ORIGINAL ARTICLE

Development and Evaluation of the Transdermal Drug-delivery System of Isradipine using Various Natural Polymers

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Abstract

Introduction: Transdermal applications, relative to other routes, are non-invasive, requiring the simple adhesion of a "patch" resulting in better patient compliance, improved bioavailability of a drug, and easy treatment termination. Hence, this investigation was aimed at delivering isradipine across intact skin as a membrane-moderated transdermal therapeutic system of Eudragit RL100, Eudragit RS100, and Eudragit E100. **Materials and Methods:** An UV spectrophotometric analytical method was developed for isradipine using a double UV spectrophotometer. The method was validated for linearity, accuracy, and precision. Isradipine was determined in triplicate by standard techniques. *In vitro* release studies in triplicate was conducted in Keshary-Chien diffusion cells across depilated rat's abdominal skin. Hypersensitivity reaction testing on depilated rabbit's skin was conducted. Stability of the drugs was studied under accelerated conditions recommended by ICH (40°C/75% R.H) for 90 days. Drug content was obtained periodically and compared. Log Kp of isradipine was found to be –5.337. Flux obtained from basic *in vitro* release (1 mg/ml) studies of isradipine was found to be 0.081 mg/cm^2/h (r = 0.985). **Results:** The flux from isradipine from reservoir gels IX and IA was found to be 0.034 mg/cm^2/h (r = 0.985) and 0.033 mg/cm^2/h (r = 0.987), respectively. The flux of membrane-moderated systems of isradipine IXRL, IARL, IXRS, IARS, IXE, and IAE was found to be 0.022 mg/cm^2/h (r = 0.977), 0.021 mg/cm^2/h (r = 0.979), 0.020 mg/cm^2/h (r = 0.977), 0.020 mg/cm^2/h (r = 0.978), 0.019 mg/cm^2/h (r = 0.975), and 0.016 mg/cm^2/h (r = 0.970), respectively. Isradipine permeates greater from xanthan gum (IX) gel compared to almond gum gel and lowest flux of the series was found to be from almond gum. K_p also tends to decrease. It was understood from the investigation that IX and almond gum can be used as drug reservoirs and Eudragit RL100, Eudragit RS100, and Eudragit E100 can be exploited as rate controlling polymeric membrane. **Conclusion:** The formulations released the drug in adequate amount and it is also contemplated in this study that even when used on human skin therapeutic concentration could be achieved in the treatment of hypertension.

Key words: Almond gum, Eudragit E100, Eudragit RL100, Eudragit RS100, Isradipine

INTRODUCTION

Developmental interest in the field of novel drug-delivery systems (TDDs) for existing drug molecules has been renewed from the past few years. A transdermal drug delivery offers controlled release of the drug into the patient, which enables a steady blood level profile, which results in reduced systemic adverse effects and improved efficacy over other conventional dosage forms. The main goal of transdermal TDDS is to deliver drugs effectively into systemic circulation through skin with predetermined rate with less inter and intrapatient variation. In addition, because transdermal patches are user-friendly, convenient, painless, and offer multi-day dosing, it is generally accepted that they offer improved patient compliance.[1-3] Isradipine was an antihypertensive can be tailored to deliver in a controlled manner for a longer duration.[4-6] Transdermal delivery

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in past two and a half decades has gained prominence in research due to its potential advantages. Furthermore, transdermal delivery of antihypertensive agents through the intact skin would have better patient compliance and plasma levels. In this investigation, it was planned to formulate transdermal formulations of Isradipine (lipophilic), using two natural gums, namely, xanthan gum (IX) and almond gum as reservoir gels planned to characterize the candidate drug for physicochemical properties. Membrane-moderated transdermal therapeutic system (TTS) shall be prepared with rate controlling Eudragit RL 100, Eudragit RS 100, and Eudragit E 100 polymers[7-9] with reservoir gels and provided with a backing laminate. The films shall be characterized by water vapor transmission studies (WVT) studies and SEM photomicrographs. Further, *in vitro* permeation of the candidate drugs shall be conducted in Keshary-Chien diffusion cells across depilated abdominal skin of male Swiss albino rat. The data were corrected with Hayton-Chien equation, to remove any sample induced bias. Furthermore, the data shall be subjected to regression analysis and analysis of variance (ANOVA). $P < 0.05$ shall be considered statistically significant. Various permeation parameters such as flux, diffusivity, and permeability coefficient shall be determined. Further, hypersensitivity studies shall be conducted on rabbit's skin. Furthermore, stability of the TTS of isradipine shall be studied at 40°C/75% relative humidity (RH).

