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Research Article

ASSESSMENT OF BIOAVAILABILITY OF SUMATRIPTAN TRANSDERMAL DELIVERY SYSTEMS IN RABBITS

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ABSTRACT

Objectives: The purpose of the study was development, characterization and assessing the bioavailability of sumatriptan transdermal films in male albino rabbits (n=15) using HPLC method of analysis.

Method: Films were prepared using 50mg sumatriptan, Eudragit® polymers, plasticizers, and penetration enhancers.

Results: Results proved that the best plasticizer was triacetin. Eucalyptus oil and oleic acid increased the amount of sumatriptan permeated through mice skin after 24h from 17.18% (without enhancer) to 74.45 and 58.72% respectively. The optimum formulation did not produce irritation to rabbit skin and the histological structure of the epidermis and dermis were intact (n=15). Following oral administration of Imigran® (GlaxoSmithKline), C_{max} was 2.609±0.186µg/ml after 2h and the $AUC_{(0-24)}$ was 18.60µg.h/ml. After transdermal administration of optimum formulation, C_{max} was 2.892±0.106µg/ml after 2h and the $AUC_{(0-24)}$ was 26.42µg.h/ml.

Conclusion: There were no significant differences between the rate of drug bioavailability following transdermal and oral medications, but there was a significant difference between the extents of the bioavailability of sumatriptan, with the transdermal film higher in value ($p<0.05$).

Keywords: Transdermal, Sumatriptan, Eucalyptus oil, Skin irritation, Bioavailability

INTRODUCTION

Migraine is a debilitating condition characterized by moderate to severe headaches and nausea[1]. Recent population studies have shown the worldwide prevalence of migraine to be greater than 10%. The prevalence of migraine in the United States has been estimated at 18% for women, 6% for men, and 12% overall[2-3]. Pharmacologic interventions constitute the treatment for migraines and are available for both acute and prevention treatment which includes medications such as aspirin, acetaminophen, non-steroidal anti-inflammatory drugs (NSAIDs), and combination products that include caffeine. Triptans are the mainstay of treatment for acute migraine of moderate to severe intensity[4]. When these agents are used early in the course of an attack, triptans abort more than 80% of migraines within 2h[5]. However, several different triptan products are available with variation in the efficacy and tolerability of different medications in this class[6].To date, seven triptan products are available for migraine treatment including almotriptan, eletriptan, frovatriptan, naratriptan, rizatriptan, sumatriptan, and zolmitriptan[7].

Sumatriptan (SOMA) is a selective serotonin (5-hydroxytryptamine; 5-HT) type 1-like receptor agonist (triptan)[8]. It is used in acute treatment of migraine attacks with or without aura and for cluster headache[9]. SOMA is structurally similar to serotonin (5-HT), and is a 5-HT (types 5-HT1D and 5-HT1B) agonist[10]. The specific receptor subtypes it activates are present on the cranial arteries and veins. Acting as an agonist at these receptors, SOMA reduces the vascular inflammation associated with migraine. The specific receptor subtype it activates is present in the cranial and basilar arteries. Activation of these receptors causes vasoconstriction of those dilated arteries. SOMA is also shown to decrease the activity of the trigeminal nerve, which, it is presumed, accounts for its efficacy in treating cluster headaches[11]. Sumatriptan succinate can be administered orally (25 and 50mg), intranasally (10 and 20mg) or by subcutaneous injection (6mg) with respective absolute bioavailability of 14, 15 and 96% when received at these doses. Considering the low bioavailability following oral and intranasal administration, due to pre-systemic metabolism and incomplete absorption, in addition to the inconveniences associated with parenteral administration, the exploitation of an alternative route of SOMA delivery— such as transdermal administration could be of benefit[12-13]. SOMA was formulated earlier in the form of oral tablets[14], buccal tablets[15], transdermal patches[16], nasal spray[14], and suppositories [17].

Transdermal is a route of administration where the active ingredients are delivered across the skin for systemic distribution. Transdermal drug delivery systems (TDDS) include patches[18], implants[19], and gels[20]. TDDS have many advantages over the oral route such as including the ability to avoid problems of gastric irritation, pH, and emptying rate effects; avoid hepatic first pass metabolism thereby increasing the bioavailability of drug; reduce the risk of systemic side effects by minimizing plasma concentrations compared to oral therapy; provide a sustained release of drug at the site of application; rapid termination of therapy by removal of the device or formulation; It can be administered to non- responsive, unconscious and nauseating patient [21-23]. However this system has its own limitations in which drugs with high doses and those which may cause irritation or sensitization of the skin cannot be formulated in TDDS. Besides, the adhesives may not adhere well to all types of skin and may be uncomfortable to wear. Along with these limitations, the high cost of the product is also a major drawback for the wide acceptance of this product[24].

The aim of the present work was to develop and characterize transdermal films of sumatriptan prepared using Eudragit® polymers: RL-100 & RS-100. In order to improve the permeation of the drug across newly-born mice skin, different natural penetration enhancers were included in the transdermal films. Finally, the bioavailability of the optimum transdermal formulation was evaluated in male albino rabbits in comparison to Imigran® (GlaxoSmithKline, Egypt, 50mg) tablets in the market. In addition, the possible skin irritation potential of the optimum transdermal film formulation was evaluated in male albino rabbits.

MATERIALS AND METHODS

Materials

Sumatriptan succinate (SOMA) was a generous gift from Sigma Pharmaceutical Industries Mubarak Industrial City, Quessna, EI-Monofeyah, Egypt. Eudragit® RS 100 and RL were a gift from Rohm Pharma, Germany. Eucalyptus oil (1,8-cineole), oleic acid, and glyceryl triacetate (triacetin) were obtained from Fluka, Sigma-Aldrich GmbH, USA. Diethylphthalate was procured from Lobochemie PVT. Ltd, India. Acetonitrile (Merck, Germany) was of HPLC grade while all other chemicals were of pure analytical grade.

Methods

Preparation of transdermal films

The transdermal films contained 50mg sumatriptan succinate and were prepared using Eudragit® RS-100 and RL-100 in different ratios: 5:0, 1:4, 2:3, 3:2, 4:1 & 0:5. The plasticizers used were either diethylphthalate (DEP) or triacetin (TA) in the concentration of 10 or 20%w/w of total film weight. To enhance drug permeation through the skin, different penetration enhancers, either oleic acid or eucalyptus oil in the ratio of 5% w/w of total film weight was included in the films. The composition of all film formulations is described in Table (I). The transdermal films were prepared by film casting technique as follows: SOMA was dissolved in 1ml of distilled water and the hydrophobic ingredients (Eudragit polymers & plasticizers) were dissolved in 9ml methanol. The aqueous and alcoholic solutions were mixed in a beaker and stirred with magnetic stirrer at 50rpm (Thermolyne Stirring Hot Plate, Type 72200, USA) for 30min to accomplish a homogeneous mixture and the resulting hydroalcoholic solution was poured in a plastic container of diameter 2cm. The solvent was allowed to evaporate at ambient conditions for 48h and the obtained medicated transdermal films were stored in a dessicator over calcium chloride ($CaCl_2$) and evaluated within one week.

Table I: Composition of film formulations

Films	SOMA (mg)	Eudragit® polymer		Plasticizer	
		RL-100 (mg)	RS-100 (mg)	TA* (mg)	DEP# (mg)
F1	50	---	500	---	0.045
F2	50	---	500	---	0.09
F3	50	500	---	0.045	---
F4	50	500	---	0.09	---
F5	50	100	400	---	0.045
F6	50	100	400	---	0.09
F7	50	100	400	0.045	---
F8	50	100	400	0.09	---
F9	50	400	100	---	0.045
F10	50	400	100	---	0.09
F11	50	400	100	0.045	---
F12	50	400	100	0.09	---

* TA is triacetin as plasticizer

DEP is diethyl phthalate as plasticizer

Films	SOMA (mg)	Eudragit® polymer		Plasticizer	
		RL-100 (mg)	RS-100 (mg)	TA* (mg)	DEP# (mg)
F13	50	200	300	---	0.045
F14	50	200	300	---	0.09
F15	50	200	300	0.045	---
F16	50	200	300	0.09	---
F17	50	300	200	---	0.045
F18	50	300	200	---	0.09
F19	50	300	200	0.045	---
F20	50	300	200	0.09	---
F21	50	500	---	---	0.045
F22	50	500	---	---	0.09
F23	50	---	500	0.045	---
F24	50	---	500	0.09	---

* TA is triacetin as plasticizer

DEP is diethyl phthalate as plasticizer

Evaluation of sumatriptan films

Film weight and thickness

Three films for each film formulation were weighed and the average weight of the films was then determined ± standard deviation (SD). The thickness of the films was determined by measuring the thickness at the 4 edges and the center of the formulated films using a micrometer screw gauge (0-1In, 0.001, ratchet, model: 103-259, Mitutoyo Corp, Japan) and the results were expressed as average thickness ± SD.

Drug content

A $2cm^2$ film was cut into small pieces, put into a 100 ml phosphate buffer saline PBS (pH 7.4), and shaken in a mechanical shaker at 37°C and 100rpm for 24h (Julabo SW-20C, Germany). Then the whole solution was ultrasonicated (Model 275T, Crest Ultrasonics Corp., Trenton, USA) for 15min. After filtration, the drug was estimated spectrometrically at wavelength of 284nm and the concentration was deduced in accordance to a preconstructed calibration curve in PBS pH 7.4 (R^2 = 0.9998, *n=3*). The experiment was repeated three times and the mean drug content for each formulation was determined.

Differential scanning calorimetry (DSC)

Samples of pure film components, the physical mixture of the drug and the excipients, in addition to F4, which was selected as a representative formulation for comparison purposes, were analyzed by differential scanning calorimetry (DSC) using a Shimadzu DSC-60 (Kyoto, Japan) to characterize the changes occurring in samples during thermal exposure. Samples of 5mg were crimped in a standard aluminum pan and heated under nitrogen atmosphere in the range between30-400°C, at a heating rate of 10°C and the characteristic peaks were recorded while using an empty pan as the reference in this instrument.

