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EFFECT OF TRANS - ESTERIFICATION OF OIL ON NANOEMULSION GEL FOR TOPICAL DRUG DELIVERY

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Voriconazole, Transesterification, Bioavailability, Globule size, Homogenization, Zeta potential, Nanoemulsion

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ABSTRACT: The research investigated the modification of nano-emulsion by using transesterfied soyabean oil, to enhanced solubility and diffusion of voriconazole. Ternary phase diagrams of soyabean oil, acid / base esters of soyabean oil, Tween 80: PEG 400 (S/CoS) and water were developed. Ester value of soyabean oil increased from 214.04 to 261.5mg KOH/1g for acid ester and 293.58mg KOH/1g for base ester confirmed transesterification. The modified nanoemulsion batches E_4, E_5, E_{A4}, E_{A5}, E_{B2} and E_{B3} showed thermodynamic stability. Nanoemulsion of Soyabean oil (E_3 and E_4), acid ester (E_{A4} and E_{A5}), and base ester (E_{B2} and E_{B3}) were selected for *in-vitro* drug diffusion studies. The globule size of batch E_4, E_{A4} and E_{B2} nanoemulsion was found to be 185.6, 162.8 and 115.4 nm, respectively. Zeta potential of batch E_4, E_{A4}, and E_{B2} was observed -35, -27 and -9mV respectively. The *in vitro* release release profiles from the E_4, E_{A4} and E_{B2} batches of nanoemulsion gel were fitted into Peppas kinetic model. Moreover, 'n' value of batch E_4, E_{A4}, and E_{B2} was 0.8844, 0.8284, 0.8475 non-fickian diffusion. The soyabean oil and soyabean acid ester oil nanoemulsion found to be stable and a promising vehicle to enhance the permeation of voriconazole for topical delivery.

INTRODUCTION: Nanoemulsion is a thermo-dynamically stable isotropically clear dispersion of two immiscible liquids, such as oil and water, stabilized by an interfacial film of surfactant molecules. In addition to the surfactant the Co-surfactant / Co-solvent is used with the oil and water phase. The dispersed phase typically comprises small particles or droplets, with a size range of 5-200 nm, and has very low oil / water interfacial tension [1, 2].

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Unlike coarse emulsions micronized with external energy, nanoemulsion is based on low interfacial tension which is achieved by adding a co-surfactant, which leads to spontaneous formation of a thermodynamically stable nanoemulsion [3, 4].

The nanosized droplets leading to increase in interfacial surface area associated with nanoemulsion would affect the transport properties of the drug [5]. Nanoemulsions have a larger capacity for micellar solubilisation compared to simple solutions, give advantages in thermodynamic stability to unstable dispersions as it can be produced with less energy input, and have a greater shelf life a low viscosity, high kinetic stability against creaming or sedimentation, and large interfacial area make nanoemulsions of increasing use in different applications [6].

Nanoemulsions have been increasingly developed for use as drug-delivery systems for parenteral, oral, ocular, and topical administration [7, 8]. Specifically, in topical delivery, nanoemulsions offer several significant advantages including no skin irritation, powerful permeation ability, and high drug-loading capacity [9, 10]. Nanoemulsion-based cosmeceuticals have improved efficacy; whereby, the active ingredient will have better skin penetration and a higher rate in successful drug delivery to the target site due to its small particle size. Besides, the long-term colloidal stability of nanoemulsions can be achieved through high potential due to the increase of the repulsive force between droplets. Nanoemulsion is a non-equilibrium colloidal system where oil phase is dispersed as fine droplets, usually with particle size from 20–200 nm, throughout the aqueous phase stabilized by surfactants. Nanoemulsions can be prepared by high-energy emulsification or by low-energy emulsification methods. However, nanoemulsions are thermodynamically unstable colloidal systems that are highly dependent on their physicochemical properties, usually based on the preparation method [11, 12].

Voriconazole is a triazole antifungal agent indicated for use in the treatment of fungal infections including invasive aspergillosis, esophageal candidiasis, and serious fungal infections caused by *Scedosporium apiospermum* (asexual form of *Pseudallescheria boydii*) and *Fusarium* spp. including *Fusarium solani*. Voriconazole is lipophilic in nature and exhibit poor solubility, diffusion and bioavailability, which limits delivery of voriconazole via topical drug delivery system. Nanoemulsion based topical drug delivery is one of the effective approach to increase solubility, dissolution, improving diffusion, permeability, drug loading and bioavailability. Hence, to formulate nanoemulsion based gel of voriconazole. Beside this, to enhance the solubility and diffusion the oil phase of nanoemulsion modified by transesterification [13].

A large amount of active principle can be incorporated in the formulation due to high solubilizing capacity that might increase thermodynamic activity towards the skin [14, 15]. The nanosized droplets provide superior adherence to skin and have large surface area thereby providing high concentration gradient and improved active constituent permeation [16]. The low viscosity of nanoemulsion restrains its clinical application due to inconvenient use, and therefore hydrogel thickened nanoemulsion systems were formulated with good stability, powerful permeation ability, and suitable viscosity for the topical delivery which provided longer contact with skin. Nanoemulsions could increase the topical delivery of voriconazol times compare with the control [17].

MATERIAL AND METHOD: Voriconazole was received as a gift sample from the Glenmark Pharmaceuticals Ltd.(goa M.S., India), Peanut oil (Gemini groundnut oil), Soyabean oil (Fortune Soyabean oil), Coconut oil (Fortune Soyabean oil), Sunflower oil (Parachute Pvt. Ltd) and Potassium hydroxide, Dichloromethane, Sodium Lauryl Sulphate, Potassium Chloride obtained from Fisher Scientific India Pvt. Ltd. Also Tween-80 and Hydrochloric acid from Merck Specialities Pvt. Ltd, Mumbai. Carbon tetrachloride, Methanol, Carbopol 934P purchased from Loba chemie Pvt. Ltd. All other chemicals and solvents were of reagent grade and were used without purification.

