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A COMPARATIVE EVALUATION OF PERMEATION ENHANCERS FOR ROPINIROLE HYDROCHLORIDE A BCS CLASS III DRUG TO BE FORMULATED AS TRANSDERMAL DRUG DELIVERY SYSTEM

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Keywords:

Ropinirole hydrochloride, Permeation enhancers, Differential scanning colorimetry, Steady-state flux, Hyaluronidase

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ABSTRACT: Ropinirole hydrochloride, a non-ergoline dopamine agonist, administered orally for the treatment of Parkinson's disease and restless leg syndrome and belonged to BCS class III drug having high solubility and low permeability. The objective of the present research study was to enhance the permeability of ropinirole hydrochloride by selecting a suitable permeation enhancing agent from different classes of permeation enhancers. Received pure drug was authenticated by determining its melting point, solubility, stability, apparent partition coefficient and using analytical tools like FTIR, DSC, PXRD and RP-HPLC. The permeation enhancing activity of eight different permeation enhancers was determined in a modified Franz-diffusion cell, the barrier used was rat abdominal skin. The donor compartment consists of an aqueous solution of drug alone, and with a 5% w/v permeation enhancer, and the receptor compartment consists of phosphate-buffered saline pH 7.4. The results of the research study suggested that the received drug was authentic and its purity at par with official pharmacopeia. The *ex-vivo* permeation kinetic studies showed that all the permeation enhancers are enhancing the drug permeation rate. The enhancement effect of different enhancers was in the following order of isopropyl myristate > dimethyl sulfoxide > groundnut oil > ethanol > β-cyclodextrin > oleic acid > tween 80 > hyaluronidase. Isopropyl myristate has got high permeation enhancing activity with the highest steady-state flux of 22.846 ± 0.549 µg/cm^2/h, and permeation enhancement rate was 4.16 folds higher than the pure drug with no enhancer, indicating isopropyl myristate is to be the best permeation enhancers than others. The study reveals that isopropyl myristate was a suitable permeation enhancer to formulate a transdermal drug delivery system of ropinirole hydrochloride.

INTRODUCTION: Ropinirole hydrochloride (RH), a drug of choice for the treatment of Parkinson's disease and restless leg syndrome. The oral bioavailability is 50% since it is undergone extensive first-pass metabolism [1].

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It is a suitable drug candidate to be formulated as a transdermal drug delivery system. RH belongs to BCS III drug having high solubility with low permeability and polar in nature. Due to this characteristic of the drug, in the present study, an attempt was made to enhance its permeation by using several permeation enhancers of a different mechanism.

The permeation enhancers are improving the skin permeability of low permeable compounds by altering the properties and characteristics of the skin by following mechanisms reversibly reduce

the barrier resistance of the skin, by lipid disruption thereby changing the structure of the stratum corneum lipid layer, protein modification by interaction with the intercellular protein, fluidization by changing the properties of the horney layer to achieve required flux [2, 3]. Ideally, permeation enhancers must be pharmacologically safe, non-irritant, non-toxic, and produce a reversible, temporarily enhance the skin permeability [4, 7]. In the current study eight different class and different mechanism of permeation enhancers were evaluated by selecting ester (isopropyl myristate), sulfoxides (dimethyl sulfoxide), vegetable oil (groundnut oil), alcohol (ethanol), cyclic oligosaccharide (β-cyclodextrin), fatty acid (oleic acid), non-ionic surfactant (tween 80) and enzyme (hyaluronidase) at 5% w/v. The permeation enhancing activity was achieved by other techniques also, it includes iontophoresis, sonophoresis, electroporation, magnetoporesis, phonophoresis, thermal ablation, radiofrequency, microneedles, jet propulsion and prodrugs [5, 6]. Among the above techniques permeation enhancers offer many advantages and strong effects [7].

MATERIALS AND METHODS:

Materials: RH obtained as a gift sample from Alembic Pharmaceuticals Ltd., Vadodara, Ahmadabad, India. HPLC grade methanol and acetonitrile were purchased from Merck Specialists Pvt. Ltd. Mumbai. Isopropyl myristate (IPM), dimethyl sulfoxide (DMSO), ethanol, β-cyclodextrin, oleic acid, tween 80, groundnut oil, potassium chloride, sodium chloride, disodium hydrogen phosphate, potassium dihydrogen orthophosphate were procured from a local supplier, Bengaluru. Hyaluronidase was purchase from Shreya Life Science Pvt. Ltd., Bengaluru, HPLC grade water, and distilled water were generated in our laboratory using Milli-Q® Millipore water purification system.