Percentage of moisture uptake

The films were initially weighed (W_1) and then exposed to either relative humidity (RH) of 97, 65 and 33% provided by saturated

solution of either sodium sulphate, sodium nitrite, and magnesium chloride in a dessicator respectively and the films were reweighed (W_2) until a constant weight for the film was obtained. The percentage of moisture uptake was calculated according to the following equation[25]:

$$Percent\ \ Moisture\ Uptake = \frac{(W_2 - W_1)}{W_1} \times 100 \quad \text{Eq. (1)}$$

Swelling index and percent film dissolution

Films were dried in a dessicator over anhydrous calcium chloride at 37°C until a constant weight was obtained (W_1). Then, films were immersed in 100mL distilled water for 3days at 37°C. Excess water present on the swollen films was removed by careful blotting with filter paper. The films were reweighed (W_2), returned to the dessicator, and dried to a constant weight; then, they were reweighed again (W_3). Percent film dissolution was determined in triplicate and the mean±SD was determined according to the following equation[26]:

$$Percent\ \ film\ \ dissolution = \frac{(W_1 - W_3)}{W_1} \times 100 \quad \text{Eq. (2)}$$

The swelling index (SI) was determined from the amount of water absorbed per unit weight of undissolved films retrieved from the distilled water after immersion according to the following equation[26]:

$$Swelling\ \ index = \frac{(W_2 - W_3)}{W_3} \quad \text{Eq. (3)}$$

Mechanical properties

The mechanical properties of the transdermal films were determined using Zwick 1425 material testing machine (Germany) according to American Standards for Testing Materials D624. Briefly, the film formulations were cut into dumbbell-shaped specimens using appropriate punching dies with a width of 4mm and a neck length of 15mm. The film specimens were tested at a crosshead speed of 50mm/min, with a load cell of 10–20N. Tensile strength (TS), also known as stress at rupture, is calculated by dividing the maximum load by the original cross-sectional area of the specimen and is expressed in force per unit area (Kg/mm^2). The percent elongation at break (E %), also known as strain at rupture, is calculated according to the following equation:

$$E\% = \frac{L - L_o}{L_o} \times 100 \quad \text{Eq. (4)}$$

Where L_o is the initial gauge length of the specimen and L is the length at the moment of rupture.

***In-vitro* release study**

In order to study the drug release, a USP dissolution tester of basket type (Classic Version 6- Vextra-Model BLHMO15K-10 Oriental Motor, Co. Ltd., Japan) with a slight modification was utilized. Glass cylinders (of 10cm length and 2.5cm diameter) were used instead of the regular baskets. A dialysis membrane with a 12,000 - 14,000 molecular weight cut off (Spectrum Laboratories Inc., USA) was soaked in PBS (pH 7.4) overnight before the study. SOMA films, placed under the presoaked cellulose membrane, were wrapped on one end of the glass cylinders and were fitted on the basket shaft from the other end. The glass cylinders were placed in the vessels of the dissolution tester, so that the membrane and film were only touching the surface of 100ml of PBS (pH 7.4) at 37°C and stirred at a constant speed of 50rpm. At predetermined time intervals (0.5, 1, 1.5, 2, 4, 8, 10 and 24h), 5ml aliquots of the medium were withdrawn for analysis and replaced with equal volume of fresh buffer solution to maintain a constant volume[27]. The absorbancies of the collected and filtered samples were measured spectrophotometrically at 284nm. The experiment was repeated three times and the results were expressed as the mean value of three experiments ± SD.

***In-vitro* permeation of SOMA through mice skin**

The same conditions used for in-vitro release study was used for in-vitro permeation, but excised newly born mice skin was used instead of cellulose membrane. The concentration of SOMA permeated through mice skin was determined spectrophotometrically at 284nm. The experiment was repeated three times and the results were expressed as the mean value of three experiments ± SD. The results obtained from the transdermal films were compared to that obtained from permeation of 1ml of SOMA solution in distilled water with a concentration of 50mg/ml placed inside the glass cylinders and served as control. The effect of different penetration enhancers (oleic acid or eucalyptus oil) utilized in the concentration of 5%w/w of total film weight on the amount of SOMA permeated through mice skin was also studied.

Skin irritation studies

The skin irritation studies were conducted on fifteen rabbits to evaluate the possible irritation potential of the optimum transdermal film on the skin. The protocol of the study was approved by the Research Ethics Committee of the Faculty of Pharmacy, Cairo University, Egypt and complied with the principles of the Declaration of Helsinki (PI 363).

Application of formulation to rabbits

Fifteen male albino rabbits were used during this study. The experiment was conducted according to the scheme designed by Jibry and Murdan[28]. The rabbits were divided into three groups. Five male albino rabbits were assigned to each treatment group as follows: the optimum transdermal films were applied on rabbits of group A, sodium lauryl sulfate solution (5%w/v) were applied on rabbits of group B and served as positive control, and rabbits of group C did not receive anything and served as negative control.

Twenty four hours before application of the treatments, the backs of the rabbits were carefully shaved with clippers. On the day of the study, a patch (2cm^2) on their lower backs was marked onto which each treatment was carefully applied. As suggested by Jibry and Murdan [28], all treatment sites were covered with sterile gauze and secured with surgical tape to prevent grooming and removal of the formulation from the skin. At different time intervals, the gauze was removed, the treated area was gently wiped with water-soaked gauze, and the site of application was visually examined for cutaneous irritation/reaction. A score for erythema (redness) was given as follows: 0, no erythema; 1, weak spotty or diffuse erythema; 2, weak but well perceptible erythema covering the total exposure area; 3, moderate erythema; 4, severe erythema with edema; 5, very severe erythema with epidermal defects (vesicles, erosions, etc.) [29]. The examination of skin of rabbits continued for 96h. After examination, the animals were sacrificed by decapitation and skin biopsies (1cm^2) were taken from all animals in different groups, preserved in 10% formalin solution for 48h before processing for histopathological studies. The skin patches were dehydrated by immersing in methyl, ethyl and finally absolute ethyl alcohol. Skin specimens were cleared in xylene and embedded in paraffin at 56°C in hot air oven (MMM group, Medcenter Einrichtungen GmbH, Germany) for 24h. Paraffin beeswax tissue blocks were prepared for sectioning at 4microns by slidge microtome. The obtained tissue sections were deparaffinized and stained by hematoxylin and eosin stains for histopathological examination through the electric light microscope[30]. The bodies and the remains of rabbits were frozen and transferred to be incinerated at Faculty of Veterinary Medicine, Cairo University.

Bioavailability of SOMA from transdermal films

Fifteen male albino rabbits weighing 2-2.5kg were chosen for the study. The protocol of the study was approved by the Research Ethics Committee of the Faculty of Pharmacy, Cairo University, Egypt and complied with the principles of the Declaration of Helsinki (PI 363). The rabbits were divided into three groups; each group consisted of five rabbits. Rabbits in group I received the optimum transdermal film (F4) [Eudragit® RL-100 (0.5g), triacetin (20%w/w), eucalyptus oil (5%w/w),

and sumatriptan (50mg)]. Rabbits of group II received Imigran® tablets, and rabbits of group III were the control group and did not receive any drug. Animals were fasted for overnight and stored in individual cages before doing the experiment. The hair of the dorsal surface of the rabbits was carefully removed by shaving using clippers. On the next morning the transdermal film containing 50mg sumatriptan was applied on the dorsal skin of the rabbits of group I for 24h period with the help of surgical adhesive tape. The blood samples (2ml) were withdrawn from the ear vein of rabbits using a 23G needle at 0, 1, 1.5, 2, 3, 4, 8, 12, and 24h post dosing and collected in heparinized tubes. Blood samples were centrifuged at 3000g for 10min (Hettich EBA85 Centrifuge, USA) to separate the plasma. The clear supernatant serum layer was collected in labeled tubes and stored immediately at -20°C until HPLC analysis was performed. In case of rabbits of group II, each rabbit received one Imigran® tablets (50mg sumatriptan) orally with the help of 100ml water. Rabbits of group III did not receive any drug. The food was allowed after 4h of drug administration and the same pattern of collecting blood samples was followed.

Determination of SOMA using HPLC method

The analysis of SOMA in the plasma of rabbit was performed using an HPLC system consisting of a Shimadzu Model LC 10AD pump, a Shimadzu Model SPD 10 ultraviolet detector, a chromatopac C-R6A integrator (Shimadzu, Japan) and a Rheodyne injector with a 20µg loop. Chromatographic separation was achieved isocratically at room temperature on a C18 column (Inertsil, 5mm, 15cm, 4.6mm). The mobile phase composed of 0.05mol/l sodium phosphate buffer (pH 7.4) and acetonitrile (65:35, v/v) and was delivered into the HPLC system at a flow-rate of 1.0ml/min. Sulpiride was used as internal standard (IS) and the ultraviolet detector was set at 225nm[31]. The HPLC was validated by measuring the intra- and inter-day precision (variation) on three consecutive days (n = 3). The intra-day precision of the analysis method was evaluated by analyzing samples of three different concentrations of SOMA (0.5, 1, and 2µg/ml) in triplicates on the same day. The inter-day precision was evaluated from the same concentration on three consecutive days. The precision of the method was determined by repeatability (intra-day) and intermediate precision (inter-day).

Sample preparation

The blood sample was collected in heparinised tubes, and the plasma sample was separated by centrifugation at 5000rpm for 15min (Hettich EBA85 Centrifuge, USA). The extraction consisted of the addition of 4ml of tert-butylmethyl ether to 1ml of rabbit plasma and mixed with 50µl of sulpiride as internal standard using liquid/liquid extraction. After shaking in a mechanical horizontal vortex (220±10cycles/min) (Vortex, Heidolph, Germany) and after centrifugation at 4000rpm for 5min (Hettich EBA85 Centrifuge), 4.4ml of the organic phase (supernatant) was transferred to 10ml conic tubes and the organic solvent was evaporated under a constant air flow at room temperature by using evaporator concentrator (eppendorf). The dried plasma was reconstituted in 450µl of the mobile phase 0.05mol/l sodium phosphate buffers, pH 7.4, and acetonitrile (65:35, v/v) and was injected into the HPLC system [31].

