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Original Article

PREPARATION AND CHARACTERIZATION OF ITRACONAZOLE TRANSDERMAL PATCHES CONTAINING SINGLE-PHASE EMULGEL

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ABSTRACT

Objective: Emulgel technique has attempts for preparation of itraconazole (ITZ) transdermal patches of reservoir type using a single-phase system with different polymers of Carbopol 934 and Carboxy methyl cellulose (CMC).

Methods: The transdermal patches were prepared by using eudragit L30 as a polymer and propylene glycol (PG) as plasticizer has been made to predict the mechanism of drug release and absorption based on the order of release. The optimized transdermal patches were characterised as surface morphology, pH, viscosity, spreadability, folding endurance, drug permeation, assay, *in vitro* dissolution and stability for 3 mo.

Results: The result of the study showed that the transdermal patches prepared with eudragit (8 %) showed 96.11±3.17 % drug release in 24 h and the optimised formulation F8, which had the highest concentration of span 20 and tween 20, displayed the highest percentage of drug penetration. The drug release kinetics was studied, including the Baker-Lonsdale model with *in vitro* drug permeation data was found that release from non-spherical matrices, the first-order model with non-fickian diffusion.

Conclusion: ITZ administered transdermally might be avoided the number of drawbacks associated with oral delivery and perhaps maintain a relatively constant plasma level during a lengthy course of treatment.

Keywords: Emulgel, Transdermal patch, Single-phase system, Release kinetics, Stability studies

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INTRODUCTION

A fungus called onychomycosis can attack either the fingernail or the toe nail. Systemic treatment for onychomycosis has been hampered by the known side effects of antifungal medications as well as the constrained blood flow to the affected nails. Onychomycosis, also known as tinea unguium, is a fungus that affects the human nail and affects around 19 p% of the world's population [1]. The anthropophilic dermatophytes that produce this condition are Trichophyton rubrum and Tri-chophyton mentagrophtes vainterdigitale. *Aspergillus spp*. and *Scopulariopsis brevicaulis* are two non-dermatophytes moulds that can act as the primary and secondary pathogens in onychomycosis. The third cause of nail fungal infection, after *Candida albicans* and *Candida parapsilosis*, is yeast [2]. In an effort to increase its penetration and solubility in the aqueous media, itraconazole (ITZ) was utilised as a model drug in this investigation.

In recent years, there has been a lot of interest in using new polymers with complex functions of emulsifiers and thickeners. This is because their ability to gel allows stable emulsions and creams to be made by reducing surface and interfacial tension and increasing the viscosity of the aqueous phase simultaneously. The gels and emulsions are used together and these types of dosage forms are called emulgels. In fact, both oil-in-water (o/w) emulsions and water-in-oil (w/o) emulsions are used to get different drugs to the skin. Adding a gelling agent to the aqueous phase of a regular emulsion turns it into an emulgel. Emulsions are easy to get rid of whenever you want and have a certain elegance [3]. They also have a strong ability to get into the skin. Emulgels used in dermatology are thixotropic, greaseless, easy to spread, easy to remove, emollient, nonstaining, water-soluble, have a long shelf life, are bio-friendly, clear, and have a nice look. Applying drugs to the skin or mucous membranes is a common way to improve or restore a basic skin function or change activity in the tissues mentioned [4].

When used, ointments, creams, and lotions, which are often used as topical agents, can be very sticky and make the patient feel bad. Also, they need to be spread by rubbing because their spreading coefficient is lower. They also show the issue with stability. Because of all of these things within the main category of semisolid preparations, the use of clear gels has grown in both cosmetic and medical preparations [5]. When a small amount of a gelling material is present, the surface tension between a colloid, which is usually 99 % water by weight, and a macromolecular network of fibres holds it still. This is called a "gel." Even though gels have many benefits, the fact that they don't dissolve in water is a major drawback. So, to get around this limitation, a method based on emulsions is used, which allows even a hydrophobic part of a drug to be effectively mixed in and given through gels [6].