Animals: Albino rat skin was used for the *ex-vivo* skin permeation experiment. The study protocol has been submitted and obtained approval from the Institutional Animal Ethics Committee, Government College of Pharmacy, Bengaluru. (Reference No.: DCD/GCP/20/E.C/ADM/2017-2018). The albino rats, either sex weighing 100–200 g (age 8–12 weeks) were received from the animal house, Department of Pharmacology, Government College of Pharmacy. Before conducting the experiment, the animals were fed food and water *ad libitum*.

Methods:

Drug Identification and Authentication:

Melting Point: The melting point of RH was determined in the MR-VIS visual melting range apparatus (Labindia Analytical Instruments Pvt. Ltd., India). The drug sample was filled in three capillary tubes and placed over a sample holder, measured the melting point by setting the temperature readability of 0.1 °C, at a flow rate of 10 °C/min. It was expressed in terms of °C.

Solubility: The saturated solutions of RH in different solvents were prepared by adding an excess amount of drug to the fixed volume of solvents. The saturated solutions were sonicated in a temperature-controlled sonicator (Serwell instruments, Bangalore) for 24 h at 25 ± 0.5 °C. Keep the solution for 2 h at room temperature to reach equilibrium [8]. Mix, filter the solution through Whatman nylon membrane (0.45 µm pore size). After suitable dilutions with the same solvent, the amount of drug present in each solvent was determined using HPLC (n=3). The instrument used for the estimation of drug solubility in different solvents was composed of Shimadzu-LC-20AD, prominence liquid chromatography (Shimadzu Corporation, Japan) equipped with LC solution software using a reverse-phase C-18 column (Gemini NX ODS, Phenomenex) 15 cm × 4.6 mm, 5 µm particle size eluted with a mobile phase composing of 70:30 v/v ratio of methanol: acetonitrile at a flow rate of 0.7 ml/min, UV detection wavelength 250 nm and injection volume 20 µl. The retention time for RH was found to be 2.7 min. The developed method was precise, with lower than 2 %RSD, and the calibration curve was linear over a concentration range of 2.5-160 µg/ml with r^2 of 1. The detection and quantification limits were found to be 0.045 µg/ml and 0.15 µg/ml, respectively [9].

Stability of RH: The stability of RH in receptor medium (PBS pH 7.4) was studied by preparing a final concentration of 20 µg/ml of RH solution by making a suitable dilution using same solvent and the solution was stored in room temperature up to 48 h.

The prepared solution was withdrawn and analyzed initially and after 24, 48 h by using HPLC. Each study was conducted in triplicate. The amount of drug present in the receptor medium was determined, and the result was expressed in percentage of RH remaining with time [10].

Apparent Partition Coefficient: The apparent partition coefficient of RH was determined in n-octanol and PBS pH 7.4 by shake-flask method [11]. The pre-saturation was achieved by thorough mixing of an equal volume of n-octanol and PBS pH 7.4 for 10 min at room temperature in a 250 ml separating funnel, allowed the content to separate into an immiscible layer. 10 mg of drug was added, and it was shaken for 45 min and allowed to settle for 1 h into two distinct phases. Both the phases were collected; centrifuged at 1000 rpm for 5 min, and the solution was filtered through Whatman nylon membrane (0.45 µm pore size). The concentration of the drugs in each phase was determined by making suitable dilutions and analyzed by HPLC as mentioned in the solubility determination. The apparent partition coefficient of RH was calculated by the following formula: Partition coefficient =log (Co/Ca). Where Co is the concentration of RH in the organic phase, and Ca is the concentration of RH in the aqueous phase.

Fourier Transform Infrared (FTIR) Spectroscopy: Shimadzu IR Affinity-1S ATR-FTIR (Shimadzu Corporation, Japan) instrument was used to record the FTIR spectrum of RH by placing the sample directly on the germanium prism, and IR spectra were recorded in the scanning range of 600 to 4000/cm [12].

Differential Scanning Calorimetry (DSC): The thermal behavior of the drug was carried out by using the DSC-8000 (PerkinElmer Inc. Germany) instrument. An approximately 1.5 mg of drug was placed in aluminum pans, and the pans were closed by crimping the lids. The filled aluminum and empty sealed pan were placed in a sample holder. The empty pan acts as a reference, covering the temperature range of 30-350 °C at a heat flow of 10 °C/min under nitrogen purging.