Statistical analysis

The experimental results were expressed as the mean of three trials ± SD (standard deviation). One-way analysis of variance was also applied to determine the level of significance followed by Tukey's HSD test. Differences were considered statistically significant when $p<0.05$. Statistical analysis of the data generated was performed using SPSS software (SPSS 7.5, Inc., Chicago, United States).

RESULTS

The formulated transdermal films were transparent, flexible and showed no blooming. The transdermal films obtained the shape of circular discs of 2cm diameter. The physicochemical properties of film were assessed in the following section.

Uniformity of film weight and thickness

Table (II) showed that the films prepared were uniform in weight and thickness. The weight of transdermal films ranged from 0.453±0.045 to 0.518±0.041g. The thickness of the prepared films varied between 0.320±0.013 to 0.417±0.015mm.

Drug content

The drug content of formulated films was found to be uniform and ranged from 48.68±0.01mg to 50.14±0.02mg, corresponding to 97.30±0.01% and 100.28±0.02% as shown in table (II).

DSC

Fig (1) demonstrated the DSC thermograms of Eudragit® RS-100 and RL-100 polymer, SOMA, and F4 as an example of transdermal film formulation. The DSC thermogram of SOMA (Fig. 1c) showed a single endothermic peak at 168.9°C corresponding to the melting point of the drug[32].

Table II: Charcterization parameters of film formulations

Films	Drug content (%) ± S.D.	Weight (g) ± S.D.	Thickness (mm) ± S.D.	Flux of SOMA released± S.D. (µg/cm²/h)
F1	97.90 ± 0.01	0.472 ± 0.033	0.320 ± 0.013	2.330 ± 0.235
F2	100.16 ± 0.04	0.518 ± 0.021	0.385 ± 0.011	0.742 ± 0.054
F3	100.20 ± 0.03	0.515 ± 0.018	0.336 ± 0.021	3.677 ± 0.056
F4	98.28 ± 0.03	0.516 ± 0.091	0.323 ± 0.017	1.305 ± 0.115
F5	97.30 ± 0.01	0.511 ± 0.039	0.366 ± 0.008	1.441 ± 0.027
F6	98.26 ± 0.01	0.517 ± 0.032	0.353 ± 0.019	0.758 ± 0.035
F7	97.62 ± 0.02	0.495 ± 0.010	0.360 ± 0.014	1.529 ± 0.162
F8	97.90 ± 0.02	0.518 ± 0.016	0.365 ± 0.020	2.992 ± 0.086
F9	100.20 ± 0.03	0.494 ± 0.065	0.410 ± 0.011	1.088 ± 0.059
F10	98.20 ± 0.01	0.510 ± 0.057	0.403 ± 0.014	3.117 ± 0.009
F11	100.22 ± 0.01	0.516 ± 0.014	0.410 ± 0.030	1.427 ± 0.159
F12	100.28 ± 0.02	0.490 ± 0.055	0.417 ± 0.005	2.970 ± 0.002

Films	Drug content (%) ± S.D.	Weight (g) ± S.D.	Thickness (mm) ± S.D.	Flux of SOMA eleased± S.D. (µg/cm²/h)
F13	100.22 ± 0.03	0.472 ± 0.314	0.357 ± 0.014	0.810 ± 0.026
F14	99.22 ± 0.01	0.517 ± 0.028	0.397 ± 0.027	1.169 ± 0.083
F15	97.56 ± 0.02	0.514 ± 0.006	0.337 ± 0.015	1.262 ± 0.006
F16	97.50 ± 0.01	0.518 ± 0.057	0.417 ± 0.015	2.839 ± 0.015
F17	100.06 ± 0.02	0.481 ± 0.013	0.383 ± 0.013	0.797 ± 0.098
F18	100.10 ± 0.03	0.518 ± 0.041	0.340 ± 0.010	2.114 ± 0.026
F19	100.08 ± 0.01	0.517 ± 0.030	0.320 ± 0.011	1.030 ± 0.056
F20	97.90 ± 0.04	0.453 ± 0.045	0.403 ± 0.016	2.553 ± 0.005
F21	99.08 ± 0.03	0.466 ± 0.076	0.347 ±0.007	3.451 ± 0.015
F22	100.10 ± 0.01	0.518 ±0.043	0.330 ± 0.019	1.514 ± 0.061
F23	98.46 ± 0.02	0.475 ± 0.049	0.377 ± 0.015	0.558 ± 0.029
F24	99.04 ± 0.01	0.514 ± 0.056	0.377 ± 0.020	0.618 ± 0.011

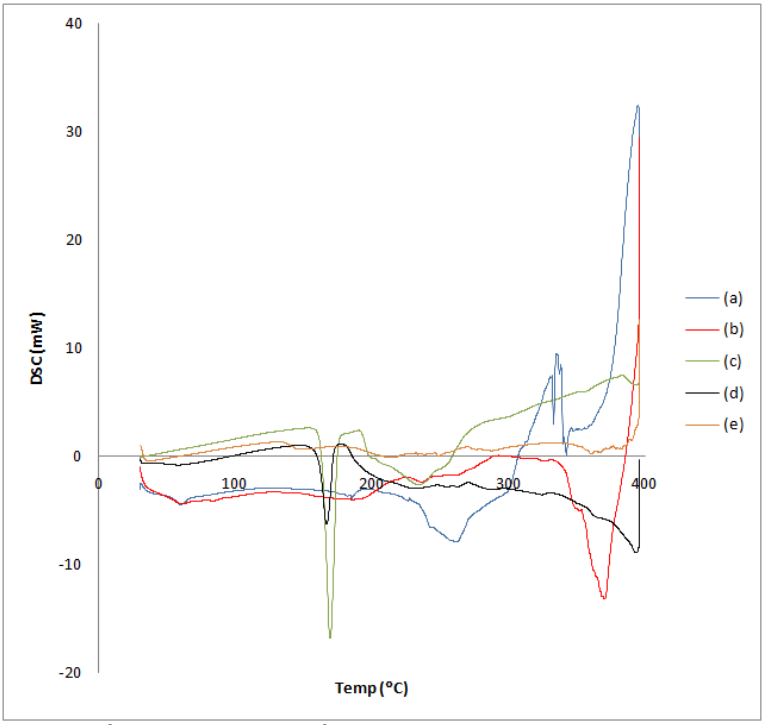


Fig. 1: DSC thermogram of: (a) Eudragit® RS-100, (b) Eudragit® RL-100, (c) SOMA, (d) physical mixture of drug and polymers (Eudragit® RS-100 and RL-100); and (e) transdermal film formulation (F4).

Percentage of moisture uptake

The results of moisture uptake of different transdermal films in three relative humidities: 33, 65, and 97% were showed in Fig (2a-f). As expected, percent moisture absorption of the film formulations stored at 97%RH conditions was relatively higher than at 33% and 65%RH. Results showed that, at 97%RH, the percent moisture absorption of (F1) film increased to its double from 5.31±0.061% to 12.97±0.127 % after 11 days, and that the percent moisture absorption of (F2) film increased from 1.62±0.058% to 8.51±0.157 %. Results obtained showed that the percent moisture absorption of (F5) increased from 5.48±0.037% to 18.13±0.127 % after 10 days and from 4.99± 0.035% to 19.35±0.071% in case of (F6) film containing 20% DEP as plasticizer as shown in Fig. (2a-b). In case of 33% and 65%RH, results indicated that film formulations absorbed relatively low amounts of moisture and reached a point of equilibrium by the end of 9days. It should be noted that storing film formulations at those two relative humidities showed no apparent physical changes at the end of study (2weeks). It was also observed that film formulations (F1, F2, F5 and F6) did not gain moisture during the study time.