Using w/o/w emulsions, it is easy to mix hydrophobic drugs into gels that are more stable, can hold more, can be made in large quantities, and cost less to prepare. Vesicular molecules can be made without intense sonication, which could cause the drug to break down and leak [7]. But making emulgel doesn't need sonication, so this problem isn't there. By using controlled release emulgels, the effects of drugs with shorter half-lives ($t_{1/2}$) can be lengthened. The aqueous materials in the emulsion make up the aqueous phase. Alcohol and water that has been cleaned are often used as agents. Oils are what make the oily part of the emulsion. Mineral oils are often used as the drug carrier and for their occlusive and sensory properties in emulsions that are applied to the skin. You can use them by themselves or with soft or hard paraffins. Emulsifiers are used to help with emulsification during production and to control stability over the course of a shelf life that can range from a few days for impromptu emulsions to months or even years for commercial preparations. For example, Tween 80, polyethylene glycol 40 stearate, Span 80, stearic acid, and sodium stearate.

In order to treat onychomycosis without the need of systemic intervention, this research has beeen done to prepare an efficient topical delivery method. The nail penetration boosting transdermal patch provide a feseable method of treating nail-related diseases including onychomycosis topically. The incorporation of the crosslinking agent glutaraldehyde and penetration enhancer triethanolamine, within the present investigation for the formulation of transdermal patches, proved to be a promising combination for enhancing the transdermal delivery of ITZ.

MATERIALS AND METHODS

Materials

Itraconazole (ITZ) was obtained as a gift sample from AD Life Sciences, Telangana, India, and Carbopol 934 and Polyethylene glycol (PG) was obtained from Loba chemicals Mumbai, India. Eudragit, Carboxy methyl cellulose (CMC), Triethanolamine, Methyl Paraben, Glutaraldehyde, Dichloromethane and surfactants were purchased from fine chemicals Mumbai, India. Without any further chemical modification, analytical grade chemicals and regulators were employed for all other purposes.

Identification, optimization and calibration curve of ITZ

Identification and authentication of ITZ pure drug by physical appearance, melting point (M4125-MEL-2, USA), FT-IR (Jasco-6600, MD) studied as per IP specifications. For optimization, the ITZ was diluted to give the concentration of 10 µg/ml and scanned between 200 nm and 400 nm for the determination of λmax and selected as 265 nm. Also prepared 2,4,6,8 and 10 µg/ml absorbance was recorded double beam UV-Visible spectrophotometer (Shimadzu Mod. No: 1700, Japan) and graph plotted against Conc. vs. Abs for calibration [8, 9].

Preformulation studies

Preformulation studies are carried out by FT-IR in according to the method described by Mohamed *et al.* (2021) and determination of physicochemical features of the ITZ such as colour, odour, density, solubility, and excipient compatibility, based on the earlier reported research in order to optimise drug administration [10, 11].

Preparation of ITZ emulgel by single-phase system

Carbopol 934 was mixed with distilled water and stirred (REMI2) slowly at 37 1 °C to make a carbopol gel, which was then left to soak for a whole night. Triethanolamine was used to make the dispersion neutral, the pH was changed to 6.5, and distilled water was added to bring the weight to 50 g. CMC gel was made by dispersing it in hot distilled water at 80 °C, letting it cool, and then adding distilled water to get the weight to 50 g [12]. Emulsion made by heating span 20 dissolved in liquid paraffin to 70 °C, then heating tween 20 and ITZ dissolved in 5 ml of ethanol to the same temperature. After adding the cross-linking agent glutaraldehyde, PG, and methylparaben, this mixture was dissolved in the aqueous phase. Next, the oil phase and the water phase were mixed together gently, and distilled water was used to make the final volume. Emulgel preparation was made by mixing the gel with the emulsion that was made, and then adding distilled water to bring the weight to 50 g. The mixture was then mixed together for 45 min with a lab homogenizer (KHH-1, Bangalore). The resulting emulgel has 10% ITZ by weight (table 1).

Preparation of release liner layer

For the preparation of Release liner, hydrophobic polymer Eudragit was used and the concentration of 6%, 8%, 10% was dissolved in 1:1 ratio of Methanol: dichloromethane, a solvent mixture of 10 ml shown in table 2. Then 6-7 drops of PG added were magnetically stirred for 10 min. Then the solution was casted for the formation of the Release liner layer [13].