Preparation of Transesterified Oil Phase:

Reflux Condensation: Transesterification of oil done by different methods-

- **By Using Base Catalyst:** Heat 100ml of oil at 120 °C for 20 min, Add 40ml of methanolic NaOH (1.25g) and reflux condensate for 2 hr. By using acid catalyst - Heat 100ml of oil at 120 °C for 20 min, Add 40ml of methanolic H_2SO_4 (0.5ml) and reflux condensate for 2 hr.
- **Phase Separation:** The product obtained from above methods transferred into separating funnel and allowed to stand for 1 hr. After 1 hr, Fatty acid ester layer separated from Glycerol. Then the supernatant layer of fatty acid ester used for further process.
- **Neutralization:** The separated fatty acid ester layer obtained from base catalyst process neutralized by using 0.5% citric acid and from acid catalyst process neutralized by using 0.5% KOH.
- **Washing:** Ester layer may contain traces of NaOH, methanol, glycerol; to remove this

residue the fatty acid ester layer treated with water at 50 °C - 60 °C for 4-5 times.

- **Heating:** After completion of washing process ester may contain same traces of water therefore in order to remove water residues ester was heated at 120 °C [18 - 20].

Construction of Ternary Phase Diagram: Based on the solubility studies and the ternary phase diagram studies, series of nanoemulsion drug delivery systems (E_1, E_2, E_3, E_4 and E_5) for Soyabean oil and (E_{A1}, E_{A2}, E_{A3}, E_{A4}, EA_5) for Soyabean oil acid ester and (EB_1, EB_2, EB_3, EB_4, EB_5) for Soyabean oil base ester, consisting of Voriconazole, were prepared. A series of nano-emulsion formulations were prepared using Tween 80 and PEG 400 as the S/CoS combination and Soyabean oil, Soyabean oil Acid ester, Soyabean oil Base ester used as the oil phase [4].

Preparation of Oil in Water (O/W) Nanoemulsion: The water phase with or without an additional emulsifier and co-solvent was also heated. Then the components of oil phase and aqueous phase added at a slow rate with gradual stirring and vortex mixing at 40 °C on a magnetic stirrer. Further homogenization carried out to obtain the needed small droplet size range of the emulsion. Finally ultra sonicator used to achieve the desired range of dispersed globules [21, 22].

Evaluation of Nanoemulsion:

Thermodynamic Stability Studies (Freeze-Thawing Cycle): The formulations were subjected to 3-4 freeze-thaw cycles, which included freezing at 4 °C for 24 hours followed by thawing at 40 °C for 24 hours. Centrifugation was performed at 3000 rpm for 5 minutes. The formulations were then observed for phase separation [3].

Dispersibility Test: The efficiency of nano-emulsion was assessed by using a standard USP XXII dissolution apparatus type II. 1.0ml of each formulation was added to 900ml of water at 37 ± 0.5 °C. A standard stainless steel dissolution paddle rotating at 50 rpm provided gentle agitation. The *in vitro* performance of the formulations was visually assessed using the grading system [23].

Percent Transmittance Study: The samples prepared for nanoemulsion were subjected to % transmittance analysis using double beam UV-Visible spectrophotometer at wavelength of 255nm [24]

$$\%Transmittance = 1\times100 / Antilog \{A\}$$

Where, {A} =Absorbance at 300nm.

***In vitro* Drug Diffusion Studies:** Each 1ml of the formulations were placed on france diffusion cell by placing dialyzing membrane 110 having width 32.34mm and diameter 21.5mm on it in 7.4 pH buffer as dialyzing medium. 1ml of aliquote was taken after each 1 hr interval for 12 hrs and volume was make up upto 10ml and then it was analyzed spectrophotometrically at 255nm [25].

Partical Size and Zeta Potential Determination: The droplet surface charge (zeta potential) was determined by photon correlation spectroscopy (PCS) using a Zetasizer (1000 HS, Malvern Instruments). The formulation (0.1ml) was dispersed in 50ml of water in a volumetric flask, mixed thoroughly with vigorous shaking and light scattering was monitored at 25 °C at 90 ° angle. Zeta potential values were determined from the electrophoretic mobility of the oil droplets *via* in-built software. The measurements were carried out on diluted emulsion formulations. 1:250 dilutions were made of formulation for the determination of zeta potential with the help of photon correlation spectroscopy [26, 27].

Stability Studies: The stability study of selected formulation was done at 40 °C with 75% RH room temperature and in freezing temperature. The test parameters such as integrity, phase separation and drug precipitation were determined for 4 week. The data were subjected to calculate the stability of nanoemulsion [28].

Formulation of Nanoemulsion Based Gel: From the evaluation of nanoemulsion, E_4 (Smix: oil, 6:4) formulas of oil, E_{A4} (Smix: oil, 6:4) acid ester, E_{B2} (Smix: oil, 4:6). Base ester selected for formulation in gel. For preparation of nanoemulsion based gel, 3gm of carbopol 934 added in 87ml of water, stirred till homogenous mixture was formed, kept it aside for overnight. Then 13ml of nanoemulsion was added drop by drop up to 100ml. The pH values were subsequently regulated to 6-9. Then other ingredient like PEG-400 added to obtain a homogeneous dispersion of gel [29].

Evaluation of Nanoemulsion Based Topical Gel:

Physical Appearance: The prepared nanoemulsion gel was inspected visually and using clarity tester for their color, homogeneity and consistency.

Viscosity and pH Determination: The viscosity of all prepared nanoemulsion gel was measured by model (DV-E) Brookfield viscometer using spindle no. 63. The pH of nanoemulsion based topical gel was determined at room temperature using digital pH meter, model NIG-333. pH meter was calibrated using 9.2 and 4.0 pH buffer solutions [30].

