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Investigate the Effect of Fatty Acids on Rheological Properties and *In vitro* Permeability of Escitalopram Oxalate from Hydroxypropyl Cellulose Gel Formulations

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Authors' contributions

This work was carried out in collaboration between all authors. All authors read and approved the final manuscript.

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ABSTRACT

The present studies evaluate rheological properties and in-vitro permeability properties of Escitalopram Oxalate (ECO) containing hydroxypropyl cellulose (Klucel HF, HPC) gels prepared with different carbon chain length containing fatty acids. The formulations were prepared by mixing solvent, escitalopram oxalate and kulcel HF (HPC) in homogenizer at 25000 RPM. A controlled stress rheometer was used to study the effect of different number of carbon chain fatty acids on the rheological properties and microstructure of HPC gels. The in-vitro permeability study was performed using human cadaver skin in order to evaluate the enhancing effect of fatty acids. The studies demonstrated that as the carbon chain length increased (C_{10}-C_{18}) the zero-shear viscosity, and yield stress value increased, which suggested that the stability of gel structure was increased with increase in carbon chain of fatty acids. Cohesive Energy was also depended on the carbon

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chain of fatty acids. There was decreased in cohesive energy as decrease in carbon chain of fatty acids. Temperature loop was created using heating and cooling temperature cycle. Oleic acid (C_{18}) gave the best thermal stability with lowest temperature loop area. Increase in carbon chain length of fatty acids decreased the permeability enhancing effect of Escitalopram Oxalate through human cadaver skin during In-vitro permeability studies. The permeability of ECO through human cadaver skin was found to be in increasing order as capric acid> lauirc acid> Oleic acid> No-enhancer. Rheological studies could be useful to investigate the internal structure of HPC gels. Fatty acids alter the rheological properties of HPC gels such as zero shear viscosity, yield stress and cohesive energy. Moreover, In-vitro permeability results demonstrated that HPC gels containing fatty acids could be potential delivery system for transdermal delivery of ECO.

Keywords: Polymer rheology; microstructure; fatty acids; diffusion; transdermal; escitalopram oxalate; viscosity; cohesive energy.

1. INTRODUCTION

Depression is a chronic or recurrent mood disorder that affects both economic and social function of about 121 million people worldwide. The World Health Organization published a research which showed that depression will be second largest disease in the world by the year 2020 for all ages and sexes [1,2]. In 1980, Tricyclic antidepressant (TCA) and Monoamine Oxidase Inhibitors (MOI) were the first choice of drugs. However, their side effects, toxicity and drug-drug interaction required newer class of agents which affecting central nervous system with fewer side effects [3,4]. Escitalopram oxalate (ECO) is one of the newer class of anti-depressant agent. It is an S-isomer of citalopram. ECO is well absorbed following oral administration, with a bioavailability of approximately 80%. Peak plasma level of ECO usually 10-30 ng/ml for 10 mg of oral dosage form with steady state plasma concentration of 20-125 nmole/L. The half-life of ECO is between 27-32 hrs. There are severe chances of overdose with current ECO oral dosage form. The possible side effects of overdose include convulsion, coma, dizziness, hypotension, insomnia, nausea, vomiting, sinus tachycardia, somnolence, and ECG changes [5].

Furthermore, the saw-tooth pattern of plasma drug concentration following oral administration often causes adverse events at maxima and loss of therapeutic effect at minima, which leads to intolerability in case of many antidepressants [6]. Therefore, studies on the transdermal route for systemic drug delivery of ECO have attracted considerable attention. Furthermore, the skin is an attractive potential route of drug administration because of avoidance of first-pass hepatic metabolism of ECO.