Table 1: Combination of various formulation code F1-F8 (%w/w)

Emulsion: gel	1:1	1:1	1:1	1:1	1:1	1:1	1:1	1:1
Constituents	**F1**	**F2**	**F3**	**F4**	**F5**	**F6**	**F7**	**F8**
ITZ (mg)	240	240	240	240	240	240	240	240
Span 20	1	1	1	1	1	1	1	1
Tween 20	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5
Liquid Paraffin	7.5	7.5	7.5	7.5	7.5	7.5	7.5	7.5
Methylparaben	0.4	0.4	0.4	0.4	0.4	0.4	0.4	0.4
Glutaraldehyde	0.05	0.05	0.05	0.05	0.05	0.05	0.05	0.05
Propylene Glycol	5	5	5	5	5	5	5	5
Dichloromethane	2	2	2	2	2	2	2	2
Ethanol	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5
CMC	0.5	1	1.5	2	-	-	-	-
Carbopol 934	-	-	-	-	0.5	1	1.5	2
Trietahanolamine	0.01	0.01	0.01	0.01	0.01	0.01	0.01	0.01
Distilled water	0.01	0.01	0.01	0.01	0.01	0.01	0.01	0.01

Table 2: Combination of different formulation code L1-L3

Ingredients	L1	L2	L3
Eudragit-L30 (%)	6	8	10
Polyethylene Glycol (drops)	6	7	7
Methanol: Dichloromethane (ratio)	1:1	1:1	1:1

Evaluation parameters for emulgel

The ITZ emulgel preparations were looked at visually to check for separation of phases, homogeneity, consistency, colour, and smell. At 25 °C, a Brookfield viscometer (Arham/lVDV-1, Mumbai, India) with spindle 6 and 10 rpm was used to measure the thickness of several emulgel formulations. At room temperature, a digital pH metre (Elico/lI-617, Hyderabad) was used to measure the pH [14]. Spreadability was calculated using the formula S = M/l/T, where M is the weight to be taken, L is the length of the slide, and T is the time for the measurement. Each sample's ability to spread was tested three times using a device made in the lab out of two glass plates. On top of the higher plate was a lower plate with 0.5 g of the sample on it. Each sample was tested three times at a constant temperature and weight, and the mean values of the spread surface area on the lower plate were calculated. The force was made by steadily adding more weight to the pan that was attached to the top plate every minute. The monograph says that the UV-Visible spectrophotometer was used three times to measure the amount of drug (drug content) in the sample.

In vitro drug permeation study

Using a Franz diffusion cell with an egg membrane covered with 1.5 g of emulgel and clamped between the donor and receptor compartments, an *in vitro* drug permeation study was done. The receptor compartment was filled with 16 ml of pH 6.8 phosphate buffer saline (PBS) kept at 37 0.5 °C, and the magnetic bead was turned at a speed of 25 rpm. The aliquots of 2 ml were taken at 1, 2, 4, 8, and 12 h and replaced with fresh PBS medium [15]. Using a UV-visible spectrophotometer (Shimadzu/2450, Japan) at 265 nm adequate, dilutions as like above conditions transdermal patches (Emulgel+liner) *in vitro* drug permeation study were conducted. As a graphical method, the zero and first order, Higuchi, Kosmeyer-Peppas,

Hixion crowel, and Baker-Lonsdale models of release kinetics were studied to find the types of release from the reservoir [16].

Evaluation of release liner layer

Using a venire caliper, the thickness of the film was assessed at 10 different locations on one film. By physically folding a short strip of the medicated patch until it broke, the folding durability of the patch was tested. The folding endurance number was determined by how many times the strip could be folded in the same location without breaking [17].

Stability tests

Stability studies were performed at different conditions such as room temperature, 25±2 °C/60%±5% RH, and 40±2 °C/75 %±5% RH and a humidity chamber (Humidity cabinet/elico-2230). The physical changes like color, liquefaction and phase separation, viscosity, pH, spreadability, assay and drug release were studies up to 3 mo [18]. Every month patches were evaluated as per specification.