MATERIALS AND METHODS

Isradipine (Complimentary sample from Ajanta Pharma, Mumbai), IX (Shah scientific, Mumbai), Almond gum (NR Chem, Mumbai), Eudragit RS 100, Eudragit RL 100, and Eudragit E100 (Rohm Polymers, Germany), Scanning Electron Microscope (Leica, U.K.), and U.V. Double-Beam Spectrophotometer (UV Pharmaspec 1700, Shimadzu, Japan) were used.

Method of preparation of transdermal reservoir gels containing Isradipine

Preparation of xanthan reservoir gels

An accurately weighted quantity 0.75 g of IX (7.5% w/w) was soaked in distilled water (10 ml) for 4 h. After swelling of the gel, drug solution in distilled water and methanol containing 2 mg/g of drug isradipine was incorporated into IX gel separately with continuous mixing in a blender.

Preparation of almond reservoir gels

An accurately weighted quantity 1.75 g of Almond gum (17.5% w/w) was soaked in distilled water (10 ml) for 4 h. After swelling of the gel, drug solution in distilled water and methanol containing 2 mg/g of drug isradipine was incorporated into IX gel separately with continuous mixing in a blender. Compositions of different transdermal reservoir systems containing isradipine are showed in Table 1.

Evaluation of the physical characteristics TDDS of isradipine

Thickness

The thickness of the films of Eudragit RL 100, Eudragit RS 100, and Eudragit E100 also of the rat's abdominal skin was determined using a micrometer (Mitutoyo, Japan). Average of five readings was considered; then, mean thickness, standard deviation, and percentage coefficient of variation were computed and are reported.

Melting point determination

Melting point of the drugs was determined by taking a small amount of drug in a capillary tube closed at one end and is placed in Thiel's melting point apparatus with liquid paraffin surrounding the tube, and the temperature at which the drug melts was noted. Average of triplicate readings was noted.

Solubility studies

The solubility of all drugs was determined in distilled water, different pH, and different solvents proposed by Diez and Moreno.[10] Since the drug is photosensitive, the glass wares were coated with 3 mm thick black paper. Triplicate readings were taken for and average was calculated.

Partition coefficient

The partition coefficient of the drugs was determined by taking equal volumes of n-octanol and distilled water in a separating funnel. A drug solution of 1 mg/ml was prepared and 1 ml of this solution was added to 25 ml of n-octanol and 25 ml of water taken in a separating funnel and occasional shaking was done for 24 h. Then, aqueous phase and octanol phase was separated. The aqueous phase and octanol phase were assayed using UV spectrophotometer to get partition coefficient. Triplicate readings were taken and average was calculated.

Determination of drug content

One gram of gel containing isradipine was placed in a volumetric flask containing 10 ml of methanol and kept aside with constant shaking for 24 h to extract the total drug present in the gel. The solution was than centrifuged at 2000 rpm for 5 min and subsequently filtered to remove any particles. Later, the absorbance of solution was measured after suitable dilution at 231 nm against drug devoid methanol as blank. Average of triplicate readings was taken. The content of the drug was calculated using a standard graph.

WVT

One gram of calcium chloride was accurately weighed and placed in a previously dried empty vials having equal diameter.

The polymer films were pasted over the brim with the help of an adhesive, and then, the vials were weighed and placed over a mesh in desiccators, containing 200 ml of saturated sodium bromide and saturated potassium chloride solutions. The desiccators were tightly closed and the humidity inside the desiccators was measured using a hygrometer and was found to be 56% RH and 84% RH, respectively. The vials were weighed at the end of every first day, second day, and third day up to seven consecutive days. The average of triplicate readings was taken. The results are shown in Table 2.

The morphology of 30 μm thick of Eudragit RL100, Eudragit RS100, and Eudragit E100 was studied in a scanning electron microscope (MODEL JSM-840 A, JOEL. JAPAN). The results are shown in Figure 1.