Spreadability: An excess of gels (about 2g) sandwiched between two glass plates having fixed the dimensions. A 300g weight was placed on the top of two plates for five minutes to expel air and to provide a uniform film of the gel between the plates. Excess of the gel was scrapped off from the edges. The top plate was then removed and the time (in sec) required by the top plate to separate out from above plate should be noted. A shorter the time interval indicates better spreadability [31].

Drug Content Detrmination: Gel formulations (100mg) was dissolved in methanol and filtered and the volume was made to 100ml with methanol. The resultant solution was suitably diluted with methanol and absorbance was measured at 255 nm using Shimadzu - 1700 UV Visible spectro-photometer. Drug content was determined from calibration curve for Voriconazole [32].

***In vitro* Drug Release:** About 1-2gm of each batch of prepared gel were placed on dialyzing membrane containing diffusion cell, phosphate buffer 7.4 in its receptor compartment, 1ml of phosphate buffer was taken after 1 hr interval up to 12 hr. Mention steady state condition in diffusion cell by placing 1ml of fresh phosphate buffer after removal of 1ml of sample from receptor compartment [33].

RESULT AND DISCUSSION:

Preformulation Studies:

Identification Test for Voriconazole:

Melting Point: The melting point of the Voriconazole was found to be 129 °C, which also complies with melting point reported in United state Pharmacopoeia 2011.

Infrared Absorption Spectrophotometry: All the prominent and primary peaks were observed in FTIR spectrum of Voriconazole **Fig. 1**.

TABLE 1: FTIR PEAKS OF VORICONAZOLE AND PHYSICAL MIXTURE OF VORICONAZOLE WITH CARBOPOL

Voriconazole		Voriconazole: Carbopol (1:1)	
Functional Group	**Frequency**	**Functional group**	**Frequency**
OH stretch	3621	OH stretch	3619
C=O stretch	1712	C=O stretch	1713
N–H bend stretch	3320	N–H bend stretch	3305
CF stretch	563	CF stretch	564
C-H “oop” stretch	823	C-H “oop” stretch	823
C-H stretch	3045	C-H stretch	3047
C=C stretch	1678	C=C stretch	1676
		C-O-C stretch (acrylate)	1210
		=C-H stretch	925
		C-O-C stretch (ethereal)	1165

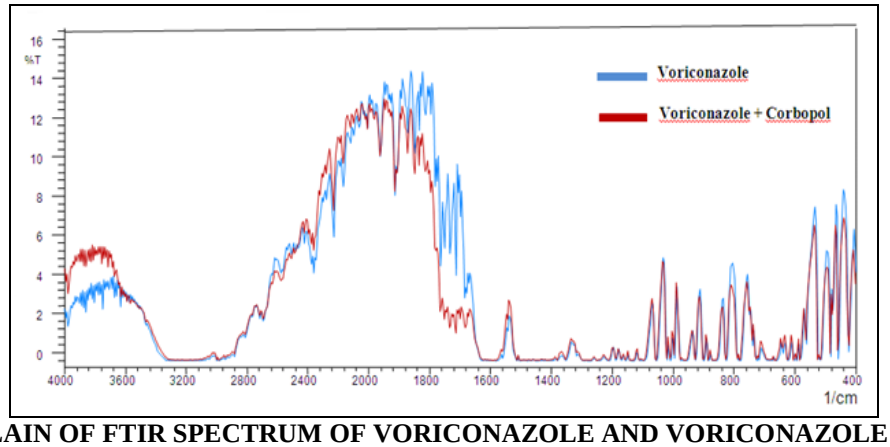
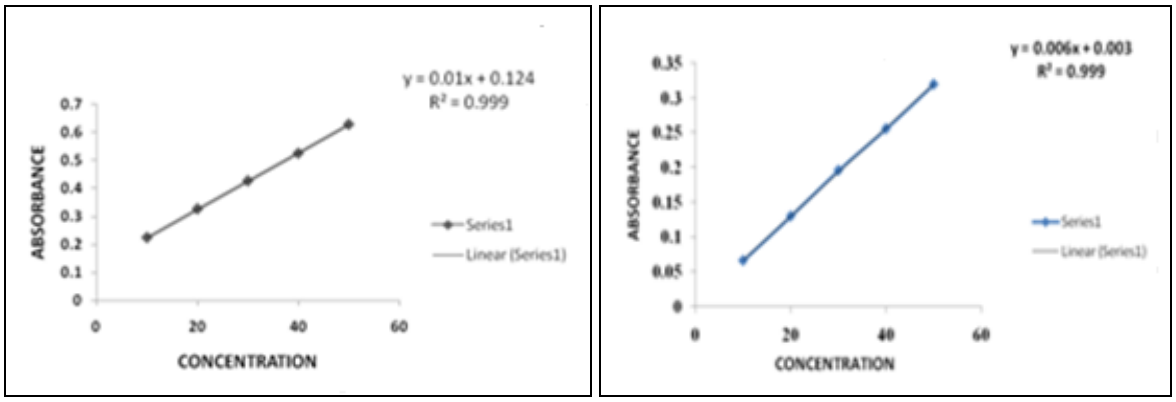


FIG. 1: OVERLAIN OF FTIR SPECTRUM OF VORICONAZOLE AND VORICONAZOLE + CARBOPOL

As shown in **Table 1** the FTIR spectra of Voriconazole, and its combination with Carbopol, Show prominent characteristic peak. Therefore an FTIR spectrum of physical mixture of voriconazole with carbopol exhibited all functional group of voriconazole suggested compatibility of voriconazole with carbopol 93P **Table 1.**

UV Spectrophotometric Analysis: The λ_{max} of Voriconazole was found to be at 255 nm [34], which also complies with the specification of United state Pharmacopoeia 2011.