RESULTS AND DISCUSSION

Identification of authentication

Physical appearance of the ITZ was examined as white crystalline odorless powder, soluble in methanol and melt at 167 °C. The absorbance was measured as 265 nm against 6.8 pH PBS as a blank and the calibration curve was plotted shown in fig. 1. Reddy (2012) investigated transdermal patches containing ITZ made with various ratios of polyvinylpyrrolidone (PVP) and hydroxy propyl methyl cellulose (HPMC) utilising a solvent evaporation process with a plasticizer that included 10% by weight of dibutyl phthalate. On a polyvinyl alcohol backing membrane that had previously been dried at 60 °C for 6 h, the drug matrix film made of PVP and HPMC was cast. The transdermal matrix-type patches with a sustained release pattern can be produced with ITZ [19, 20].

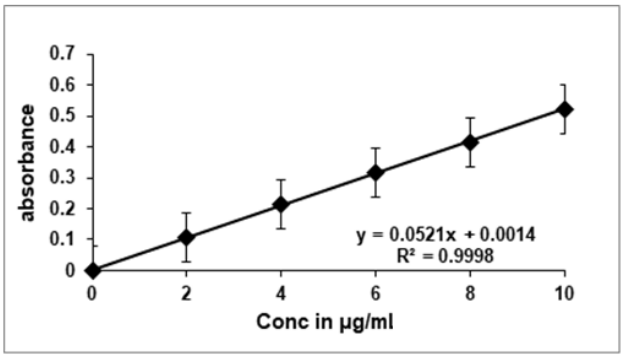

Fig. 1: Calibration curve of ITZ

FTIR spectroscopy

The compatibility between ITZ and various polymers (1:1) and other excipients (1:0.5) was performed by using FT-IR spectroscopy. The results of FT-IR study are shown (fig. 2) from ITZ reveals a number of characteristic bands representing O-H stretching (alcohol, 3417.86 and 3316.22 cm^{-1}), C=O stretching (1739.78 cm^{-1}), C=C stretching (1435.04 cm^{-1}, and aromatic, 1597.73 cm^{-1}), $CH_2CH_2OCH_2$ bending (1184.29 cm^{-1}), C-H (1343.14 cm^{-1}) and stretching vibration [21].

The physical mixture of CMC bands revealed that the ITZ has decreased wavelength with physical mixture and emulgel, suggesting that the complex has formed through hydrogen bonding. Peaks at 3458.37, 2981.95, 1739.79, 1435.04, and 1184.29 cm^{-1} correspond to O-H-stretching (alcohol), C-H stretching (SP3), C=O stretching, C-C stretching, and $CH_2CH_2OCH_2$ bending vibrations of reduced intensity. In addition, it demonstrates that the N-H expanding band does not arise at 3478.09 cm^{-1}, indicating intermolecular hydrogen holding between the ITZ and the emulgel. The single peak found at 2894.52 and 2789.22 cm^{-1} (C-H extending) may represent the drug-carrier complexing option site.

Evaluation of ITZ-emulgel

The resulting emulgel formulations were visually examined for their consistency (smoothness), homogeneity (homogenous/monolithic), colour (creamy white), and phase separation from formulation F1-F8. The result shown creamy white, homogenous, smooth and no separation of layer found throughout F1-F8. ITZ-emulgel proved that the formulations and its above parameters were suitable for the formulation and the emulgel were estimated for pH, viscosity, spreadability, assay and data for emulgel and; the results are in table 3.

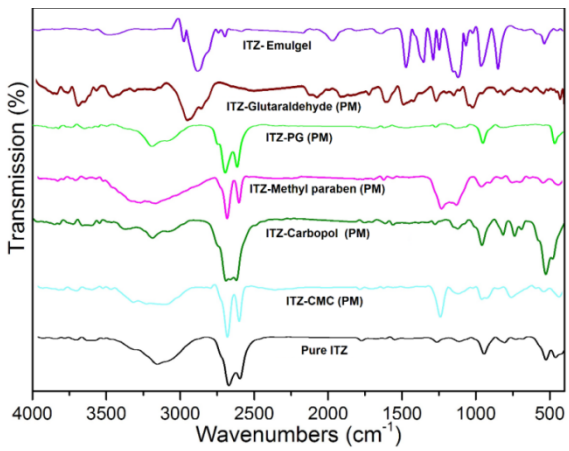

Fig. 2: FT-IR spectrum of ITZ with various excipients used for the preparation of emulgel