Polymers that can form a gel or matrix are key component for transdermal drug delivery system (TDDS) [7,8]. One of the representative of that polymer system is Hydroxypropyl cellulose (Klucel-HF, HPC), a non-ionic, hydrophilic and pH independent polymer. It is widely used in pharmaceutical industry as a thickening agent or gelling agent to achieve sustained release of the small molecules from different dosage forms. A polymer gel is a solid-in-liquid colloid in which the solid phase forms a network structure that immobilizes the liquid and produces solid or semisolid like properties. Gelation arises either from chemical cross-linking through covalent bond formation or from physical cross-linking through polymer-polymer interactions [9,10]. Rheological properties of polymer are useful as they can provide some of the fundamental finished product properties such as storage stability, effect of formulation variable on the microstructure, consistency of the product, drug releasing from polymer entrapment and etc. [11]. Rheology is a powerful tool to obtain information and characterized microstructure of wide range of materials such as solutions, polymer melts, gels, particulate systems etc. [12]. Rheological measurement mainly performs in two modes: 1) Rotational (shear) mode and 2) Oscillation (Dynamic) mode. During low stress/strain, inter and intra-particle molecules arrangements are only slightly disturbed during measurement which make microstructure in quiescent conditions [13]. This is the primary advantage of oscillation mode over rotational mode, which destroy the internal structure of sample. Moreover, oscillation mode can also useful in illustrating the elastic and viscous behavior of sample [14]. It has been reported that surfactants greatly modify the rheological properties of cellulose ether, poloxamer, poly-co-acrylic acid and carbopol [15-17]. Little attention has been focused to the

effect of fatty acids on the rheological properties of transdermal gels. The fatty acids are frequently incorporated to modulate drug release rate by promoting the drug permeability through human cadaver skin [18].

The objective of this research was to evaluate the effect of number of carbon chain of fatty acids on the rheological properties of hydroxypropyl cellulose gels. Rheological properties were investigated using viscometry and oscillation mode to evaluate the viscoelastic and internal structure properties of the HPC gels. Furthermore, the effect of fatty acids on the permeability of ECO through human cadaver skin was also evaluated.

2. MATERIALS AND METHODS

2.1 Materials

Escitalopram oxalate (ECO) was purchased from Tacoland Corporation, CA, USA. Klucel HF (HPC) was gifted from Hercules, Wilmington, DE, USA. Human cadaver skin was purchased from NY Firefighter skin bank, NY, USA. Oleic acid, lauric acid, capric acid and sodium azide were purchased from Sigma Aldrich, St. Louis, MO, USA. Polyethylene glycol 400 (PEG-400), propylene glycol (PG), isopropyl alcohol (IPA), dimethyl sulfoxide (DMSO), ethanol 190 proof and glycerin was purchased from Pharmaco-Appear co, Brookfiled, CT, USA.

2.2 Methods

2.2.1 Gel preparation

Appropriate quantities of propylene glycol, polyethylene glycol-400, DMSO, isopropyl alcohol, ethanol, glycerin and water are given in Table 1, were mixed together and required quantities of different fatty acids (8% w/w) was added into the solvent mixture according to Table 1. ECO (5% w/w) was added and mixed until it was dissolved in the solvent mixture. Klucel-HF was dispersed in drug solution, and homogenized at 25000 RPM for 30 min.

2.2.2 Rheological measurements

An advanced Gemini II rheometer (Malvern Instruments, USA) with a cone-plate configuration (diameter 40 mm, Gap 150 μm, and cone angle 4°) was used for the rheological measurements of the gels. The gel sample was gently loaded onto the rheometer peltier plate using a tablespoon. Care was taken to minimize shearing during sample removal and sample loading. Rheological tests were performed in two different modes: 1) Rotational and 2) Oscillation.

2.2.2.1 Rotational mode

Flow Curve Test: Viscosity curves were generated in controlled-rate mode, with shear rates ranging from 0.01-100 S^{-1} at temperatures of 25℃ and the apparent viscosity as a function of shear rate was monitored. In each case, the shear rate was increased over a period of 198 s and 50 data acquisition points were recorded. Most pharmaceutical gels showed shear thinning behavior which could be described by Cross model [19]:

$$(\eta - \eta_\infty) / (\eta_0 - \eta_\infty) = [1 / \{1 + (K^* \gamma)^m\}] \quad (1)$$

The cross model described the relation between apparent viscosity and shear rate where, η_0 is zero shear viscosity, η_∞ is high shear viscosity, K and m are constant, K has the unit of time and m