Plot of Calibration Curve: UV spectroscopy can be utilized for qualitative and quantitative analysis of compounds. The Beer's curves of Voriconazole were prepared in Methanol and 7.4 pH buffer and the calibration curves as shown in **Fig. 2**.



A **B**

FIG. 2: CALIBRATION CURVES OF VORICONAZOLE IN (A) METHANOL (B) 7.4 pH BUFFER

Coefficient of regression (R^2) value of Voriconazole in Methanol and 7.4 pH buffer were 0.999 and 0.999 respectively which are very near to the unity. So, it showed that a good linear relationship between these two variables.

Excipients Evaluation: All the excipients *i.e.*, lipids (Peanut oil, Coconut oil, Sunflower oil, Soyabean oil), were evaluated by studying the parameters such as acid value, saponification value, ester value, iodine value and peroxide value, as given in **Table 2**.

As shown in **Table 2**, acid value, saponification value, iodine value, peroxide value and ester value of oils was in the range of given standards. From the data obtained by characterization of lipid/oil, soyabean oil acid and base ester show higher ester value than other oil and their esters.

TABLE 2: EVALUATION OF OILS / LIPIDS PHASE USED IN VARIOUS LIPIDS, SURFACTANTS AND CO SOLVENT

Oil and its esters	Acid Value (mg KOH/g)	Sap. Value (mg KOH/g)	Iodine Value (g I_2/100g)	Peroxide value (meq/kg oil)	Ester value (mg KOH/1g)
Soyabean Oil	0.953	215.1	133.6	8.2	214.047
Acid Ester	0.633	262.2	142.1	10.6	261.5
Base Ester	0.942	294.52	142.1	11.8	293.58
Coconut Oil	1.12	208	135.2	8	206.80
Acid Ester	1.011	175.6	135.9	12.2	173.2
Base Ester	1.23	260	138.5	12.4	258.7
Sunflower Oil	1.064	244.5	132.2	6.6	243.8
Acid Ester	1.011	190.9	129.4	7.8	189.88
Base Ester	0.982	211.7	130.07	8.8	210.71
Peanut Oil	3.029	190.2	119.6	3.4	187.14
Acid Ester	3.133	194.8	118.3	4.8	190.86
Base Ester	3.987	204.9	121.1	2	200.91

Solubility Determination: The solubility of Voriconazole was found to be more in soyabean oil (102.5mg/ml). The solubility of voriconazole was observed increases in esters of soyabean oil (105.5 and 111.3mg/ml), suggests that ester of oil act as a super solvent for highly voriconazole [35].

Pseudo Ternary Phase Diagram: The data obtained from evaluation and solubility study of sunflower, soyabean, coconut, peanut oil and its esters, substantiate proper trans-esterification and improved solubility of voriconazole in soyabean oil and its esters [4, 36].

From prepared Smix ratio, all type I (where surfactant concentration constant) and 2:1, 3:1 ratio of type II (where co-surfactant concentration constant) was shown phase separation after addition of water beside this Smix also immiscible with oil. Therefore, 4:1, 5:1 and 6:1 Smix ratio of type II which showed stable phase continued for further studies. Pseudoternary phase diagrams were plotted according to different batches of Soyabean oil and its acid as well as base ester. The dots shown in figures indicate the nanoemulsion region.

As shown in **Fig. 3** the maximum emulsification region was obtained in Smix (4:1) with Soyabean oil, Smix (5:1) with acid ester and Smix (4:1) with Soyabean oil base ester concentration in respectively [37].