Permeation studies using hairless abdominal rat skin

Preparation of skin

The abdominal skin of excised hairless rat skin was separated along the epidermal junction and was heated for 50 s with a stream of 60°C water. The heat-treated skin was cleared of subcutaneous fatty substance using soft cotton bud and kept in normal saline solution to flatten and smooth. This step caused the layer to unwrinkle. This skin was mounted on to the donor cell of the Keshary-Chien cell.[11]

In vitro permeation

The *in vitro* permeation of drug isradipine was determined by taking the drug solution in the donor compartment.

Table 1: Formula for different transdermal reservoir systems containing isradipine

Ingredients	IX (mg)	IA (mg)	IXRL (mg)	IARL (mg)	IXRS (mg)	IARS (mg)	IXE (mg)	IAE (mg)
Isradipine	2	2	2	2	2	2	2	2
Xanthan gum (7.5% w/w)	1000	-	1000	-	1000	-	1000	-
Almond gum (17.5% w/w)	-	1000	-	1000	-	1000	-	1000
Eudragit RL 100	-	-	40	40	-	-	-	-
Eudragit RS 100	-	-	-	-	40	40	-	-
Eudragit E 100	-	-	-	-	-	-	40	40

Table 2: Cumulative amount of water vapor transmitted at 56% RH and 84% RH (*n*=3)

S. No.	Time (days)	WVT at 56% RH (g)			WVT at 84% RH (g)		
		RL 100	RS 100	E 100	RL 100	RS 100	E 100
1.	0	0	0	0	0	0	0
2.	1	0.047	0.042	0.036	0.057	0.052	0.044
3.	2	0.097	0.084	0.072	0.114	0.104	0.088
4.	3	0.147	0.126	0.108	0.171	0.156	0.132
5.	4	0.197	0.168	0.144	0.228	0.208	0.176
6.	5	0.247	0.210	0.180	0.285	0.260	0.220
7.	6	0.297	0.252	0.216	0.342	0.312	0.264
8.	7	0.347	0.294	0.252	0.399	0.364	0.308

Scanning electron microscopy of rate controlling membrane (30 μm)

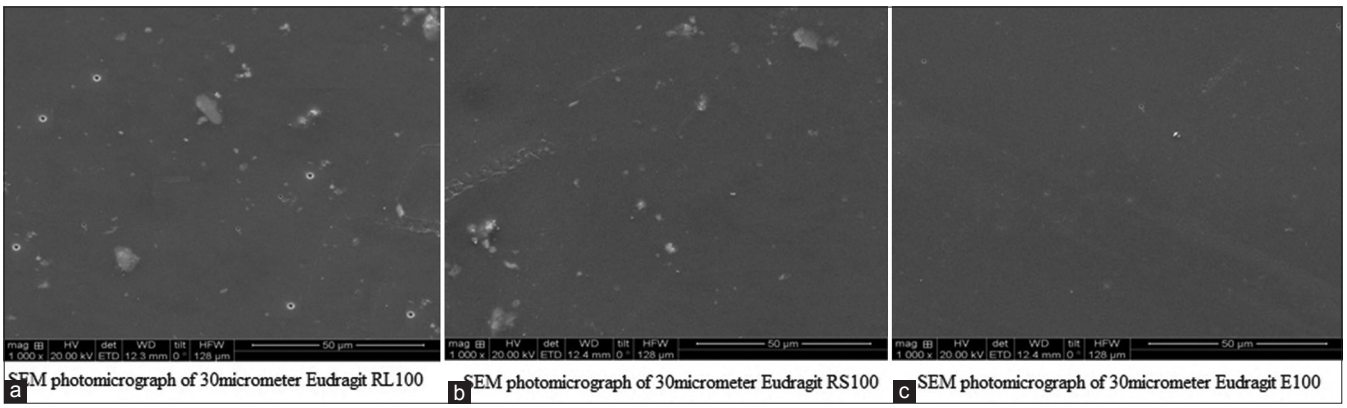

Figure 1: (a-c) SEM photomicrograph of 30 μm, Eudragit RL 100, Eudragit RS 100, and Eudragit E 100