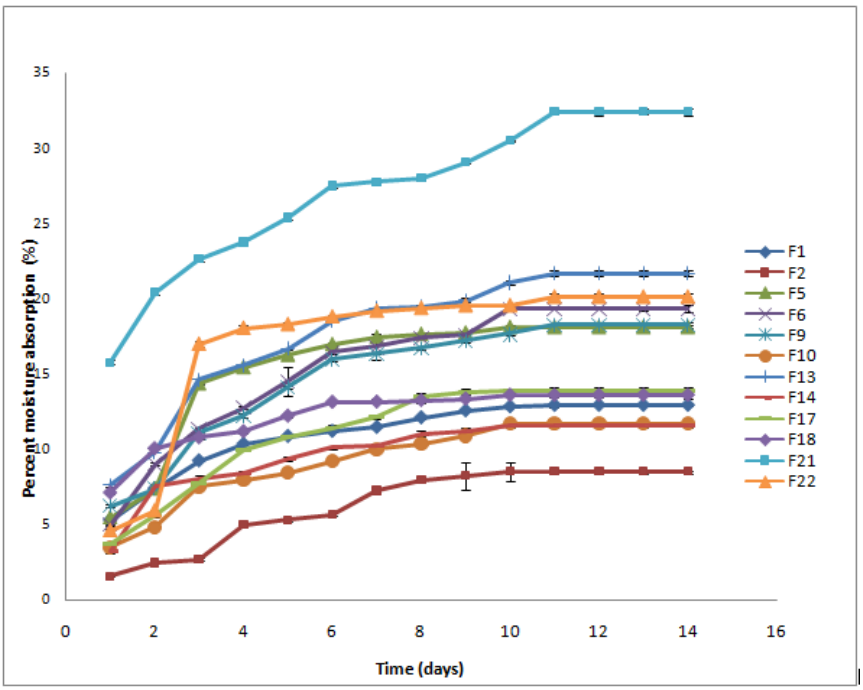


Fig. 2-a: Moisture absorption of film formulations containing DEP at RH 97%

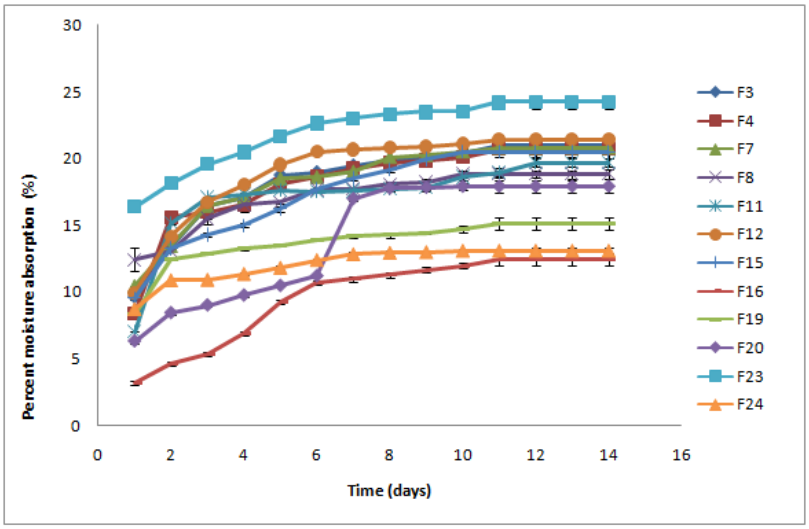


Fig. 2-b: Moisture absorption of film formulations containing TA at RH 97%

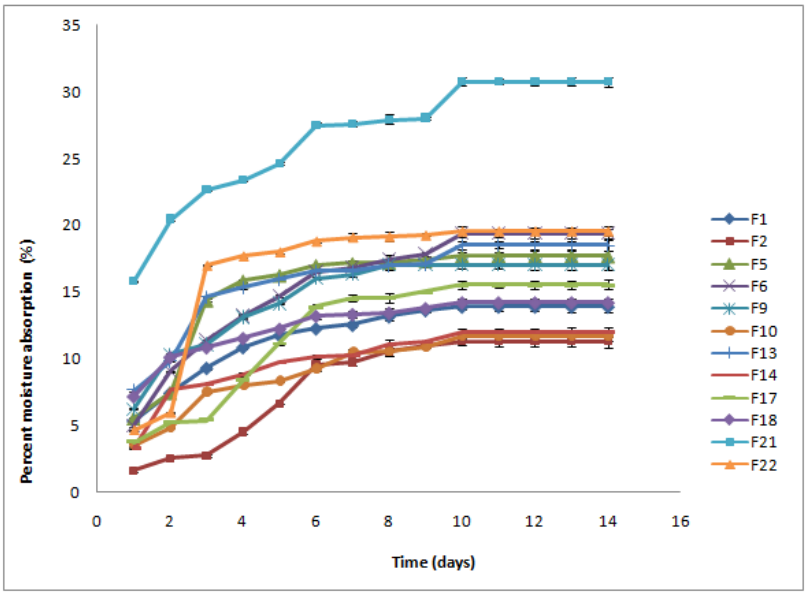


Fig. 2-c: Moisture absorption of film formulations containing DEP at RH 65%

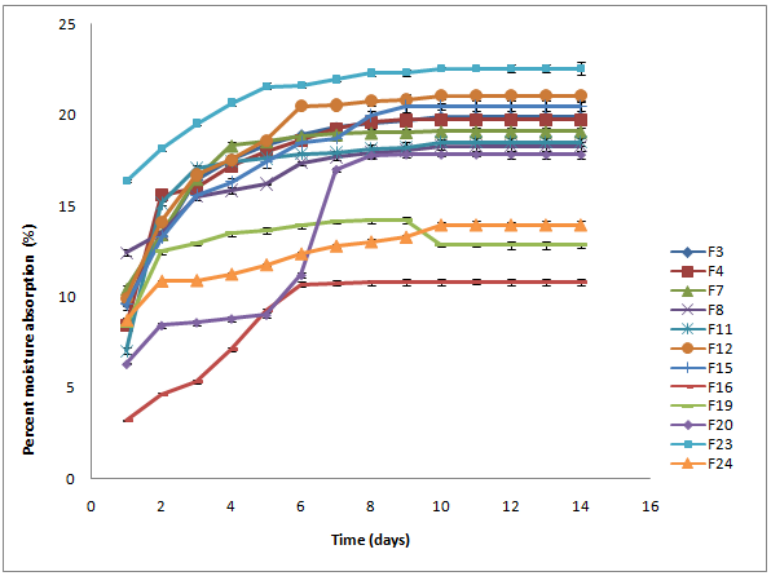


Fig. 2-d: Moisture absorption of film formulations containing TA at RH 65%

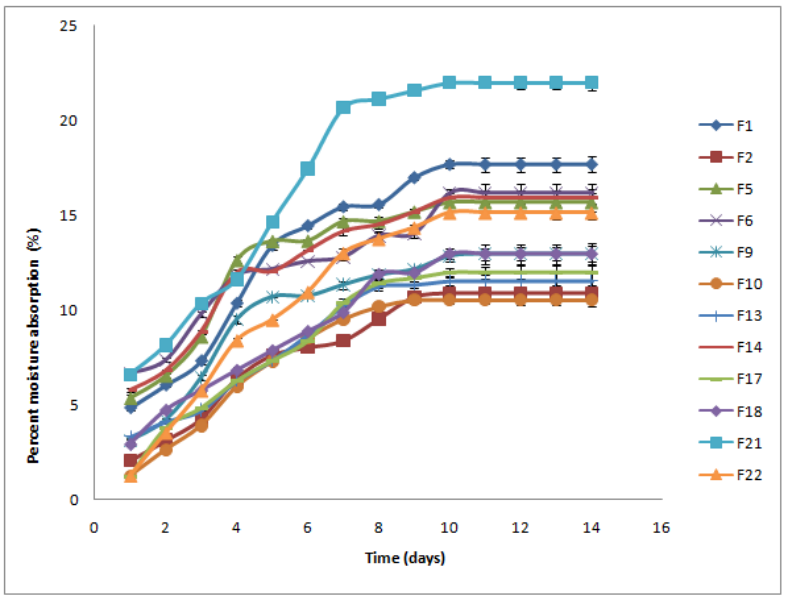


Fig. 2-e: Moisture absorption of film formulations containing DEP at RH 33%

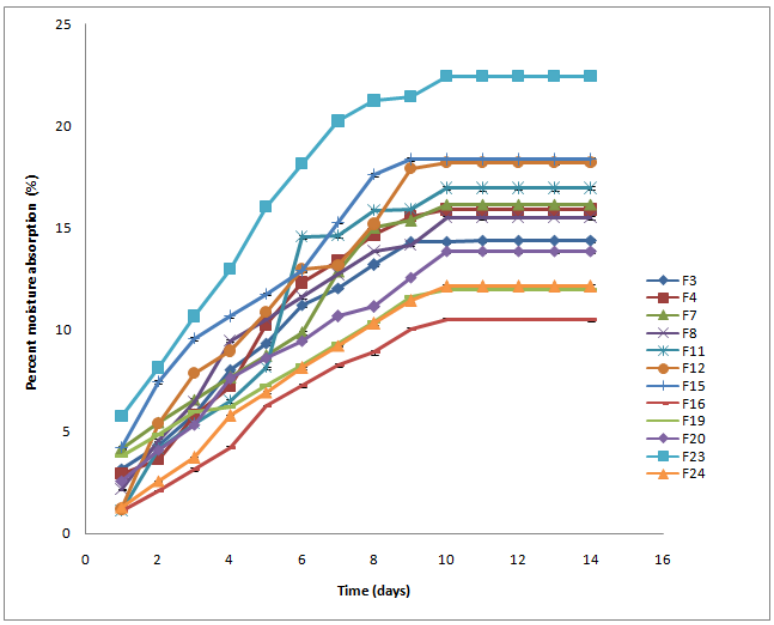


Fig. 2-f: Moisture absorption of film formulations containing TA at RH 33%

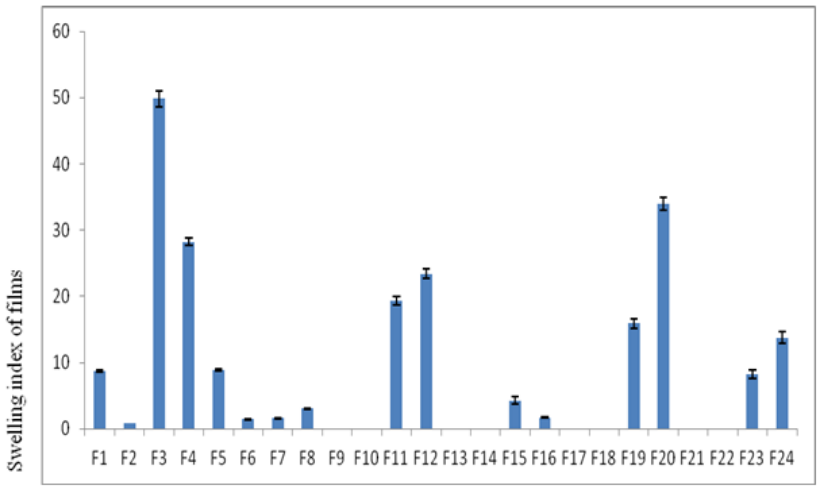


Fig. 3: Swelling index of the formulated SOMA transdermal films

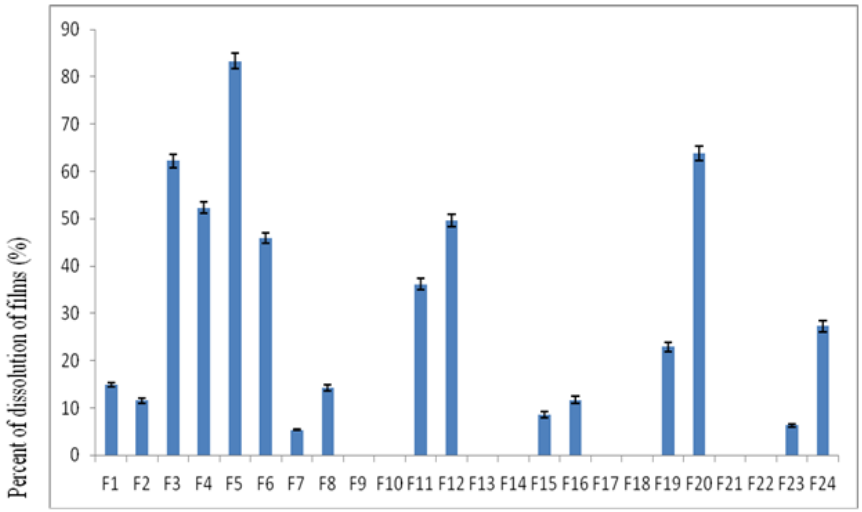


Fig. 4: Percent dissolution of the formulated SOMA transdermal films

Swelling index (SI) and percent film dissolution

Fig (3 and 4) showed the water uptake capacity of the films which was measured by the swelling index (SI) and percent dissolved of those films. Data revealed that transdermal films formed of Eudragit® RL-100 polymer alone exhibited the highest SI in comparison to other films formulations. These results suggested that those films would be more permeable to the drug than other film formulations[33]. The percent of films dissolved increased with the incorporation of Eudragit® RL-100 polymer in the films compared to the films prepared with Eudragit® RS-100 films. Moreover, the increase of Eudragit® RL-100 polymer to Eudragit® RS-100 in the film formulations (F11-F12) to a ratio of 4:1 led to the significant increase in percent films dissolution ($p<0.05$).