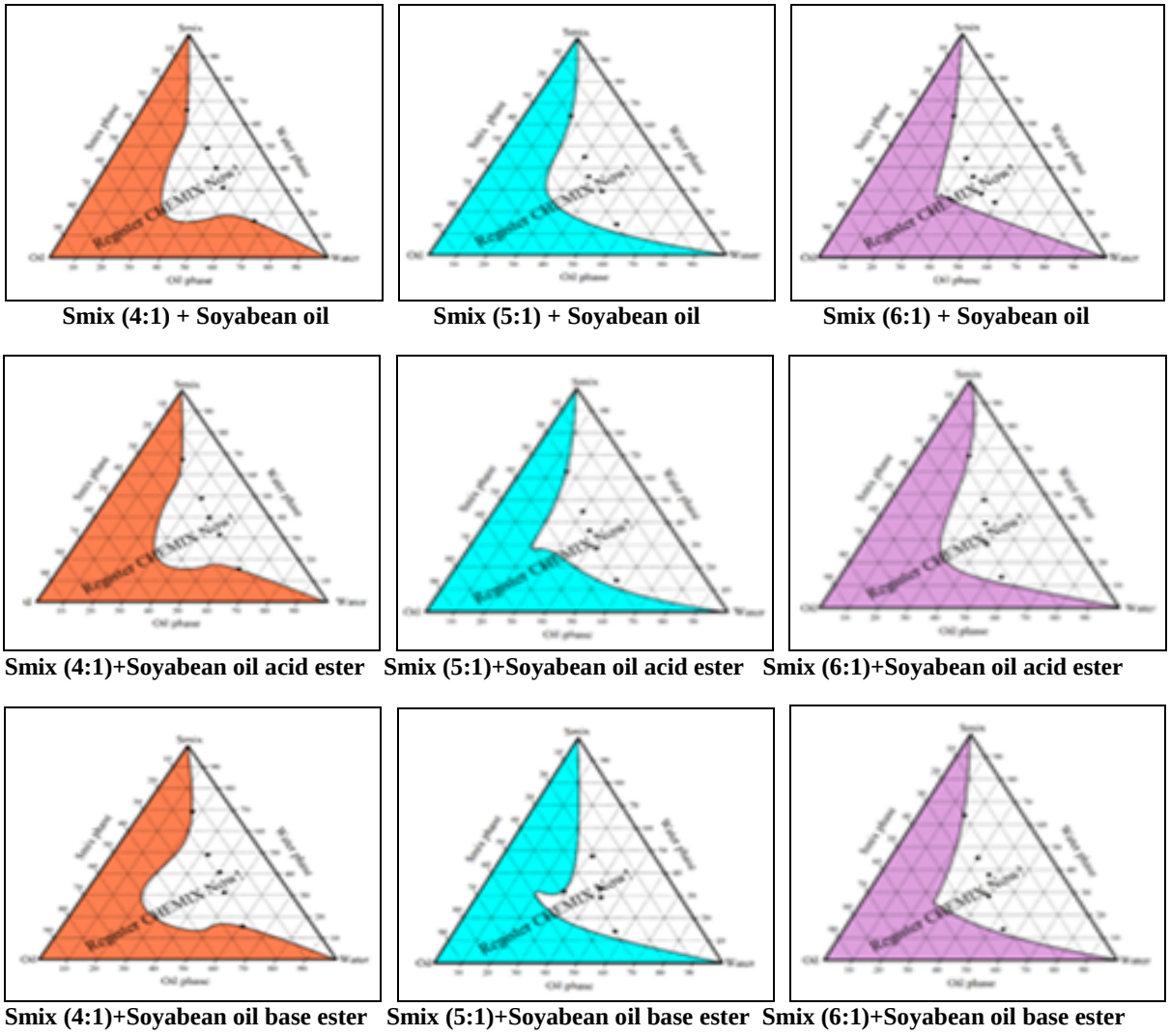


FIG. 3: PSEUDO TERNARY PHASE DIAGRAM OF RATIO (A) Smix (4:1) (B) Smix (5:1) (C) Smix (6:1) OF SOYABEAN OIL, SOYABEAN OF ACID ESTER AND SOYABEAN OIL BASE ESTER

Drug Loading in Nanoemulsion: Smix (4:1) with Soyabean oil, Smix (5:1) with Soyabean oil acid ester, Smix (6:1) with Soyabean oil base ester were selected for voriconazole loading in formulation. From the observation of solubility studies of Voriconazole in mixture of components of nanoemulsion it was revealed that solubility of Voriconazole increases with increasing in surfactant concentration. The maximum solubility of Voriconazole in Soyabean oil and its acid as well as base ester was found to be 121.3; 115.2 and 120.9 mg/ml respectively.

Characterization of Nanoemulsion:

Thermodynamic Stability Studies (Freeze-Thawing Cycle): The results obtained from thermodynamic stability studies, indicated that the formulations E_4, E_5, E_{A4}, E_{A5}, E_{B2}, E_{B3}, and E_{B5} of Nanoemulsion of Soyabean oil and its acid and base ester were found to be stable. This attributes that all the components of the system observed compatible with each other and form a single homogeneous phase [3].

Dispersibility Test: The dispersibility of formulation increases with decreasing the proportion of oils with simultaneously increasing the ratio of S/CoS results in reduction of interfacial tension between oil globules and aqueous phase. The formulation E-4, E-5, E_{A4}, E_{A3}, E_{A5}, E_{B2} and E_{B3} has good dispersibility [21].

Percent Transmittance Study: The transparency indicates the good dispersibility of very finely or smaller globules of lipids in water. The results of percent transmitancy order was found to be 79.77, 49.47, 44.12, 42.66, 41.97 *i.e.* E-2>E-1>E-5>E-4>E-3 for Soyabean oil formulations and 77.37, 76.73, 69.73, 51.33, 43.12 *i.e.* E_{A3}>E_{A1} >E_{A5},> E_{A4}>E_{A2} for soyabean oil acid ester formulations 55.83, 52.71, 50.30, 47.93, 42.86 *i.e.* $E_{B1.}$>E_{B3}> E_{B4},>E_{B5}>E_{B2}. E2 formulation of Soyabean oil nanoemulsion, E_{A3} formulation of acid ester nanoemulsion, E_{B1} formulation of base ester nanoemulsion was found to be more transparent than other formulation.

Conductance Measurement: Condutance measurement of prepaired formulation indicated that there is no significant change in conductivities with oils proportion as well as surfactant / co-solvent proportions. Hence, the formulation was found to be stable in lipid phase due to the excellent absorptivity of surfactant / co-solvent as film on oil globules containing drug [23].

Viscosity and pH Determination: The results indicate that increasing shear rate decreases the viscosity of formulation. Therefore, all these formulation represent the pseudoplastic flow (non-Newtonian system) [21]. A viscosity of acid and base ester of soyabean oil was found to be in the range of viscosity of soyabean oil nanoemulsion. The pH of the all formulation was found to be in the range of 6-8, suggested applicable for topical application of skin.

Drug Content Analysis: The drug content analysis indicates that the quantity of drug of each formulation was observed more than 93.8% than the amount of drug loading. The percent drug content of Soyabean oil (E_4), acid ester (E_{A4}) and base ester (E_{B2}) was more *i.e.* 98.6 ± 0.054, 98.6 ± 0.042 and 98.2 ± 071 respectively. Therefore, it can be might be told that the entire drug is well uniformly distributed and there is no precipitation in the each. The percentage relative standard deviation (% RSD) is less than 2% indicates the reproducibility of process used for the formulation of nanoemulsion [21].

***In vitro* Drug Release Studies:** *In vitro* drug release studies were performed to study the release behavior of formulation from lipid phase around the droplet. **Fig. 4** indicates % drug release from Nanoemulsion through dialysis membrane. On the basis of Thermodynamic stability studies; Soyabean oil Nanoemulsion E-$_3$, E-$_4$, Soyabean oil acid ester Nanoemulsion batch $E_{A4,}$ $E_{A5,}$ Soyabean oil base ester Nanoemulsion batch $E_{B2}E_{B3}$ were selected for *in vitro* drug diffusion studies [23].

