (cPs)
FG1	88.68±0.24	6.74±0.15	12283±841
FG2	89.79±0.2	6.63±0.28	14621±952
FG3	87.07±0.13	6.79±0.58	15701±520
FG4	90.12±0.12	6.35±0.41	13181±867
FG5	91.82±0.76	6.72±0.39	11872±120
FG6	88.35±0.15	6.68±0.18	14685±839
FG7	89.13±0.25	6.85±0.42	15468±108
FG8	86.69±0.41	6.64±0.24	16587±521

*Data expressed as Mean±SD (n=3)

In vitro Diffusion Study

The *in vitro* drug diffusion study of the formulated niosomal gels was found to be in the range of 64.80% to 73.74% at the end of 8 h and higher percentage cumulative drug release was found in FG5 formulation prepared with span 60:cholesterol ratio (1.5:1) niosomal suspension in carbopol 934(1%) i.e. 73.74% and the lowest percentage cumulative drug release was found in the FG8 formulation with span 60:cholesterol ratio (1:1) with 1.5% carbopol 940 gel base shown release of 52.63%. The carbopol 934 gels showed higher drug release as compared to carbopol 940 gels. It was due to the fact that FG5 formulation containing carbopol 934 showed lower viscosity of 11872 cps as compared to FG8 formulation containing carbopol 940 which showed viscosity of 16587 cps. It was concluded that as the concentration of the gel increased the release rate of the gel decreased. The *in vitro* drug release study of pure drug incorporated in the gel base carbopol 934 was carried out. The percentage cumulative drug release was found to be 52.63%.

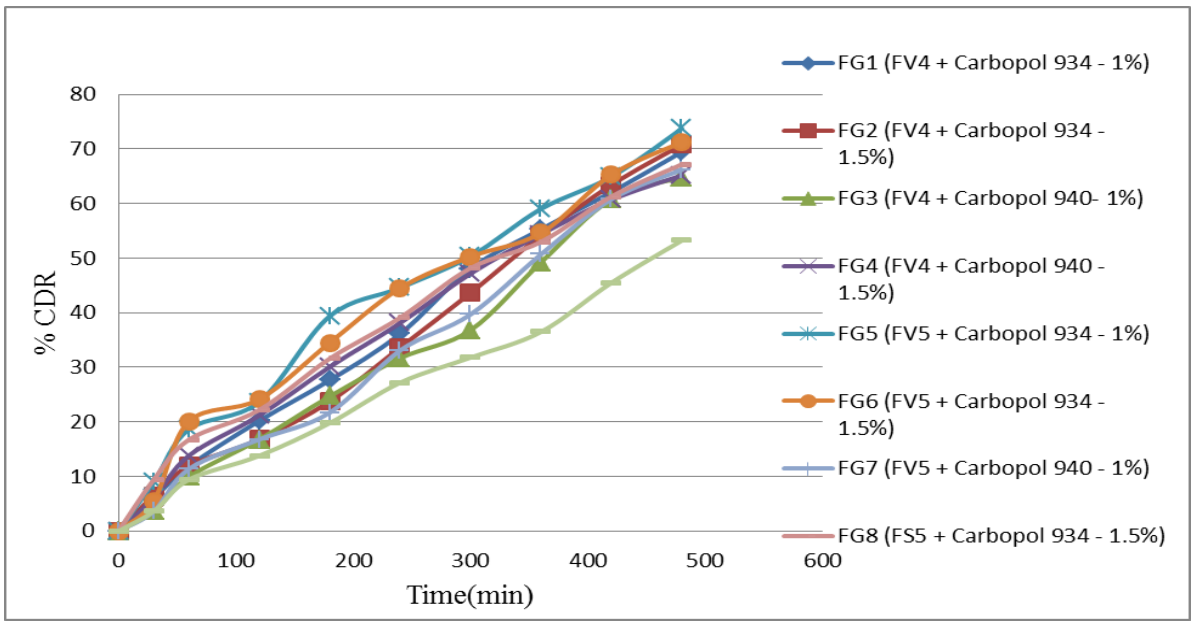

Fig. 4: *In vitro* drug release studies of niosomal gels.

Kinetic study of in vitro release data

The drug release data indicated that formulation FG2, FG4, FG5, FG6 and FG7 followed the Higuchi order kinetic pattern. The obtained pattern states that the initial drug concentration in the matrix is higher and diffusion takes place in one direction. FG1, FG3 and FG8 followed zero order reaction which means the release rate is in dependent of drug concentration. The obtained results are shown in Table 4.

Table 4: Kinetics of drug release data.