Mechanical properties

All results of the mechanical properties of SOMA Eudragit® films are shown in table (III). Results obtained revealed that, in general, when increasing the ratio of the Eudragit® RS-100 polymer there was a corresponding increase in the percentage of elongation (E%) and a decrease in the tensile strength (TS) of films. Increasing the concentration of the TA in the Eudragit® films from 10 to 20% led to a significant increase in the %E from (23.751±0.145) in case of F3 to (256.042±0.265) in case of F4; and a significant decrease in the TS of the films, as F3 films exhibited TS of (0.202±0.012) which reached (0.052±0.002) in case of F4 ($p<0.05$). Similar results were obtained by increasing the concentration of the DEP in the Eudragit® film from 10 % (F1) to 20% (F2) to a corresponding increase in elongation and a corresponding decrease in tensile strength.

Table III: Mechanical properties of film formulations

Films	Tensile strength (TS) (kg/mm^2) ±SD	Elongation % (E%)±SD
F1	0.109 ± 0.021	60.040 ± 0.235
F2	0.069 ± 0.003	80.830 ± 0.365
F3	0.202 ± 0.012	23.751 ± 0.145
F4	0.052 ± 0.002	256.042 ± 0.265
F5	0.069 ± 0.009	3.955 ± 0.521
F6	0.068 ± 0.011	63.334 ± 0.235
F7	0.023 ± 0.008	21.669 ± 0.412
F8	0.057 ± 0.001	253.330 ± 0.325
F9	0.218 ± 0.021	8.335 ± 0.365
F10	0.080 ± 0.006	143.750 ± 0.125
F11	0.098 ± 0.002	9.999 ± 0.231
F12	0.030 ± 0.001	92.918 ± 0.362
F13	0.142 ± 0.019	19.584 ± 0.128
F14	0.079 ± 0.001	205.833 ± 0.224
F15	0.198 ± 0.025	23.751 ± 0.235
F16	0.039 ± 0.035	223.500 ± 0.651
F17	0.162 ± 0.004	11.666 ± 0.289
F18	0.077 ± 0.012	192.080 ± 0.537
F19	0.209 ± 0.009	20.001 ± 0.356
F20	0.057 ± 0.023	290.832 ± 0.489
F21	0.358 ± 0.069	17.917 ± 0.785
F22	0.076 ± 0.001	35.001 ± 0.832
F23	0.093 ± 0.006	99.584 ± 0.651
F24	0.053 ± 0.001	294.160 ± 0.716

***In-vitro* release of SOMA through synthetic membrane**

The release profile of SOMA formulations composed of different ratios of Eudragit® RL-100: RS-100 in PBS (pH 7.4), at 37.5°C and at 50 rpm, with plasticizer TA or DEP in different concentrations was graphically illustrated in Fig (5 and 6). It could be noticed that drug released from control solution was much higher than that from all films prepared ($p<0.05$). The flux of drug release from F control was 4.290±0.253µg/cm^2/h while the highest flux obtained from films was 3.677 ± 0.056µg/cm^2/h from F3 (Table II). The release of SOMA

formulations composed of Eudragit® RS-100 alone (F2, F24) and Eudragit® RS-100: RL-100 in the other ratios (1:4, 2:3, 3:2, 4:1 and 0:5) showed a decrease in the extent of the drug released in comparison with formulations (F4, F10, F12, F18 and F20) which was composed of higher ratio of Eudragit® RL-100. The release parameters of SOMA from transdermal films through cellulose membrane were shown in table (IV). The calculated correlation coefficient (R^2 value) of each formulation was compiled in table (V). The kinetic analysis of in-vitro release data showed that the release of SOMA from most formulated transdermal films followed diffusion order with the exception of (F4, F6, F11, F16 and F22) which followed zero order.

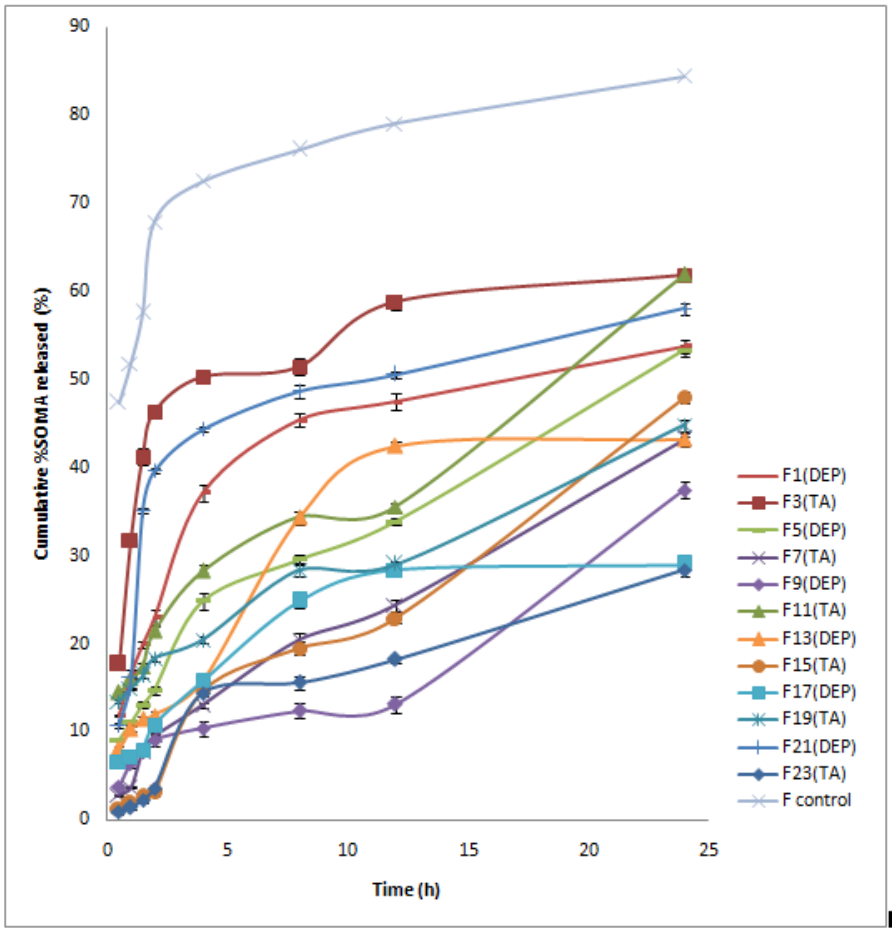


Fig. 5: Release of SOMA from films plasticized with 10% plasticizer through cellulose membrane. (F control: 1 ml of SOMA solution (50mg/ml)).

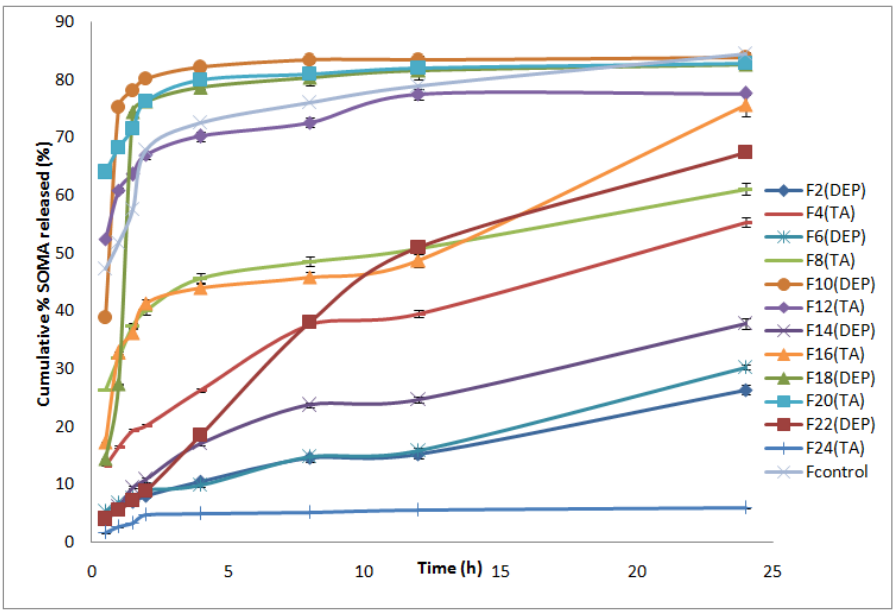


Fig. 6: Release of SOMA from films plasticized with 20% plasticizer through cellulose membrane. (F control: 1 ml of SOMA solution (50mg/ml)).

Table V: Kinetic analysis of in-vitro release data showing R^2* value of each order.