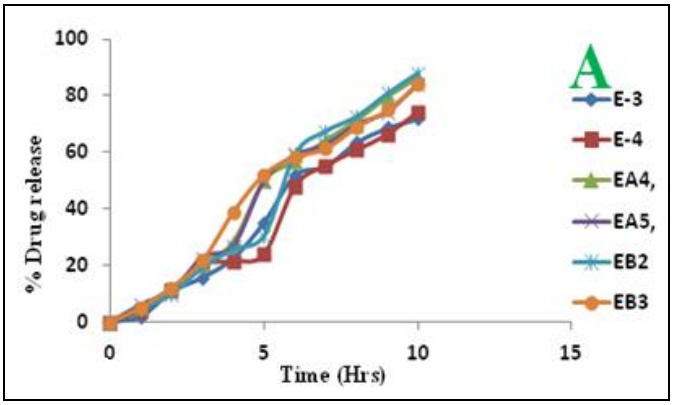


FIG. 4: % VORICONAZOLE RELEASE FROM SOYABEAN OIL NANOEMULSION, SOYABEAN OIL ACID ESTER NANOEMULSION AND SOYABEAN OIL BASE ESTER NANOEMULSION

The % drug release of voriconazole from Soyabean oil-Nanoemulsion (E_3) (E-$_4$), Soyabean oil acid ester Nanoemulsion (E_{A4}) (E_{A5}) and Soyabean oil base ester Nanoemulsion (E_{B2}) (E_{B3}) at different sampling interval. In case of Soyabean oil acid and base ester nanoemulsion, E_{B2} E_{B3} of Soyabean oil base ester Nanoemulsion Show more drug release than $E_{A4,}$ E_{A5}. From the above results it indicates

that, as the concentration of oil increases and surfactant concentration decreases drug release decreases.

Release Kinetic: From the kinetic studies it was found that all the batches E_4, E_5, E_{A4}, E_{A5}, E_{B2} and E_{B3} shows the correlation coefficient value (r^2) 0.9944, 0.9939, 0.9933, 0.9925, 0.9954 and 0.9911 by korsmeyer-peppas kinetics. The correlation coefficient obtained by korsmeyer-peppas kinetics more near to 1 as compared to other kinetics suggested prepared formulation exhibit korsmeyer-peppas kinetics release.

The 'n' value for batches E_4, E_5, E_{A4}, E_{A5}, E_{B2} and E_{B3} was found to be 0.8447, 0.7996, 0.8055, 0.7971, 0.8110, and 0.8088 respectively. The 'n' value for all batches are in the range of 0.5 – 1, hence it shows non Fickian diffusion which state that drug is release from nanoemulsion gel by diffusion manner.

Particle Size Analysis: It has been reported that the smaller particle size of the emulsion droplets may lead to more rapid absorption and improve the bioavailability particle size analysis was carried out for batch E_4, E_{A4} and E_{B2} was found to be 185.6, 162.8 and 115.4 respectively. Particle size of nanoemulsion of soyabean oil and its acid and base ester was found to be in the range of nanoemulsion. Soyabean oil acid and base ester nanoemulsion showed Particle globule size and proper distribution of particles which might be reduces particle size in formulation

Zeta Potential Determination: Particles with zeta potentials more negative than -45 mV are normally considered stable. (Ali *et al*., 2012). The zeta potential of the Soyabean oil (E_4), Soyabean oil acid (E_{A4}) Soyabean oil base (E_{B2}) nanoemulsion was found to be -35.5, -27.7and -9.15 respectively. These results indicated decrease in droplet size in trans-esterified oil containing nanoemulsion, shifted zeta potential from -35 mV to -27 mV and -9mV. The negative zeta potential of nanoemulsion suggested stability.

Stability Study: An accelerated storage testing was carried out to predict the long-term physical stability. No phase sepration occurred in Soyabean oil Nanoemulsion gel (E_4), Soyabean oil acid ester nanoemulsion gel (E_{A4}) as well as Soyabean oil base ester nanoemulsion gel (E_{B2}). Hence these nanoemulsion were physically stable [38].

Characterization of Nanoemulsion Based Gel:

Homogeneicity, Appearance and Consistency: The prepared soyabaen oil based nanoemulsion and its acid base ester nanoemulsion gel (E_4, $E_{A4,}$ E_{B2}) formulations were white, viscous, creamy preparations with a smooth and homogeneous appearance. They were easily spreadable with acceptable bioadhesion and fair mechanical properties.

pH and Viscosity Determination: The pH values of all developed formulae was in range 6-8 which is considered acceptable to avoid the risk of irritation upon application to the skin [25]. The prepared Soyabean oil, Soyabean oil acid ester, Soyabean oil-base ester nanoemulsion gel showed viscosity on 30 rpm 78.12, 72.83 and 78.58, on 50 rpm 63.45, 57.2 and 62.48, on 60 rpm 54.66, 49.2 and 49.5 respectively.

Viscosity results indicate that at Basic pH 7.4 phosphate buffer (equivalent to pH of skin) it changes into a highly viscous preparation. The viscosity value in the range of 50 cps to 100 cps significantly improves the contact time of the formulation on the skin surface and lower viscosity values offers no significant advantage. The viscosity study also show that the selected composition suitable for the use.

Spreadability: Spredability of developed oil nanoemulsion gel and acid base nanoemulsion gel were found to be 37.2, 36.6 and 34.71 respectively which indicate that all the polymers used gave gels spread by small amount of shear, revealed that increasing the concentration of any of the gelling agents was always associated with a decrease in the spreadability [28].