Table 3: Physiochemical test results for F1-F8 formulations

Formulation code	pH	Viscosity (cp)	Spreadability (cm. sec^{-1})	Assay %
F1	6.4±0.43	3600±170.22	3.0±0.01	98.41±3.54
F2	6.1±0.63	3300±155.54	3.5±0.40	99.15±3.65
F3	6.7±0.25	3900±174.73	3.2±0.55	98.02±3.61
F4	6.0±0.72	3650±147.91	3.4±0.48	99.47±3.87
F5	6.3±0.11	4300±178.67	3.5±0.62	98.83±4.91
F6	6.4±0.24	3100±189.43	4.1±0.12	97.54±5.34
F7	6.7±0.88	4800±131.55	2.5±0.75	98.74±2.34
F8	6.5±0.02	3100±122.24	2.3±0.23	99.90±2.10

Each value represents mean, *n* = 3±SD.

In vitro drug permeation data for emulgel

The prepared emulgel formulations were determined by its drug release by dissolution with Franz diffusion cell under sink condition. As shown in fig. 3a, it is clearly evident that emulgel based formulations carbopol emulgel (F5-F8) and showed better drug release (>60 %) than the CMC emulgel (F1-F4) formulation (>90 %). Formulations F3, F4, F5 and F6 showed least drug release (<80 %) among all formulations. The overall % Cumulative drug release from different formulations through cellophane membrane in decreasing order is follows: F1>F2>F3>F4>F5>F6>F7>F8. Percent drug release of all formulations (F1-F8) was conducted by taking diffusion cells with cellophane membrane and results showed that carbopol emulgel-based formulations (F8) showed less ITZ release than CMC emulgel-based (F-F4) formulations [22]. The carbopol emulgel (F8) showed less drug release (58.26±2.01 %), CMC emulgel (F1-F4) showed high ITZ release of 89.97±4.01, 84.32±3.87, 63.42±2.99, and 60.31±2.81 % respectively.

For topical distribution, Chudasama *et al.* (2011) were prepared a novel oil-in-water micro emulsion-based gel with 1% ITZ. To find possible excipients, the solubility of ITZ in oils and surfactants was assessed [23]. ITZ that contains a microemulsion was prepared for topical use.

Evaluation of release liner

Evaluation parameters of the release layer containing different concentrations of eudragit are listed in below table 4. 6 to 10 % Tensile strength were used to prepare the release liner, in which appearance, folding endurance and tensile strengths are ideal with 8 % of eudragit produced a significant value i.e. transparent, 302±10.12, and 3.9±0.24. Based on the result obtained from this study, preparation of release liner using eudragit 6% was the optimum concentration [24].

In vitro permeation data of drug reservoir through release liner

In vitro permeation study carried through same as emulgel dissolution methods and release data were obtained up to 24 h due to eudragit reservoir system here cumulative percentage ITZ release of F8 formulation of emulgel through 8% eudragit release liner shown in fig. 3b.

Table 4: Parameters of release liner at different concentrations

Test	Eudragit (%)		
	6	8	10
Folding endurance (Numbers)	286±8.89	302±10.12	345±12.88
Tensile strength (kg/cm^2)	3.2±0.99	3.9±0.24	4.3±1.05
Appearance	Transparent	Transparent	White

Each value represents mean, *n* = 3±SD.

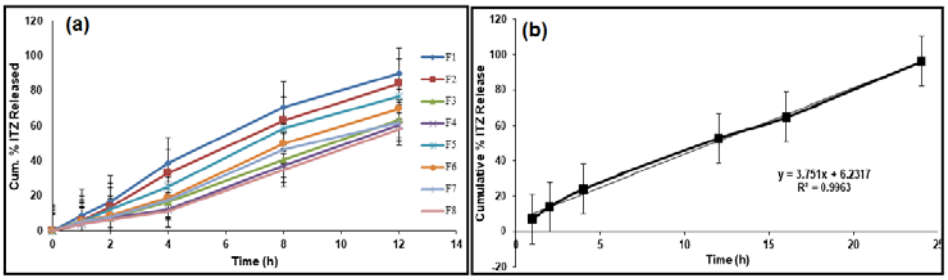

Fig. 3: Drug release profile of from (a) emulgel (F1-F8) and (b) transdermal patches-(F8)

Drug release kinetics

Using PCP DISSO V2 software, the improved formulations *in vitro* drug release pathways were identified, and R and K values were derived from several models. The result obtained are tabulated the mechanism of drug release shown in table 5. The mechanism of drug release was explored by subjecting the data to kinetic analysis by fitting to various mathematical equations and models, viz., zero order, first order, Higuchi and Peppas models (table 5). On the basis of higher regression values obtained, the ITZ-emulgel formulation followed first-order kinetic (R^2 = 0.998) and followed the Korsmeyer-Pepas equation (R^2 = 0.997) pattern [25].