Films	R^2* value order of drug release			
	Zero	First	Diffusion	Type of release
F1	0.736	0.607	0.896	Diffusion
F2	0.976	0.831	0.990	Diffusion
F3	0.781	0.557	0.898	Diffusion
F4	0.995	0.924	0.940	zero
F5	0.872	0.734	0.961	Diffusion
F6	0.994	0.904	0.960	zero
F7	0.972	0.720	0.992	Diffusion
F8	0.768	0.669	0.833	Diffusion
F9	0.947	0.866	0.868	zero
F10	0.549	0.389	0.678	Diffusion
F11	0.983	0.931	0.916	zero
F12	0.893	0.825	0.981	Diffusion
F13	0.845	0.774	0.892	Diffusion
F14	0.905	0.677	0.990	Diffusion
F15	0.760	0.591	0.902	Diffusion
F16	0.822	0.646	0.776	zero
F17	0.788	0.687	0.898	Diffusion
F18	0.457	0.304	0.598	Diffusion
F19	0.975	0.895	0.989	Diffusion
F20	0.685	0.645	0.825	Diffusion
F21	0.551	0.386	0.727	Diffusion
F22	0.989	0.800	0.972	zero
F23	0.861	0.603	0.952	Diffusion
F24	0.521	0.406	0.710	Diffusion

*R^2: correlation coefficient

Table IV: The release and permeation parameters of SOMA through synthetic and natural membranes respectively.

Films	% SOMA released through cellulose membrane after 24h (%) ±SD	% SOMA permeated through mice skin after 24h (%) ±SD	Permeation rate (µg/cm²/h) ±SD	Enhancement ratio (ER) ±SD	
				Oleic acid	Eucalyptus oil
Control	84.46±0.422	20.182±0.591	0.443±0.032	---	---
F4	55.36±0.235	17.182±0.693	0.351±0.011	2.6±0.011	2.9±0.012
F10	83.182±0.890	13.504±0.356	0.309±0.09	---	---
F12	77.647±0.239	19.722±0.103	0.296±0.053	2.4±0.023	2.5±0.065
F18	82.663±0.590	11.635±0.253	0.263±0.089	---	---
F20	82.931±0.567	18.546±0.635	0.312±0.056	---	---

Effect of the plasticizers

The increase in the concentration of the plasticizer resulted in an increase in the percent of the drug released from films. In case of films formed of Eudragit® RL-100 (F3, F4, F21 and F22) the average cumulative percent of SOMA released through cellulose membrane after 24h were: 61.82±0.715, 55.36±0.235, 58.00±0.666 and 67.50±0.412% respectively, while the fluxes of SOMA from formulation films (F3, F4, F21 and F22) were found to be 3.677±0.056, 1.305±0.115, 3.451±0.015, and 1.514±0.061µg/cm²/h respectively. Result of the in-vitro release study showed that the released of SOMA from film formulations using TA was significantly faster than those of film formulations using DEP ($p<0.05$).

***In-vitro* permeation of SOMA through mice skin:**

Fig (7) showed controlled permeation profiles of the drug film formulation (F4, F10, F12, F18 and F20). The average percent of SOMA permeated from these formulations through mice skin were found to be 17.182±0.693, 13.504±0.356, 19.722±0.103, and 11.635±0.253 and 18.546±0.635% respectively in comparison to 20.182±0.591% from the control aqueous solution (50mg/ml). The permeation of SOMA from the above mentioned film formulations across excised newly born mice skin were further studied. In addition, those film formulations showed optimum physicochemical properties as shown before .Thus, the permeation of SOMA from the investigated film formulation were shown in (Fig 8 & 9) with use penetration enhancer for the developed formulation, the cumulative amount of drug permeated through newly born mice skin (micrograms per square centimeter) was plotted as a function of time (h). Table (IV) showed the percent of SOMA permeated from the developed systems through the skin in 24h ranged from 11.635±0.253% (F18) to 19.722±0.103% (F12) in comparison to 20.182±0.591% which was permeated from the control aqueous solution (50mg/ml).

Effect of the penetration enhancer

Penetration enhancers were added to optimum film formulation to improve the penetration of SOMA through skin layers and into blood supply. Two different penetration enhancers of natural origin were used (oleic acid and eucalyptus oil). Results showed that the penetration enhancers increased the average amount of SOMA permeated through mice skin significantly in comparison to plain control film with no penetration enhancer ($p<0.05$) as shown in Fig (8 & 9). The percentage of drug permeated through mice skin from formula F4 when using oleic acid increased from 17.182±0.693% to 58.728±0.02% whereas when using eucalyptus oil increased from 17.182±0.693% to 74.58±0.198%. The percent drug permeated through mice skin after 24h from film F12 using oleic acid increased from 19.722±0.103 to 63.225±0.645% whereas when using eucalyptus oil it increased to 66.273±0.421%. The enhancement ratio (ER) for eucalyptus oil was found to be 2.5±0.065 in case of (F12) and 2.9±0.012 in case of (F4). As for oleic acid, the ER was 2.4±0.023 in case of (F12) and 2.6±0.011 in case of (F4).

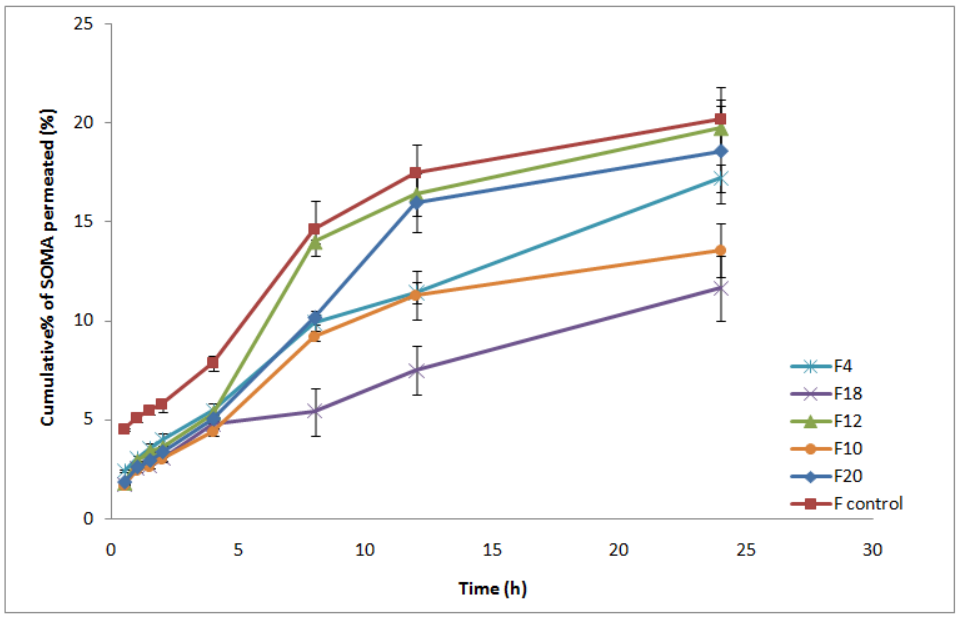


Fig. 7: Permeation of SOMA through mice skin without penetration enhancers.

(F control: 1 ml of SOMA solution (50mg/ml)).

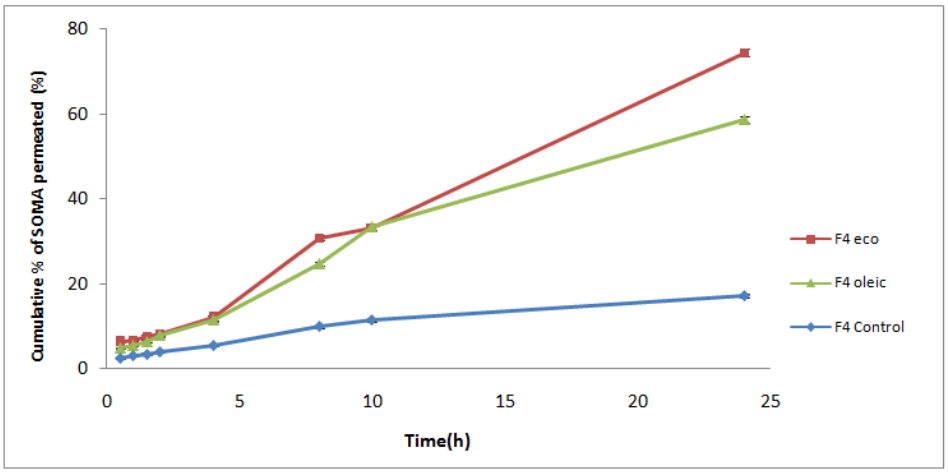


Fig. 8: Permeation of SOMA through mice skin with penetration enhancers. F control is for transdermal SOMA film without penetration enhancers.

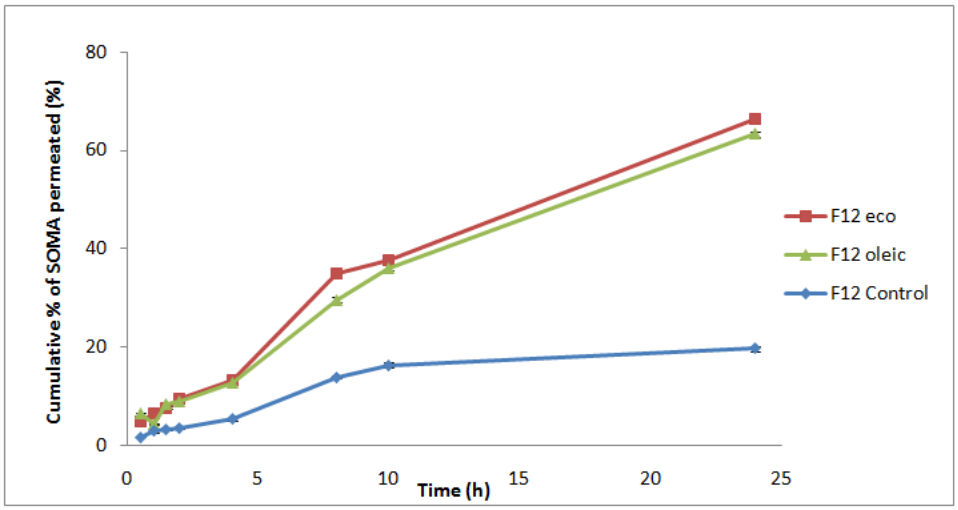


Fig. 9: Permeation of SOMA through mice skin with penetration enhancers. F control is for SOMA transdermal film without penetration enhancers

Evaluation of skin irritation

Evaluation of the irritation potential of the optimum film formulation was done by the scoring system erythema which was caused by the increased blood flow in the dermis of rabbits. It could be considered as tool to monitor the response the topical preparations applied on the skin the erythema scores upon exposure of skin to the optimum film formulation (F4) as well as after exposure to SLS solution (5% w/v) were presented in table (V**I**).