Similarly, the gel was placed in the donor compartment so that the epidermis faces the donor compartment. The receptor compartment was filled with methanol. Since the drug used in the study is reported to be photo sensitive, all the studies were carried under dark environment. For this purpose, Keshary-chien diffusion cells were coated with 3 mm thick dark paper. The membranes of different polymers were used and the gel was placed on the membrane and the membrane of patch is placed on the epidermal layer of the skin. Teflon-coated magnetic bead was placed in the receptor compartment and the whole assembly was placed on a magnetic stirrer at a temperature of 37°C ± 0.5°C and the receptor fluid was stirred at 50 rpm. Throughout the work, samples of 1 ml were withdrawn at regular intervals of time 1, 2, 3 h, and so on. These were suitably diluted and the absorbance measured at their respective wavelength maxima. The volume of the receptor compartment was maintained constant by replacing equal volume of methanol. Similarly, a drug devoid gel of same composition was taken and simultaneously diffusion was carried out in a separate cell. Average of triplicate readings was taken.

Hypersensitivity

Hypersensitivity reactions were tested by patch testing method upon rabbit skin for the formulations. Procedure for the patch testing method on rabbit skin includes, the rabbits were divided into two groups each having six animals. The ventral surface of rabbits was depilated. The test gels were applied on to the depilated area of the animal with a backing laminate of aluminum foil. These rabbits were kept under observation for 7 days and observed any of the symptoms such as flushing (redness of skin), papules and wheals and erythema, vesicles, and marked edema.

Stability studies

The stability experiments were conducted to investigate the influence of temperature and RH on the drug content in different formulations. The formulations were exposed to temperature maintained at 40°C/75% RH in a hot air oven. The sample was removed from the oven and was analyzed for drug content. Further periodically, *in vitro* diffusion studies were carried out as described in section 4.8.2 and were compared with unconstrained diffusion profile. Average of triplicate readings was taken. Data were analyzed. The observations were tabulated.[12,13]

Statistical analysis

In vitro data were subjected to regression analysis by least square method. The standard deviation was calculated and reported. *In vivo* data were analyzed by ANOVA. $P < 0.05$ was considered to be statistically significant.

RESULTS AND DISCUSSION

Study of physical characteristics of transdermal gel containing isradipine

Characterization of pure bulk drug is an essential tool in assessing the drug's ability to permeate through intact skin. In general, a small molecule with low water solubility and high lipid solubility is a suitable candidate for transdermal permeation. Therefore, initial physicochemical characteristics of pure drug were determined. The results found are discussed henceforth. Melting point of isradipine was found to be 168°C. The solubility of isradipine in distilled water was found to be 0.066 mg/mL, in pH 1.2 is 0.041 mg/mL, in pH 2.2 is 0.053 mg/mL, in pH 7.0 is 0.070 mg/mL, in pH 7.4 is 0.113 mg/mL, and in pH 8.0 is 0.121 mg/mL. As the pH increases, the solubility of the drug increases. The n-octanol**:** Water partition coefficient of isradipine was found to be 1.544 and log K_p computed using Pott's and Guy equation was found to be –5.337 which is within the range of requirements for TTS patch. The molecular weight of isradipine is <400 daltons and its solubility in water is less, but it is found to be highly lipid soluble (log K_p >2). Hence, the drug was found to be suitable for transdermal studies, and therefore, it was used in further work. A simple and precise analytical method was developed to quantify isradipine as discussed in sec 4.3. The method was validated for linearity, accuracy, and precision. The study of water vapor transmission of Eudragit RL 100, Eudragit RS 100, and Eudragit E 100 of 30 µm at 56% and 84% R.H reveals that all the films transmit water vapor when exposed to 56% R.H. and 84% R.H. Data were subjected to regression analysis. Scanning electron photomicrographs of Eudragit RL 100, Eudragit RS 100, and Eudragit E 100 (30 µm) reveal the presence of regular and uniform pores in the films. Adequate density of pores is clearly visible within a distance of 50 µm. The physical characteristics data on solubility and partition coefficient showed that isradipine is less soluble in water and is lipophilic. *In vitro* release study in methanol across depilated rats skin showed that the drugs could permeate through the intact skin, when in solution (1 mg/ml). Hence, further membrane moderated formulations were developed with a drug impermeable backing laminate on one side so that drug always diffuses only through one face that is in contact with epidermal layer of the skin. Free films of Eudragit RL 100, Eudragit RS 100, and Eudragit E 100 of 30 µm thickness were casted on mercury surface to act as rate controlling membranes.