Table 1. Preparation of ECO containing HPC gel

Ingredients	Formulation (%W/W)			
	FO-25	FL-25	FC-25	F-25
ECO	5	5	5	5
DMSO	10	10	10	10
Glycerine	6	6	6	6
PEG-400	20	20	20	20
PG	20	20	20	20
IPA	20	20	20	20
Water	10	10	10	10
Oleic Acid	8	-	-	-
Lauric Acid	-	8	-	-
Capric Acid	-	-	8	-
Klucel HF	1	1	1	1
Mixing Speed (X1000) RPM	25	25	25	25

is dimensionless. The degree of shear thinning can be dictated by value of m (0 < m < 1). When m approaches zero, the material called Newtonian and for non-Newtonian shear thinning pharmaceutical gels m have value approaching unity. The value of η_0 and η_∞ can further use to evaluate the structural parameter lambda according to following equation [20]:

$$K = 1- (\eta_\infty / \eta_0)^{1/2} \quad (2)$$

$$\lambda = (1- (\eta_\infty / \eta)^{1/2}) / K \quad (3)$$

According to indirect microstructure theories, λ=1 represent the completely build structure while λ= 0 represents the breakdown structure.

2.2.2.2 Oscillation mode

Amplitude Sweep Test: Amplitude Sweeps were performed in controlled strain mode over the strain range of 0.01- 10 at a frequency of 1 Hz at 25°C respectively. During each sweep, 20 data points were collected. A double logarithmic axis was used and the linear Viscoelastic (LVE) range, that is, the deformation ranges over, which the elastic modulus value remains relatively linear and constant, was calculated. During LVE range stress and strain have same value. Amplitude sweep can be used to calculate the cohesive energy. Cohesive energy is the energy required to break all the bonds associated with one of its constituent molecules. It is, therefore measure of the inter-molecular energy for a formulation. Cohesive energy increases the intensity of molecule interaction. Cohesive energy of different gel system could be calculated according to following equation [21]:

$$C.E. = ½ (G' X A^2) \quad (4)$$

Where, C.E. is the cohesive energy and G' is the storage modulus (Pa). During amplitude sweep, with increasing strain, the value of G' and G'' is linear during LVE range and after that it significantly dropped due to structural break down. The strain at this turning point is A.

Temperature Sweep: The thermal stability of formulations was evaluate using two types of temperature ramps, namely a temperature cycle test and temperature ramp tests. In the *temperature cycle test* a constant deformation 0.1 strain was applied at frequency of 1 Hz. The temperature was increased linearly from 5°C to 80°C at a rate of 1°C/min with 800 data points acquisition. Thereafter temperature was decreased back to 5°C with the same parameters. Thus, heating and cooling rates were kept constant 1°C/min. These heating and cooling ramp created a temperature loop. During the *temperature ramp test*, a constant deformation of 0.1 strain was applied at frequency of 1 Hz. The temperature was increase linearly at the rate of 1°C/min from 5°C to 80°C.

2.2.3 *In-vitro* permeation studies

All In-vitro permeation studies were carried out using vertical type Franz-diffusion cells with diffusional area of 1.76 cm^2. These cells have a static receiver solution reservoir with a side arm sampling port design. During the course of an experiment, 0.5 ml of the receptor solution were collected at pre-determined time for analysis and replaced with a same amount of fresh receiving media. The receptor compartment (volume 13 ml) was filled with receiving media (PBS pH=7.4 (0.01% Na Azide)) after degassing to avoid air bubbles. The receptor compartment was maintained at 32℃ by means of a water bath circulator and a jacketed surrounding cell. The solution in receiver compartment was continuously stirred by means of coated magnetic stirrer. Human cadaver skin was soaked in PBS for 1 hr. Before mounting between the donor and receiving compartment and was secured by means of a pinch clamp. 1 gm of each formulation was placed in donor compartment. Each formulation was run 3 times to get better average of permeation of Escitalopram Oxalate through the human cadaver skin.

2.3 Data Analysis

The effect of different carbon chain length fatty acids on the rheological properties were evaluated using Microsoft-Excel 2016. Data analysis was performed using Minitab 17 to evaluate area under the loop for temperature cycle data.

3. RESULTS AND DISCUSSION

3.1 Effect of Fatty Acids on Rheological Properties

Most of the pharmaceutical gel formulation showed thixotropic behavior that describes a degradation of the polymer structure during the loaded phase; thus, a reduction in viscosity with time occurs when shear stress/shear rate is applied. Therefore, a thixotropic material would have shear-thinning (increase polymer

disentanglement) behavior when a gradually increasing shear was applied [22,23]. Fig. 1 represents the instantaneous viscosity vs. shear rate profile for formulations. Application of the cross model to instantaneous viscosity vs. shear rate profile indicated that the gels are significantly shear thinning with 'm' approaching unity, and at low shear rates yield stress was also observed.