Formulation	Zero Order (R^2)	First Order (R^2)	Higuchi Matrix (R^2)	Peppas Model		Hixon Crowell	Best Fit Model
				(R^2)	(n)		
FG1	0.9963	0.7442	0.9441	0.9815	0.6356	0.7771	Zero
FG2	0.9129	0.7685	0.9949	0.9771	0.9984	0.7997	Higuchi
FG3	0.9928	0.7888	0.9153	0.9474	0.9103	0.7888	Zero
FG4	0.9891	0.7041	0.9931	0.9638	0.9604	0.7451	Higuchi
FG5	0.9772	0.6499	0.9959	0.9733	0.8184	0.7006	Higuchi
FG6	0.9744	0.6656	0.9756	0.9687	0.9821	0.7107	Higuchi
FG7	0.9145	0.7854	0.9938	0.9464	0.9812	0.8116	Higuchi
FG8	0.9868	0.6612	0.9702	0.8151	0.9714	0.9464	Zero

Ex vivo skin permeation studies

The *ex vivo* permeation study of optimized formulation FG5 and pure gel was carried out by using the rat skin. The drug release of optimized formulation was found to be 67.24% and pure gel release was found 53.25% at the end of 8 h. Thus, the formulation FG5 showed better drug release as compared to marketed formulation as publicized in Fig. 5.

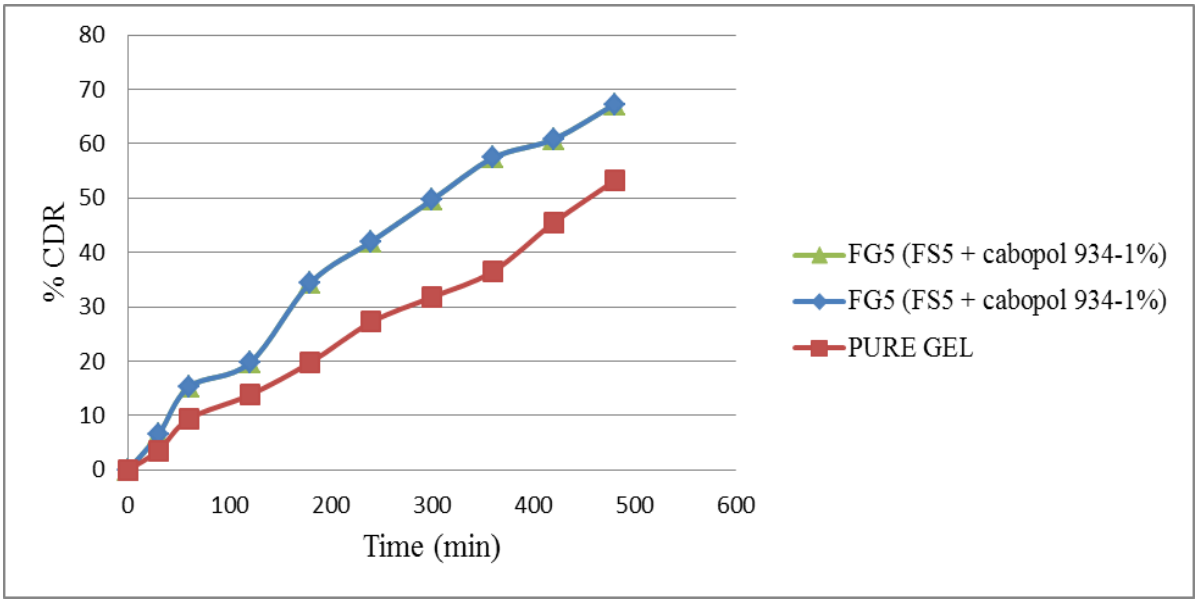

Fig. 5: *Ex vivo* skin permeation study of FG5 v/s pure gel.

In vitro antibacterial study

The *in vitro* anti-bacterial study was carried out by petri-dish method using methicillin-resistant *Staphylococcus aureus.* The optimized formulation shown the better antibacterial activity with larger area of zone of inhibition 39mm and the pure gel showed the zone of inhibition of 37mm. The results are shown in Fig. 6.