Drug Contents Analysis: The drug content of the formulated gel was estimated and the results were in the official limits with range of 80 % to 99 %. The drug content determination also showed that the drug was uniformly distributed throughout the gel [28]. From the **Fig. 5** showed % drug release of voriconazole at different sampling interval. An increased drug release rate was achieved in soyabean oil acid and base ester nanoemulsion gel as compared to soyabean oil gel. Voriconazole was

released in a controlled manner from (E_4), (E_{A4}), (E_{B2}) gel and 65.12%, 72.58%, 75.84% of voriconazole was released within 7 h.

In case of Soyabean oil acid and base ester nanoemulsion, E_{B2} show faster drug release than E_{A4}. On basis of above graph it also concluded that ester nanoemulsion of soyabean oil has higher rate of release than soyabean oil nanoemulsion this is due to ester form of oil phase [16, 17].

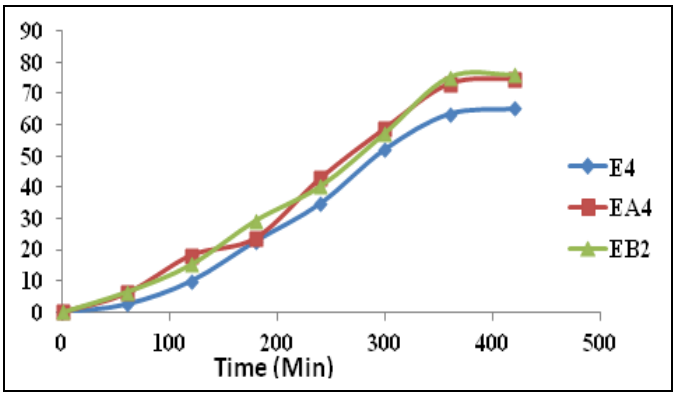


FIG. 5: % VORICONAZOLE RELEASE FROM SOYABEAN OIL NANOEMULSION BASED GEL AND SOYABEAN OIL ACID AND BASE ESTER NANOEMULSION BASED GEL

Release Kinetic: From the above kinetic studies it was found that all the batches E_4, E_{A4}, and E_{B2} shows the correlation coefficient value (r^2) (0.9974, 0.9955, 0.9964) more near to 1 as compared to other kinetics suggested prepared formulation exhibit korsmeyer-peppas kinetics release. The 'n' value for batches E_4, E_{A4} and E_{B2} was found to be 0.8844, 0.8284, 0.8475 respectively. The 'n' value for all batches are in the range of 0.5 – 1, hence it shows non Fickian diffusion which state that drug is release from nanoemulsion gel by diffusion manner.

CONCLUSION: Voriconazole nanoemulsion was prepared using spontaneous nanoemulsification method for improving its solubility and dissolution. Drug-excipient chemical compatibility facilitated to anticipate the potential degradation of vorinazole in various excipients and was helpful to design a suitable strategy for its stabilization in proposed formulation. Screening of surfactants and cosurfactants studies helped to identify the most suitable excipients, whereas the phase diagrams gave a good idea about the concentrations of the nanoemulsion components that should be employed to achieve self-nanoemulsifying formulations.

The Thermodynamic stability studies could differentiate the stability of different compositions and facilitated the selection of most stable formulation. The optimized voriconazole nano-emulsion could withstand the extensive dilution and exhibited 75% drug release in 10 hours irrespective of pH of medium. The results obtained in the present work also show that Nanoemulsion gel containing acid and base ester oil as oil phase is a suitable carrier system for the incorporation of voriconazole, and satisfies the best attributes for transdermal application *i.e.* Non-newtonian flow, good spreadability, and suitable release profile.

This debut study suggests that acid and base ester oil phase containing nanoemulsion gel could reduce the stratum corneum barrier effects and could enhance the transdermal permeation and penetration of voriconazole. The prepared nanoemulsion based gel of voriconazole exhibited stable formulation, whereas nanoemulsion with transesterified oil phase containing nanoemulsion based gel showed greater drug diffusion as compared with simple oil containing nanoemulsion based gel. The increase in voriconazole release from transesterified oil containing nanoeulsion gel suggested improved solubility of voriconazole in acid and base ester of soyabean oil. It is considered to be stable topical formulation of voriconazole.

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REFERENCES:

1. Haritha A, Basha S, Koteswara P and Chakravarthi V: A brief introduction to methods of preparation, applications and characterization of nanoemulsion drug delivery systems 2012; 43(2): 299-306.
2. Jaiswal M, Dudhe R and Sharma R: Nanoemulsion: an advanced mode of drug delivery system. Biotech 2015; 5: 123–127.
3. Gupta A, Eral H, Attona A and Patrick S: Doyle. Nanoemulsions: formation, properties and applications. The Royal Society of Chemistry 2016; 1-16.
4. Kumar H and Singh V: Nanoemulsification - a novel targeted drug delivery tool Journal of Drug Delivery and Therapeutics 2012; 2(4): 40-45.