A different carbon chain length fatty acids containing gels exhibited similar shear thinning behavior (m= 0.90) but significantly low zero-shear viscosity value. The observed zero-shear viscosity values were proportional to the carbon chain length of fatty acids present in the formulation. The zero-shear viscosity value for C_{18} carbon chain containing fatty acid was almost 108% higher than the formulation containing C_{10} carbon chain fatty acid. The increase in zero-shear viscosity could be due to viscous nature of oleic acid.

The cross-model's time constant K is related to the shear dependent structural breakdown. A high value of K implies a relatively large shear dependent contribution to structural breakdown. In another word, when K is large, breakdown occurs at relatively low shear rate. Observed value of K was also proportional to the number of carbon chains in fatty acids.

Most of the pharmaceutical gels have physically cross-linked structure [23]. In cross-linked microgel structure individual particles are closely packed with their neighbor was responsible for the yield stress. The magnitude of the yield stress is a measure of the strength of the closed-pack structure that must be exceeded for the formulation to flow appreciably [24]. The observed yield stress values were depended on the fatty acid's carbon chain length. Observed yield stress value for capric acid was 0.73 Pa, which was almost 45% lower than C_{18} chain containing fatty acid (Table 2).

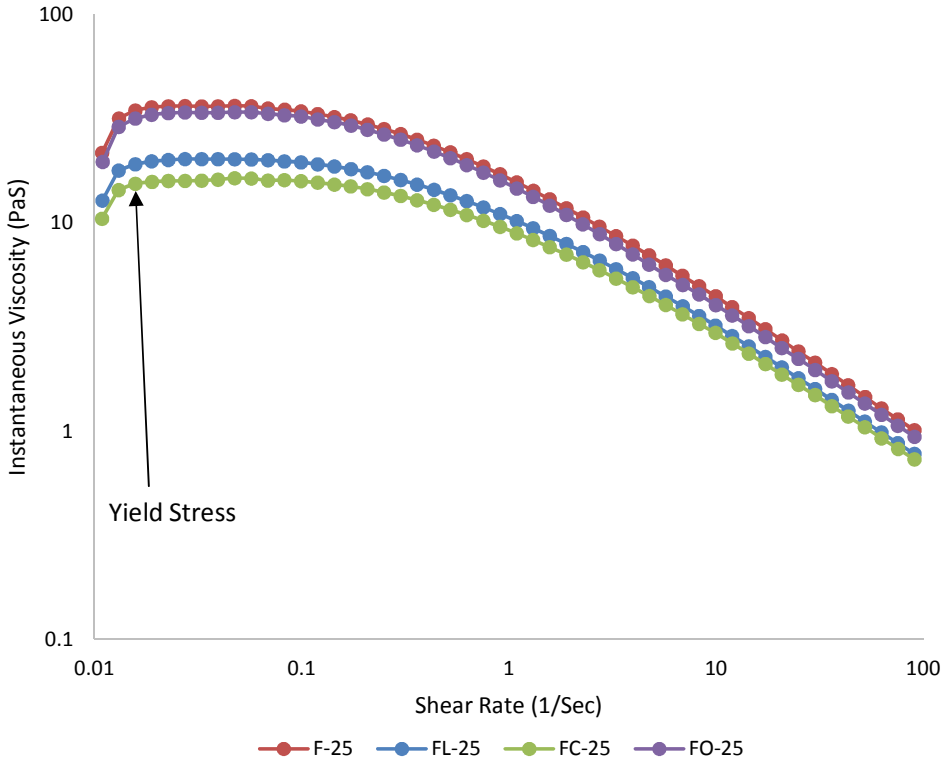

Fig. 1. Instantaneous viscosity vs. shear rate profile master curve for FO-25, FL-25, FC-25 and F-25 (n=3)

Table 2. Flow curve parameters (n=3)

Formulation	Cross model parameters*					λ^*	Yield Stress (Pa) ± S.D.
	η_0 (PaS)	η_∞ (PaS)	M	K (Sec)	R^2		
FO-25	33.15	0.47	0.9035	1.004	0.9822	0.893	1.33± 0.02
FL-25	19.93	0.37	0.8801	0.7962	0.986	0.896	0.85 ± 0.3
FC-25	15.92	0.35	0.8887	0.6585	0.987	0.896	0.73 ± 0.1
F-25	35.8	0.46	0.8848	1.06	0.9834	0.899	1.43 ± 0.07