The ITZ was released via first-order kinetics and a diffusion-controlled mechanism using transdermal patches. Additionally, tested the effectiveness of the penetration enhancer oleic acid on the *in vitro* permeation of drugs [23].

Stability studies

The accelerated stability evaluation was showed with optimized formulation and the ITZ-emulgels were exposed to 25±2 °C/60 %±5 % RH, 40±2 °C/75 %±5% RH and room temperature for periods of 1st, 2nd and 3rd months intervals for its physical properties such as viscosity, pH, spreadability, assay and dissolution studies and the

was no evident of degradation up to 2 mo with above condition. Table 6 shown at 3rd interval ITZ-emulgels exhibits around 83±6.89 % of drug release with *in vitro* dissolution at 40±2 °C/75±5% RH [26]. The result of the table shown.

Table 5: Mechanism of ITZ-emulgel drug release kinetics

Models	Regression equation	Mechanism
Zero order	y =-3.421x+76.76 R^2 = 0.828	Release irrespective of concentration
First order	y =-0.046x+2.018 R^2 = 0.998	Release respective of concentration
Higuchi Equation	y = 21.86x-18.01 R^2 = 0.981	Matrix doesn't swell and diffuse
Korsmeyer-Pepas equation	y = 0.791x+0.878 R^2 = 0.997	Non-fickian transport
Hixson crowell equation	y =-0.117x+4.762 R^2 = 0.936	Dissolution occurs in planes that are parallel to the drug surface
Baker-Lonsdale model	y =-96.88x+90.73 R^2 = 0.777	Drug doesn't released from matrix

Table 6: Various stability parameters of ITZ-emulgel at 40±2 °C/75±5% RH

Parameters	Initial	1 Mo	2 Mo	3 Mo
Folding endurance (Numbers)	302±10.12	297±11.15	288±13.41	278±13.89
Tensile strength (kg/cm^2)	3.9±0.24	3.8±0.45	3.7±0.91	3.5±0.42
Appearance	Transparent	Transparent	Transparent	Transparent
Viscosity (cp)	3100±122.24	2981±134.11	2870±141.23	2790±144.16
pH	6.5±0.02	6.4±0.04	6.3±0.05	6.2±0.07
Spreadability (cm. sec^{-1})	2.3±0.23	2.2±0.76	2.1±0.16	2.1±0.89
assay	99.90±2.10	97.12±5.45	96.44±5.31	95.90±4.22
In vitro dissolution (24 h)	96.11±3.17	92.66±4.85	89.60±5.78	83.60±6.89

Each value represents mean, *n* = 3±SD.

Using the preparation of pseudoternary phase diagrams, the components and their concentration ranges of oils, surfactants, and co-surfactants for the production of microemulsion were screened. The developed micro emulsion-based gel with Lutrol F127 has tremendous potential for drug distribution via transdermal route since it was the formulation of Lutrol F127 gel base that performed the best among the formulations under study and included 1 % ITZ [23].

CONCLUSION

Hence the studies concluded that the ITZ served topically as transdermal patches for the treatment of aspergillosis and mycosis with required physicochemical prosperities such as surface morphology, viscosity, spreadability, pH, drug content, release rate form liner and stability. The ITZ emulgel was created utilising light liquid paraffin as the oil phase, emulsifying agents tween 20 and span 20, and CMC and carbopol 934 polymers added into gel using various ratios. The importance of ITZ emulgel showed high permeation selected for further reservoir type of transdermal drug release system using Eudragit as release liner and showed controlled first order drug release for 24h.

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AUTHORS CONTRIBUTIONS

All this study performed or conducted by the author.

CONFLICTS OF INTERESTS

The author declare that there are no conflicts of interest.

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