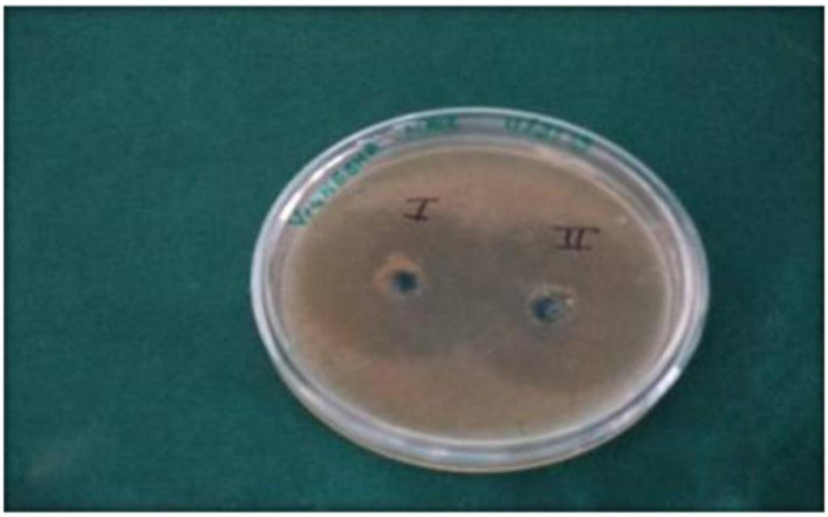

Fig. 6: *In vitro* antibacterial activity (zone of inhibition) of FG5 gel and pure gel against strain methicillin resistant staphylococcus aureus.

Skin irritation test

The wistar rats were used for the skin irritation test. The control group was not applied with any formulation whereas the standard group was applied with saline. The optimized formulation was applied in test group and observed for irritation at the end of 24 h. No irritation was observed in any of the groups i.e., controlled, standard and test. The control group and test group are shown in Fig. 7 and Fig. 8 respectively.

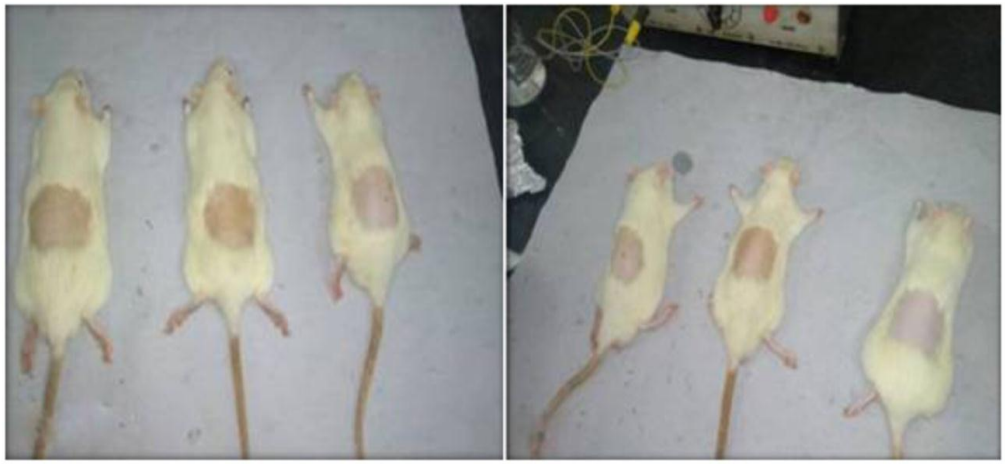

Fig. 7: Control group tested with pure gel (0.5% drug equivalent to Linezolid pure drug suspension + carbopol 934-1%).

Fig. 8: Test group tested with optimized formulation FG5 (FV5+carbopol 934-1%).

CONCLUSION

This study was an attempt to formulate Linezolid niosomal gel for topical delivery and based upon the experimental investigation it can be concluded that the vesicle size of the prepared niosomes were found in the range of 100 to 500 nm, the optimized formulation FV5 showed

smallest vesicle size of 125 nm, percentage drug content of 93.1% and % entrapment efficiency of 87.5%. *In vitro* % drug release was found maximum in the formulation FV5 (Span:Cholesterol 1.5:1) which showed 80.5% release after 8 h. On the basis of obtained results of Linezolid niosomal formulations FV4 and FV5 were considered as optimized formulation for preparation of niosomal gel.

The niosomal gels were formulated by incorporating optimized formulation FV4 and FV5 into the gel base. The *in vitro* drug diffusion study higher percentage cumulative drug release was found in FG5 formulation prepared with span 60: cholesterol ratio (1.5:1) niosomal suspension in carbopol 934 (1%) i.e., 73.74%. The release of formulation FG2, FG4, FG5, FG6 and FG7 followed the Higuchi order kinetic pattern. The *ex vivo* drug release of FG5 was found to be 67.24% and pure gel release was found to be 53.25% at the end of 8h, showing better drug release compared to the pure gel. Linezolid niosomal gel is safe to use as no skin irritation occurred in wistar rats. Hence, it can be concluded that Linezolid was proven to be a suitable candidate for formulating niosomes and niosomal gel for topical delivery can achieve better patient compliance.

ACKNOWLEDGEMENT

The authors would sincerely like to thank Apotex research Pvt. Ltd., Bangalore for providing gift sample of Linezolid. The authors are also thankful to the principal KLE College of Pharmacy, Belagavi and Dr. Prabhakar Kore Basic Science Research Centre, Belagavi for providing laboratory facilities.

Conflict of interest

There are no conflicts of interest.

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