The rabbit skin patches treated with SLS solution suffered from much higher erythema levels all over the study period (96h). Strong, infiltrated erythema with superficial erosions involving at least 50% of the test area was observed after 6h and was scored as (3). At the end of 12h, extensive erosions involving at least 50% of the test area were revealed and were scored as (4). At the end of 48h, extensive erosions involving at least 50% of the test area were revealed and were scored as (5). The application of SLS solution (5%,w/v) for several days, as a positive control, caused extensive irritation in the form of erythema, acanthosis, and thickening with polyps formation in spinosum of epidermis (p) with oedema (o) and inflammatory cells (arrow) infiltration in the dermis, focal hemorrhage in dermal layer as shown in Fig. (10-C, D, E & F). Under occlusion conditions, it caused inflammation, erythema, and significant changes in skin morphology. On the other hand, the optimum formulation (F4) was well tolerated by all skin rabbit as shown in Fig. (10-G). As the time of the experiment progressed (12h), the erythema level increased. Moderately intense erythema involving around 30% of the test area was evidenced after 24h and was scored as (2). Within 24h, the erythema diminished and skin recovery took place.

Table V**I: Evaluation of skin irritation by scoring method**

Time (h)	Film formulation (F4)	*SLS	Control
0	0	0	0
3	0	2	0
6	1	3	1
12	1	4	1
24	2	4	1
48	2	5	1
72	3	5	1
96	3	5	1

0= no erythema.

1= weak spotty or diffuse erythema.

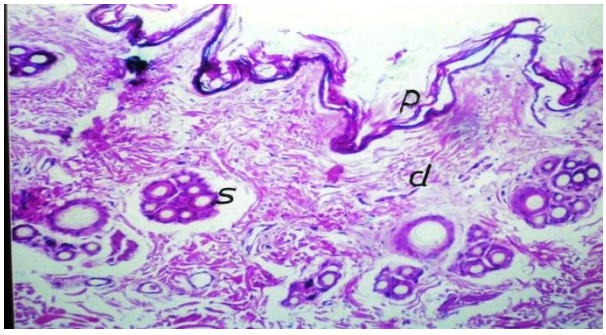
2= weak but well perceptible erythema covering the total exposure area.

3= moderate erythema.

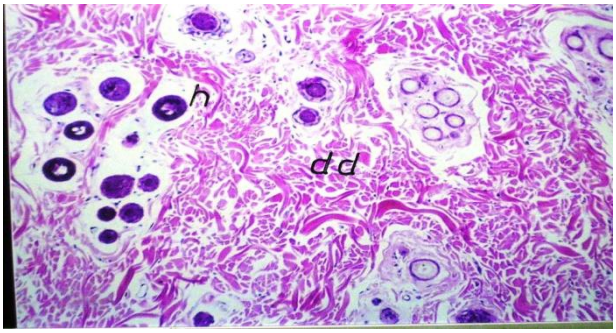
4= severe erythema with edema.

5= very severe erythema with epidermal defects.

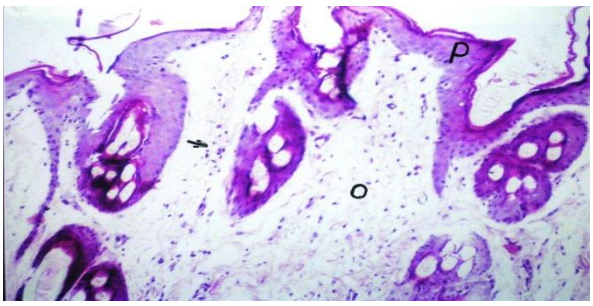
*SLS is sodium lauryl sulphate solution (5% w/v)



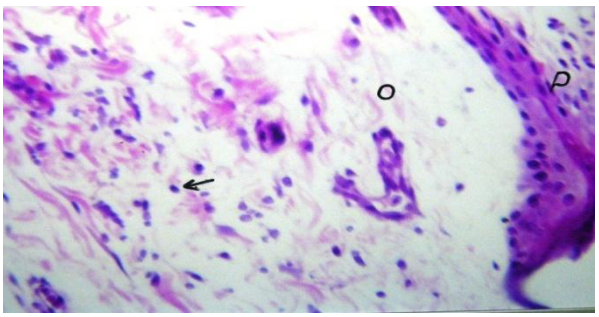
(A)



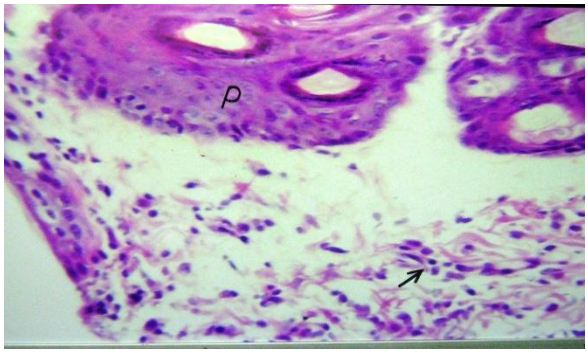
(B)



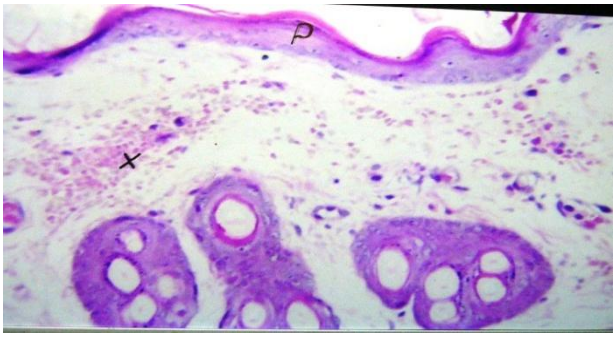
(C)



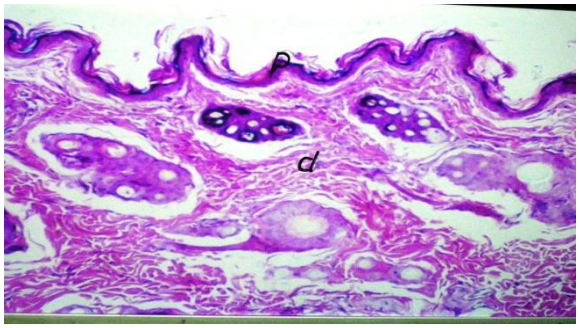
(D)



(E)



(F)



(G)

Fig. 10: Histopathological micrographs of rabbit skin biopsies: (10-A) group of rabbits kept as control showed no histopathological findings epidermis (p) and the dermal layer (d) with sebaceous gland (s); (10-B) group of rabbits kept as control showing the deep dermal layer (dd) with hair follicle (h); (10-C) group of rabbits treated with sodium lauryl sulphate showing acanthosis and thickening with polyps formation in spinosum of epidermis (p) with oedema (o) and inflammatory cells (arrow) infiltration in the dermis; (10-D) group of rabbits treated with sodium lauryl sulphate showed the magnification of Fig (C) to identify the oedema (O) in dermis; (10-E) group of rabbits treated with sodium lauryl sulphate showing the magnification of Fig (C) to identify the acanthosis in spinosum of epidermis (p) and inflammatory cells infiltration (arrow) in the dermis; (10-F) group of rabbits treated with sodium lauryl sulphate showing focal hemorrhage (x) in dermal layer; and (10-G) group of rabbits upon application of transdermal SOMA film showing the intact histological structure of the epidermis (p) and dermis (d).

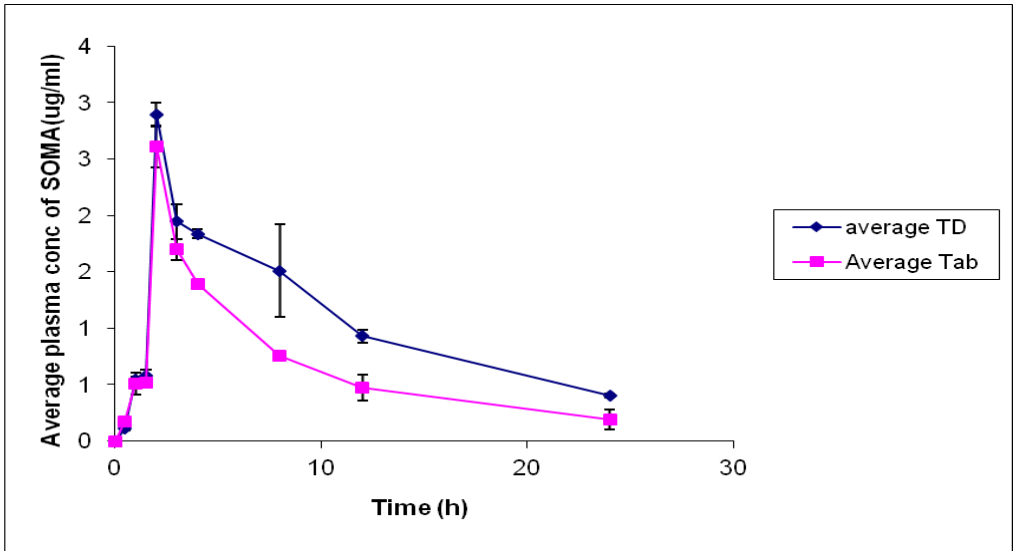


Fig. 11: Average plasma concentration time profile of SOMA following oral Tab administration and transdermal film (TD) application in rabbits.