In vitro permeation study of isradipine in various gels or in membrane moderated systems of Eudragit RL100, Eudragit RS100, and Eudragit E100 across depilated rat's abdominal skin

The process of drug release in most controlled-release devices including transdermal patch is governed by diffusion[14,15] and

the polymer matrix has a strong influence on the diffusivity as the motion of a small molecule is restricted by the three-dimensional network of polymer chains. The data were corrected using Hayton-Chen equation[16] to remove any sample induced bias during the *in vitro* diffusion across intact skin. Furthermore, the data was subjected to regression analysis by least squares method. The permeation study was conducted for 12 h. The *In vitro* data were analyzed by ANOVA and $P < 0.05$ was considered significant. When cumulative amount of drug permeated (mg/mL) of all the formulations were plotted, a straight line was obtained. Flux (J) was obtained from the slope of the curves of dq x 1/s versus time "t." Correlation coefficient "r" was found to be high and the values of flux (J), "r," permeability coefficient (K_p), and diffusivity (D), were derived from the *in vitro* data and are shown in Table 3.

In vitro data obtained were corrected to remove any sampling induced bias in concentration- time profiles, using Hayton-Chen equation. The basic *in vitro* study was conducted by preparing a 1 mg/mL solution of drug in methanol and the data obtained were plotted as dq/S versus time (h). From slope of the curve, flux of isradipine 0.081 mg/cm^2/h was obtained. *In vitro* permeation studies showed that isradipine permeate through the skin and also from the gels of IX and almond gum gel (IA). During permeation, a significant amount of isradipine in the receptor fluid from IX gel was found at 0.75 h and 1 h, respectively, and significant amount of isradipine in the receptor fluid from IA was found after 0.75 h and 1 h, respectively. Therefore, it was ascertained that it would take considerable time for the receptor fluid to hydrate the skin and later the receptor fluid might seep into the gel and then leaches the drug inside the gel matrix on its return path, thus contributing to the lag time of >0.5 h. The flux of IX and IA found to be 0.034 mg/cm^2/hand 0.033 mg/cm^2/h, respectively. Isradipine permeates greater from IX gel compared to IA and lowest flux of the series was found to be from IA. Diffusivities were found to be 0.0032 and 0.0030, respectively, and permeability coefficients "K_p" were found to be 0.018 and 0.017, respectively. The flux of membrane-moderated systems of Eudragit RL100, Eudragit RS100, and Eudragit E100, IXRL, IARL, IXRS, IARS, IXE, and IAE, was found to be 0.022 mg/cm^2/h, 0.021 mg/cm^2/h, 0.020 mg/cm^2/h, 0.020 mg/cm^2/h, 0.019 mg/cm^2/h, and 0.016 mg/cm^2/h, respectively. Significant amounts of isradipine in the receptor fluid from IXRL was found after 1 h, from IARL after 1 h, from IXRS after 1 h, from IARS after 1 h, from IXE after 1 h, and from IAE after 1 h. Diffusivities were found to be 0.00022, 0.00021, 0.00021, 0.00020, 0.00019, and 0.00017 and permeability coefficients "K_p" were found to be 0.0117, 0.0113, 0.0111, 0.0103, 0.0098, and 0.0089, respectively. Lag times were observed to increase with membrane moderated systems. Stability of the formulations IX, IA was conducted at 40ºC/75% R.H. for 90 days. At the end of each day, drug content was estimated and found satisfactory. It was observed that percentage reduction in drug content was not significantly altered. Hypersensitivity reactions test was conducted on depilated rabbit's skin for 7 days. Every day at regular intervals, the skin of the rabbit was observed for any of the symptoms, flushing, or erythema or edema or papules or wheals. *In vitro* permeation studies showed that isradipine permeates from the matrix of any of the above mentioned reservoir gels across the skin. The flux of IX and IA found to be 0.034 mg/cm^2/h and 0.033 mg/cm^2/h, respectively. Isradipine permeates greater from IX gel compared to IA and lowest flux of the series was found to be from IA. The increased lipophilicity "pushes" the drug into the skin. Enzymes in the skin hydrolysis isradipine to a high extent during the permeation process, thus the greatly increased lipophilicity "pulls" the molecule out of the skin layer in to the receptor fluid. During diffusion studies, it was observed that isradipine in the receptor fluid from IX gel was found after 0.75 h and significant amount of isradipine in the receptor fluid from IA was found at 0.75 h. Significant amounts of isradipine in the receptor fluid from IXRL were found after 1 h, from IARL after 1 h, from IXRS after 1 h, from IARS after 1 h, from IXE after 1 h, and from IAE after 1 h. It is hence clearly seen that the lag periods increase when rate controlling films are casted. Furthermore, it is seen that nearly complete amount of drug is released at the end of 12 h diffusion study from the reservoirs alone and Lag periods for gels permeation is not given.