**: Cross model and λ was calculated from the master curve of three replicates*

Cellulosic derivative polymer has a –OH group in their structure, which forms hydrogen bonds between polymer chins. These hydrogen bonds partially or fully destroyed by the interaction between –OH group of solvents. These interactions affect the internal structure of polymer gels [25]. Addition of fatty acid disrupt the stable structure and this could be due to formation of hydrogen bonding between fatty acid and polymer chains. This hypothesis could be supported by evaluating cohesive energy for each formulation, which was related to the carbon chain of fatty acids. Table 3 showed that as increase in carbon chain of fatty acid, cohesive energy was also increased. This was suggested that energy required to break H-bond between oleic acid and polymer chain could be more energy consuming than the H-bond between lauric acid or capric acid and polymer chains.

Furthermore, storage modulus (G') is correlating with the deformation energy stored in sample during shear process and represents as an elastic behavior of sample. According to Fig. 2, formulation F-25 had the highest storage modulus (G') value, which suggested incorporation of fatty acids in formulation lower the elastic behavior of the HPC gel. However, the LVE region for F-25 was lower, which suggested that the stability of HPC gel was increased due to the presence of fatty acid in the formulation.

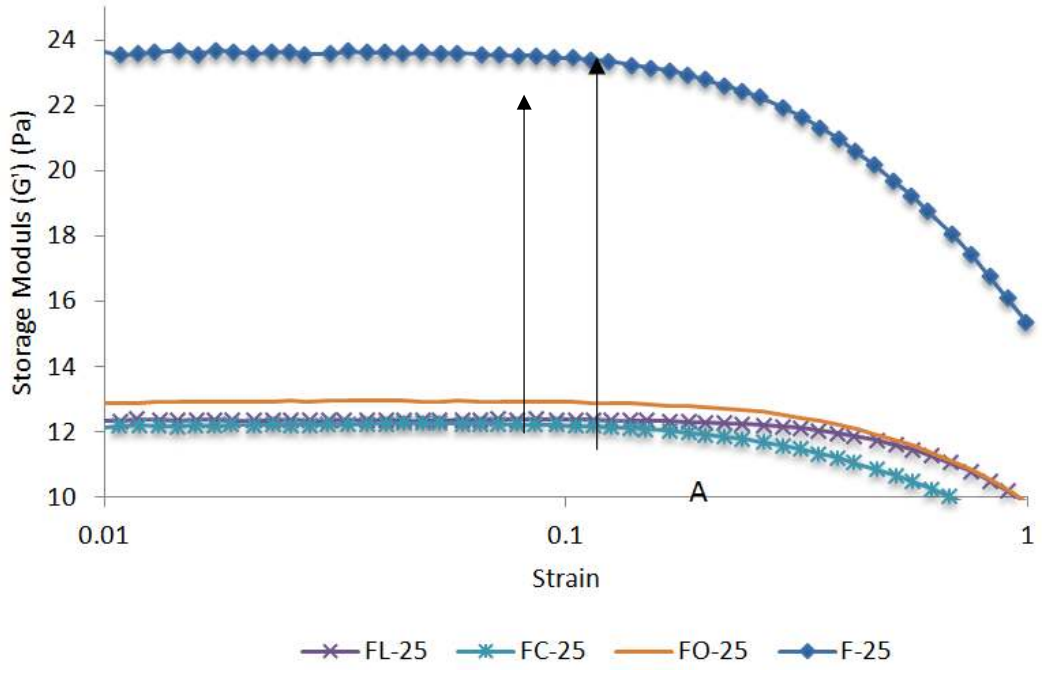

Fig. 2. Representative graph of Storage Modulus (G') vs. Strain Profile for FO-25, FL-25, FC-25 and F-25

The stability of any gel depends on the mobility of particles, which are present in the sample. By increasing mobility, probability of particle-particle interaction increase and stability of the product decrease [26]. In order to determined temperature stability of gels, it was important to monitor the rheological properties of sample through temperature cycle. When complex modulus was monitored throughout the temperature cycle, it created the loop. The area of the loop determined the stability of gels. For thermally stable gels, the microstructure was not disturbed with temperature and it showed smaller loop area as compare to thermally unstable gel formulations. Furthermore, if the energy required to break the bonds is lower, than the formulation will not able to tolerate the higher temperature and the structure will break down at lower temperature. This assumption was confirmed by running the temperature cycle. Formulation with oleic acid showed lowest temperature loop area, while formulation F-25 showed highest temperature loop area.