5. Patel R, Patel G and Bharadia P: Nanoemulsion: An Advanced Concept of Dosage Form. IJPI's Journal of Pharmaceutics and Cosmetology 2011; 1-5.
6. Tadros T, Izquierdo P, Esquena J and Solans C: Formation and stability of nano-emulsions. Adv Colloid Interface Sci 2004; 108–109: 303–318.
7. Shen Q, Wang Y and Zhang Y: Improvement of colchicine oral bioavailability by incorporating eugenol in the nanoemulsion as an oil excipient and enhancer. Int Journal Nanomedicine 2011; 6: 1237–1243.
8. Araújo FA, Kelmann RG, Araújo BV, Finatto RB, Teixeira HF and Koester LS: Development and characterization of parenteral nanoemulsions containing thalidomide. Eur Journal Pharm Sci 2011; 42(3): 238–245.
9. Hagigit T, Abdulrazik M, Valamanesh F, Behar-Cohen F and Benita S: Ocular antisense oligonucleotide delivery by cationic nanoemulsion for improved treatment of ocular neovascularization: an *in-vivo* study in rats and mice. J Control Release 2012; 160(2):225–231.
10. Abdulkarim MF, Abdullah GZ, Chitneni M, *et al*.: Topical piroxicam *in vitro* release and *in vivo* anti-inflammatory and analgesic effects from palm oil esters-based nanocream. Int J Nanomedicine 2010; 5: 915–924.
11. Sonneville-Aubrun O, Simonnet JT and Alloret F: Nanoemulsions: a new vehicle for skincare products. Adv Colloid Interface Sci 2004; 108–109: 145–149.
12. Mason TG, Wilking JN, Meleson K, Chang CB and Graves SM: Nanoemulsions: formation, structure, and physical properties. J Phys Condens Matter 2014; 18(41): 635–666.
13. Schuchardta U, Serchelia R and Matheus R: Transesterification of Vegetable Oils: a Review J. Braz. Chem. Soc 1998; 9: 199-210.
14. Scheuplein R and Blank IH: Permeability of the skin. Physiological Reviews 1971; 51: 702-747.
15. Ritika A, Harikumar SL and Aggarwal G: Microemulsion system in role of expedient vehicle for dermal application. Journal of Drug Delivery and Therapeutics 2012; 2(4): 23-28.
16. Schmalfub U, Neubert R and Wohlrab W: Modification of drug penetration into human skin using microemulsions, Journal of Controlled Release 1997; 46: 279-285.
17. Thakur A, Kaur M and Kumar S: Nanoemulsion in enhancement of bioavailability of poorly soluble drugs: a review Pharmacophore 2013; 4(1): 15-25.
18. Boocock D, Konar S and Mao V: Fast Formation of High-Purity Methyl Esters from Vegetable Oils JAOCS 2013; 75: 9.
19. Atadashi I and Musa: The effects of alcohol to oil molar ratios and the type of alcohol on biodiesel production using transesterification process. Egyptian Journal of Petroleum 2016; 25: 21–31.
20. Silas K, Bitrus and Gutti B: Lipid extraction and transesterification techniques of microalgae –a review. International Journal of recent research in physics and chemical sciences 2015; 2(1): 26-37.
21. Tamilvanan S and Kumar S: Manufacturing techniques and excipients used during the formulation of oil-in-water type nanosized emulsions for medical applications 2012.
22. Elosaily G: Formulation and In-vitro Evaluation of Nystatin Nanoemulsion-Based Gel for Topical Delivery. J of American Science 2012; 8-12.
23. Baboota S, Abdullah and Mustafa G: Mechanistic approach for the development of ultrafine oil-water emulsions using monoglyceride and blends of medium and long chain triglycerides: enhancement of the solubility and bioavailability of Perphenazine. J. Excipients and Food Chem 2012; 4(1): 55-89.
24. Jadhav K, Shetye S and Kadam V: Design and Evaluation of Microemulsion Based Drug Delivery System Int J of Advances in Pharmaceutical Sciences 2013; 156-166.
25. Ali M, Alam S and Alam N: Formulation, characterization and *in-vivo* study of nanoemulsion topical gel of beclomethasone dipropionate for psoriasis. World J of Pharmacy and Pharmaceutical sciences 2012; 4(1): 45-69.
26. Singh P, Kumar B and Jain S: Development and Characterization of a Nanoemulsion Gel formulation for Transdermal delivery of Carvedilol 2012; 57: 33-45.
27. Modi J and Patel J: Nanoemulsion – Based Gel Formulation of Aceclofenac for Topical Delivery. International Journal of Pharmacy and Pharmaceutical Science Research 2011; 6-12.
28. Nazim S and Dehghan M: Studies on Hydrotrope Potato Starch Gel as Topical Carrier for Rofecoxib. Pharmacia Sinica 2011; 2(2): 227-235.
29. Hamed R and Basil M: Nanoemulsion-based gel formulation of Diclofenac diethylamine: design, optimization, rheological behavior and *in vitro* diffusion studies 2015; 980-989.
30. Helal D, Dalia ER and Nabarawi M: Formulation and evaluation of fluconazole topical gel. Int J Pharm Pharm Sci 2012; 4: 176-183.
31. Desai S, Doke A and Disouza J: Development and evaluation of antifungal topical niosomal gel formulation. Intl J of Pharmacy and Pharmaceutical Sciences Int J Pharm Pharm Sci 2011; 3: 224-231.
32. Shaik R, Sree D and Aravind G: Development and validation of new analytical method for voriconazole for injection by using uv-spectrophotometer. Int. J.A. PS. BMS 2012; 1(3): 240-247.
33. Rowe R and Paul J: Sheskey, Handbook of Pharmaceutical Excipients, fifth edition 2006
34. Anderson BD: Chemical and related factors controlling lipid solubility. BT Gattefosse 1999; 92: 11-8.
35. Carey C, Small M and Bliss M: Lipid digestion and absorption. Ann. Rev. Physio. 1983; 45: 651-77.
36. Debnath S and Kumar S: Nanoemulsion-a method to improve the solubility of lipophilic drugs. Int J Advances In Pharma Sci 2011; 2: 2–3.
37. Harwansh R, Patra K and Pareta S: Nanoemulsions as vehicles for transdermal delivery of glycyrrhizin. Brazilian J of Pharmaceutical Sciences 2011; 43(2): 299-306.
38. Masoud M, Sharabi-Nov A and Pikkel J: Noncompliance with Ocular Hypertensive Treatment in Patients with Primary Open Angle Glaucoma among the Arab Population in Israel: A Cross-Sectional Descriptive Study. Journal of Ophthalmology 2015; 1-7.

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