Validation of the HPLC method of analysis of SOMA

The retention times of SOMA and IS (sulpiride) were 10.1and 7.6 min respectively. The calibration curve was constructed by measuring the relative peak area ratio of different SOMA solutions (concentrations of 0.1, 0.5, 1, 2, 2.5 and 3µg/ml in mobile phase) to that of IS (100µg/ml in methanol) spiked with plasma. The validation of the HPLC method of analysis of SOMA showed that the intra- and inter-day precision (variation) on three consecutive days (n = 3) ranged from 1.6 to 3.5% respectively. The intra-day precision showed a relative standard deviation (RSD %) of 0.1-0.2%. The inter-day precision showed a RSD % of 0.1-0.5%.

Bioavailability of SOMA from transdermal films in rabbits:

The mean plasma concentrations of SOMA at different time intervals following the application of the optimum SOMA transdermal film formulation (F4) and (Imigran®, 50mg) oral tablet to rabbits were shown in Fig. (11). Following oral administration of SOMA (50mg), the average maximum serum concentration (C_{max}) of SOMA attained was 2.609±0.186µg/ml and was achieved after 2h. The area under the serum concentration-time curve from time 0 to 24h (AUC_{0-24}) and the $AUC_{0-\infty}$ were found to be 18.60± 0.009 and 19.45±0.012 µg.h/ml respectively. After administration of transdermal F4 formulation to rabbits, the drug level in serum was detectable till 2h with C_{max} of 2.892±0.106µg/ml and the AUC_{0-24} and $AUC_{0-\infty}$ were found to be 26.42± 0.019 and 24.80±0.016µg.h/ml respectively.

DISCUSSION

Uniformity of film weight and thickness

Results obtained showed that the films prepared were uniform in weight and thickness as shown in table (II).

Drug content

The results proved that the formulated transdermal films were uniform in SOMA content as shown in table (II).

DSC

The absence of the characteristic peaks of SOMA and Eudragit® polymers in the DSC thermogram of the formulated transdermal film (F4) (Fig. 1d) demonstrated the complete miscibility of the drug in transdermal film and the absence of incompatibility between the drug and film components.

Percentage of moisture uptake

The results of moisture uptake of different transdermal films in three relative humidities: 33, 65, and 97% showed that, generally, the presence of plasticizers in the Eudragit® film weakened its resistance to solubility in distilled water. Of the two plasticizers used, TA was found to be more effective in reducing the water resistance of films. This could be attributed to the increase in the ratio of the Eudragit® RS-100 in those film formulations, which is characterized by its hydrophobic nature. Also it was obvious that the increase of Eudragit® RL-100 ratio to that of Eudragit® RS-100 in the film formulations led to an increased water absorbing ability of these prepared films. This could be due to the hydrophilic nature of Eudragit® RL-100 polymer compared to Eudragit® RS-100 polymer. The hydrophilic nature may be attributed to the fact that Eudragit® RL-100 polymers contain double the quaternary ammonium groups of Eudragit® RS [34].

Swelling index (SI) and percent film dissolution

The water uptake capacity of the films was measured by the swelling index (SI) and percent dissolved of those films. The results proved a significant increase in percent film dissolution containing Eudragit® (RL-100) alone ($p<0.05$). This might be attributed to the increase in the ratio of the polymer which was freely permeable to water as a result of using Eudragit® (RL-100)[35].

Mechanical properties

All results of the mechanical properties of SOMA Eudragit® films showed that when increasing the ratio of the Eudragit® RS-100 polymer there was a corresponding increase in the percentage of elongation (E%) and a decrease in the tensile strength (TS) of films. Also, increasing the concentration of the TA in the Eudragit® films from 10 to 20% led to a significant increase in the %E. This was due to the fact that plasticizers acted by inserting themselves between the polymer strands, breaking the polymer-polymer bond, which led to an increase the molecular mobility of the polymer strand[36]. Thus it was expected that as the concentration of the plasticizer increased, the degree of the film stiffness decreased whereas the film ductility increased. For Eudragit® RL-100 and RS-100 films, the best plasticizer to do this effect was TA. This was revealed by the optimum mechanical properties obtained by films plasticized with this plasticizer. Also the main reason of adding plasticizers to film forming polymers is to improve flexibility and processability of the films. Upon addition of plasticizer, flexibilities of polymer macromolecules or macromolecular segments increase as a result of loosening of tightness of intermolecular forces[37]. It was also found that weakening of interaction of the polymer chains led to a decrease in the tensile strength and an increase in the percent elongation of the films[38].

***In-vitro* release of SOMA through synthetic membrane**

Results of *in-vitro* release study showed that the release of SOMA formulations composed of Eudragit® RS-100 alone (F2, F24) and of Eudragit® RS-100: RL-100 in the other ratios (1:4, 2:3, 3:2, 4:1 and 0:5) was relatively higher than that from film formulations containing high ratio of Eudragit® RL-100 alone. These results could be attributed to the lower content of quaternary ammonium groups present in Eudragit® RS-100 than in Eudragit® RL-100, resulting in less swelling in the aqueous medium[39]. In addition, the inclusion of Eudragit® RL-100 polymer in the films prepared with Eudragit® RS-100 led to a slight reduction in the release profile of the drug compared to that from Eudragit® RL-100 alone (F6 & F4) ($p>0.05$). In case of the films prepared using Eudragit® RS-100 (F1, F2, F23, F24), it was found that the drug released decreased significantly ($p<0.05$); and that the release of SOMA from films containing plasticizers at 20% level (F2 & F24) was decreased after 24h compared to drug release from films containing 10% plasticizers (F1 & F23). These results might be due to the fact that (F2 & F24) films were more flexible and showed no cracks, which led to a sustained drug release than the films (F1 & F23) which more brittle, whereas in case of the films prepared using Eudragit® RL-100 (F3, F4, F21, F22) there was an increase in the drug release due to drug hydration and its rapid release from the matrix [39]. Thus, results of in-vitro drug release from the prepared transdermal films concluded that films prepared using 20% plasticizers (F4 & F22) acquired optimum drug release than films (F3 & F21).

Effect of the plasticizers

The increase in the concentration of the plasticizer in the formulated films resulted in an increase in the percent of the drug released from those films. Besides, the result of the in-vitro release study showed that the release of SOMA from film formulations using TA was significantly faster than those of film formulations using DEP. This was attributed to the fact that the plasticizers with lower molecular weight (like TA) had more molecules per unit weight compared to the plasticizers with higher molecular weight. Those molecules could more easily penetrate between the polymer chains of the film forming agent and could interact with the specific functional groups of the polymer[40]. In addition low molecular weight plasticizer improved the miscibility within the polymer[41]. Both TA and DEP acted by reducing the secondary bonds (e.g. hydrogen bond) of the polymer and themselves forming secondary bonds[40].

***In-vitro* permeation of SOMA through mice skin**

The difference in the drug permeation patterns from different transdermal film formulations could be related to different in the polymer used and the ability of the drug to penetrate skin layers. After 24h, it was clear that film formulation F20 was the highest cumulative amounts of drug permeated.

Effect of the penetration enhancer

Penetration enhancers increased the average amount of SOMA permeated through mice skin significantly in comparison to plain control film with no penetration enhancer. The mode of action of these enhancers may be due to enhancement of drug partitionining and diffusion and the process of diffusion was dominant[42]. The permeation enhancement effect of oleic acid through natural skin membrane was due the filling of oleic acid between the polymer chain spacing and blocking the diffusion path channel with the primary plasticizer[43]. On the other hand, eucalyptus oil enhanced SOMA permeated through mice skin by modifying the solvent nature of the stratum corneum, thus improving drug partitioning into the tissue[44]. A previous study proved that large amounts of terpene were found in the epidermis after application from a matrix-type patch. It is well known that terpenes permeated through skin well by modifying drug diffusivity through the natural skin membrane[45]. It was also found that the film formulation prepared using eucalyptus oil as penetration enhancer provided higher penetration enhancement of SOMA than that of film formulation using oleic acid. This might be due to filling of oleic acid between the polymer chain spacing and blocks the diffusion path channel with primary plasticizer of TA. Many literatures have stated that oleic acid acts as a secondary plasticizer leads to lesser release of drug like (salicylic acid)[43]. Oleic acid has been found to increase the epidermal permeability through a mechanism involving the stratum corneum lipid membranes. Oleic acid when incorporated into skin lipid, disrupts molecular packaging and alters the level of hydration, thus allowing drug penetration[46].

Evaluation of skin irritation

The skin irritation study done on albino rabbit skin showed that the optimum film formulation did not produce irritation to the skin, and that after 5days the histographs showed intact histological structure of the epidermis and dermis. The results of the in-vitro permeation data and the histopathological study proved that the natural penetration enhancer increased the amount of sumatriptan permeating through rabbit skin without incurring any irritation or inflammation reactions.

Validation of the HPLC method of analysis of SOMA:

The adopted HPLC method of analysis of SOMA in plasma of rabbits proved to be sensitive as the lowest concentration detected was 0.1µg/ml. The method also proved to be highly reproducible and reliable. So the system meets the required system suitability and the area RSD% indicated a good degree of precision for the HPLC analysis system.

Bioavailability of SOMA from transdermal films in rabbits:

When compared statistically, there was no significant difference ($p>0.05$) between the C_{max} and T_{max} attained following either oral or transdermal formulations but there was significant difference ($p<0.05$) between the $AUC_{(0-24)}$ of the two medications. This proved that there was no significant between the rate of bioavailability of SOMA following administration of the transdermal film or oral tablet. On the other hand, there was a significant difference between the extents of the bioavailability of SOMA from the two medications, with the transdermal film higher in value.

CONCLUSION

Transdermal films of sumatriptan prepared using Eudragit® RL-100 polymer and plasticized with 20%w/w triacetin and using 5%w/w eucalyptus oil as chemical penetration enhancer proved to be an optimum film formulation delivering the drug in a controlled manner. The extent bioavailability of sumatriptan from the transdermal films was significantly higher than Imigran® tablets (50mg) in rabbits. The use of naturally occurring materials as permeation enhancers for sumatriptan confirmed the safety of this medication with respect to skin irritation. This transdermal dosage form could be of particular benefit to patients treated with sumatriptan for migraine attacks owing to the associated nausea symptoms, which inherently pose a hurdle in administering this medication orally.

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