In temperature sweep, when G' is equal to G", It is called sol-gel transition temperature. During the whole range of temperature ramp G' and G'' was inversely propositional to temperature (Fig. 3). The initial decrease of modulus could be related to the increase in fluidity with increasing temperature. This decrease might also be attributed to the energy dissipation movement of the molecules and decreased in intermolecular interactions, which in turn decreased the energy needed for the flow, thus decreased the interference of the hydrodynamic domains [27,28]. Table 3 provided all thermos-rheological parameters for formulations.

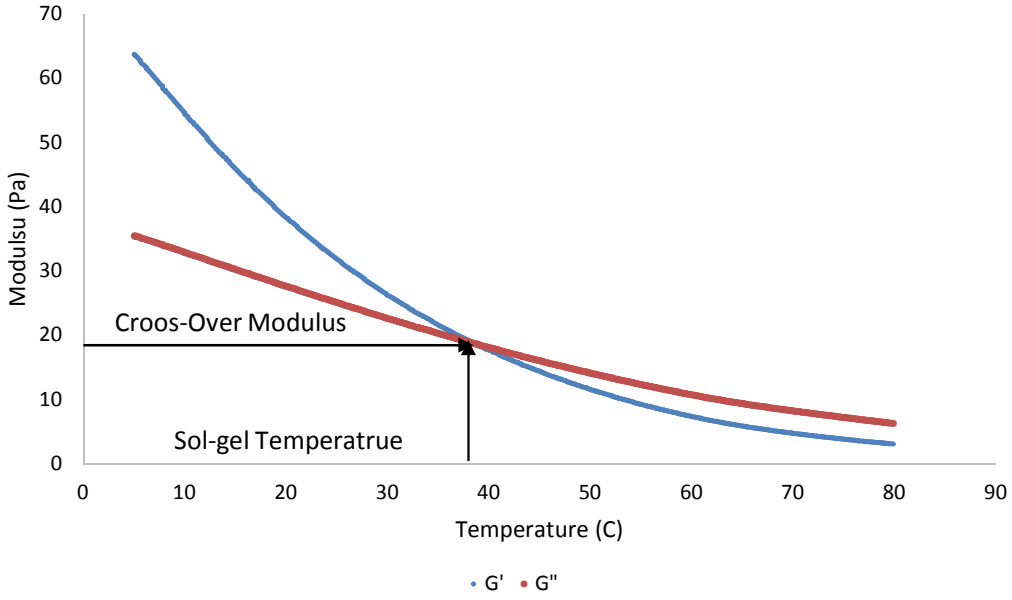

Fig. 3. Representative graph of temperature sweep for formulation F-25

Table 3. Thermo-rheological parameters (n=3)

Formulation	Cohesive energy (J/m^3) ± S.D.	Temperature loop area ($J°C/m^3$) ± S.D.	Cross-over temperature (°C) ± S.D.	Cross-over modulus (Pa) ± S.D.
FO-25	6.3 ± 0.02	215.91 ± 0.5	32.7 ± 0.5	15.1 ± 0.17
FL-25	5.45 ± 0.05	330.32 ± 1.0	30.1 ± 1.0	13.8 ± 0.11
FC-25	4.76 ± 0.1	337.6 ± 0.7	27.5 ± 0.3	13.6 ± 0.14
F-25	6.65 ± 0.07	389.04 ± 1.2	38.2 ± 1.0	14.8 ± 0.13

3.2 Effect of Fatty Acid on Permeability of Escitalopram Oxalate

The flux of each formulation was obtained through the slope of cumulative amount of ECO permeated (µg) through human cadaver skin verses Time (Hr) profile (Fig. 4). The lag time was evaluated by extrapolating the regression line. It showed that different fatty acids affect the flux profile of ECO. Lower carbon chain fatty acids showed higher diffusion of ECO from human cadaver skin as compare to higher carbon chain fatty acids. Enhancement ratio was calculated from equation 5 for each formulation and presented in Table 4.

$$E.R. = \frac{Flux\ of\ Formulation\ with\ enhancer}{Flux\ of\ Formulation\ without\ enhancer} \quad (5)$$