Table 3: Various kinetic parameters derived from *in vitro* permeation study of TTS formulations

Formulations	"r"	Flux's mg/sq.cm/h	Kp	D
IX	0.985	0.034	0.018	0.0032
IA	0.987	0.033	0.017	0.0030
IXRL	0.977	0.022	0.0117	0.0002
IARL	0.979	0.021	0.0113	0.0002
IXRS	0.977	0.020	0.0111	0.0002
IARS	0.978	0.020	0.0103	0.0002
IXE	0.975	0.019	0.0098	0.0001
IAE	0.970	0.016	0.0089	0.0001

Hypersensitivity reactions

Hypersensitivity reactions test was conducted on depilated rabbit's skin for 7 days. Every day at regular intervals, the skin of the rabbit was observed for any of the symptoms, flushing, or erythema or edema or papules or wheals. The observations are tabulated and are given in Table 4.

Stability studies

Stability of the formulations IX, IA was conducted at 40°C/75% R.H. for 90 days. At the end of each day, drug content was estimated, and the data obtained. It was observed that percentage reduction in drug content was not significantly altered. Stability studies according to ICH

Table 4: Hypersensitivity reaction study of membrane-moderated systems of Eudragit RL100, Eudragit RS 100, and Eudragit E 100

Film	RL 100			RS 100			E 100		
Time in Days	A	B	C	A	B	C	A	B	C
1	–ve	–ve	–ve	–ve	–ve	–ve	–ve	–ve	–ve
2	–ve	–ve	–ve	–ve	–ve	–ve	–ve	–ve	–ve
3	–ve	–ve	–ve	–ve	–ve	–ve	–ve	–ve	–ve
4	–ve	–ve	–ve	–ve	–ve	–ve	–ve	–ve	–ve
5	–ve	–ve	–ve	–ve	–ve	–ve	–ve	–ve	–ve
6	–ve	–ve	–ve	–ve	–ve	–ve	–ve	–ve	–ve
7	–ve	–ve	–ve	–ve	–ve	–ve	–ve	–ve	–ve

Table 5: Stability studies according to ICH guideline at 40°C/75% R.H

Time in days	Formulation (mg)	
	IX	IA
	DC*±S.D	DC*±S.D
0	1.93±0.003	1.79±0.002
1	1.93±0.005	1.79±0.002
2	1.91±0.003	1.77±0.002
3	1.91±0.001	1.75±0.001
7	1.81±0.002	1.72±0.001
15	1.77±0.001	1.65±0.004
30	1.77±0.004	1.56±0.002
45	1.75±0.004	1.45±0.003
60	1.68±0.005	1.39±0.001
90	1.57±0.003	1.31±0.001

*DC: Average of triplicate readings

guidelines at 40°C and 75% R.H indicated that the drug content from either of the gels is not significantly altered for 3 months. Hypersensitivity reactions study on depilated rabbit's skin for 7 days showed that the film of Eudragit RL 100, Eudragit RS 100, and Eudragit E 100 do not cause any allergenic reactions, the results are shown in Table 5.

CONCLUSION

The physical characteristics data on solubility and partition coefficient showed that Isradipine is less soluble in water and is lipophilic. *In vitro* release study in methanol across depilated rats skin showed that the drugs could permeate through the intact skin, when in solution (1 mg/ml). Hence, further membrane moderated formulations were developed with a drug impermeable backing laminate on one side so that drug always diffuses only through one face that is in contact with epidermal layer of the skin. Free films of Eudragit RL 100, Eudragit RS 100, and Eudragit E 100 of 30 µm thickness were casted on mercury surface to act as rate controlling membranes.

DECLARATIONS

Ethics approval and consent to participation

Not applicable.

Consent for publication

No conflicts of interest among the authors.

Availability of data and material

All required data are available.

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