Several researchers have demonstrated that the fatty acids with carbon chain of C_{10}-C_{12} increase the permeation of hydrophilic drug molecule through human cadaver skin as compare to C_{18} carbon chain fatty acids [29-31]. The permeability coefficient (P) has been calculated using following equation:

$$P = \frac{J}{C} \quad (6)$$

Where, J is the flux obtained from the Cumulative amount (Q) verses time (µg/cm^2/Hr), C is the initial concentration applied in the donor compartment (µg/ml). The decreased in the flux profile of ECO with oleic acid could also be explained by higher yield stress and zero shear viscosity data. Furthermore, the cohesive energy was also found higher as compare to lauric acid and capric acid, which proposed the greater interaction between oleic acid and HPC polymer chains.

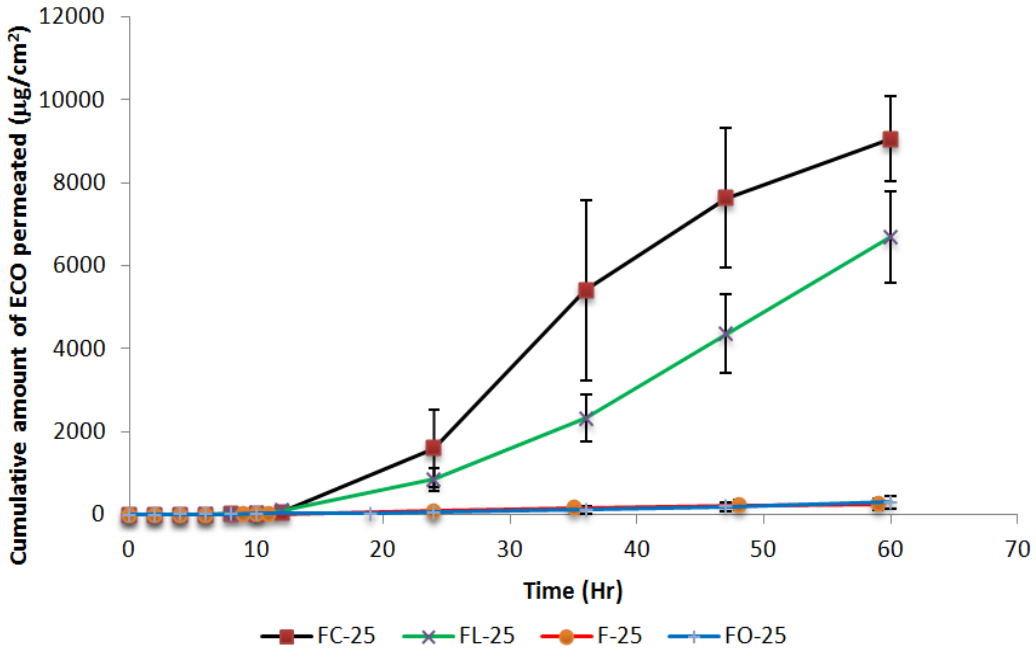

Fig. 4. Effect of fatty acids on the permeability of ECO through human cadaver skin (n=3)

Table 4. Transdermal parameters (n=3)

Formulation	Flux (µg/cm^2/Hr) ± S.D.	Permeability co-efficient X 10$^{(-4)}$ (cm/Hr)	Enhancement ratio
FO-25	23.17 ± 4.66	4.63	4.59
FL-25	184.05 ± 5.51	36.81	36.45
FC-25	205.58 ± 5.17	41.12	40.71
F-25	5.05 ± 2.27	1.01	1.00

4. CONCLUSION

Rheological studies conducted on HPC gels showed that presence of fatty acids could alter the microstructure of the gel system. Furthermore, HPC gels displayed shear-thinning behavior with observed yield stress value. Moreover, zero shear viscosity of formulation was depended on the carbon chain length of fatty acids. Length of carbon chain in fatty acids altered the microstructure of HPC gels, which was validated through the cohesive energy. Different carbon chain length of fatty acids showed significantly different thermo-rheological properties that could be due to the difference in microstructure of HPC gels. In-vitro permeability results demonstrated that HPC gels containing fatty acids could be potential delivery system for transdermal delivery of ECO.

CONSENT

It is not applicable.

ETHICAL APPROVAL

It is not applicable.

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COMPETING INTERESTS

Authors have declared that no competing interests exist.

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