Powder X-ray Diffraction (PXRD): The PXRD pattern of the pure drug was recorded in PANalytical X'Pert' Powder X-Ray Diffractometer (PANalytical B.V. Lelyweg 1, Netherlands). The drug sample was exposed to Cu K-α-1 radiation, 40kV voltage, 30mA current and scanned from 2 to 60° 2θ, at a scan step size (2θ) of 0.0300 and a scan step time of 0.8000 s, in order to confirm nature, i.e., crystalline or amorphous [12].

High-Performance Liquid Chromatography (HPLC): The HPLC method, as mentioned in the determination of solubility, was adopted to determine the purity and quantification of RH in pure drug (API). 20 µg/ml concentration of working standard and pure drug solution was prepared by making a suitable dilution using the mobile phase. Further, the working standard and pure drug solution were injected into the HPLC system in triplicate, and peak area response was recorded. The purity of RH in a pure drug against the working standard of peak area was calculated and expressed in terms of percentage.

***Ex-vivo* Skin Permeation Experiment:** The albino rat used for this experiment was anesthetized by using chloroform, and long hairs were cut and shaved with the help of scissors and scalp vein. The full thickness of the abdominal skin was removed and placed in hot distilled water at 55 °C for 30 sec to remove adhered subcutaneous fat then dipped into fresh distilled water after the skin was thoroughly inspected visually for its integrity and stored at -20 °C until it is used [13]. On the day of the experiment, the rat skin was thawed to room temperature, cut into the required surface area and immersed in PBS pH 7.4 for 30 min, which was used as a receptor medium.

The *ex-vivo* skin permeation experiment was carried out in a modified Franz-diffusion cell with a diffusion surface area of 3.462 cm^2 through rat abdominal skin used as a barrier. The receptor compartment was filled with a PBS pH 7.4. The rat skin was clamped between the receptor and donor compartment considering the stratum corneum facing the donor. The donor compartment contains a saturated solution of 1.0% w/v drug alone and with 5% w/v concentration of permeation enhancers used. To achieve the sink conditions the receptor medium in the receptor compartment was stirred at 100 rpm with magnetic beads on a magnetic stirrer and maintained at 37 ± 0.5 °C. At predetermined time intervals of 1, 2, 3, 4, 5, 6, 7, 8,

and 12 h, 1.5 ml of aliquots were withdrawn from the sampling port of the receptor compartment and replaced immediately with an equal volume of fresh receptor medium. During sampling care was taken to avoid any bubble formation as the trapped air may reduce the permeation area. After appropriate dilution, the samples were analyzed by using HPLC, as mentioned in the solubility determination to determine the content of RH (n=3).

The content of the drug permeated per cm^2 was calculated from the slope of the standard calibration curve. The difference between the values of the drug permeation and skin control was used as the actual value in each experiment. The steady-state flux ($\mu g/cm^2/h$) is the slope of the linear portion of a cumulative amount of drug permeated versus time plot divided by the surface area of the cell.

The permeability coefficient (cm/h) was determined by dividing the steady-state flux into drug concentration in the donor compartment at time zero. The enhancement ratio was calculated by dividing the steady-state flux of the drug with enhancer and without enhancer [14].

RESULTS AND DISCUSSION:

Drug Identification and Authentication:

Melting Point: The melting point RH was found to be 247.7 °C, which complied with the available data in the standard literature [15] and also complied with official standard data that is in the range of 243 °C to 250 °C.

Solubility Studies: The solubility of RH in water was found to be 165.68 ± 1.85 mg/ml, indicates good solubility in water. The solubility of RH in 0.1 N HCl, methanol, acetonitrile, acetate buffer (pH 4.6), phosphate buffer (pH 6.8 and 7.4) and PBS (pH 7.4) were found to be 138.76 ± 2.79, 274.45 ± 1.82, 141.82 ± 0.97, 189.09 ± 2.74, 153.45 ± 1.87, 211.56 ± 2.01 and 310.44 ± 0.89 mg/ml, respectively. These values were compared with the available data in the standard literature [16]. Among the solvents tested, PBS pH 7.4 would be a better choice of medium for the *ex-vivo* skin permeation experiment.

Stability of RH: There were no significant changes observed in drug stability at pH 7.4 PBS. The percentage of drugs remaining in PBS pH 7.4 at room temperature with time initial, 24, and 48 h were found to be 100.2, 99.25, and 98.95, respectively **Fig. 1**. The cumulative % RSD was found to be 0.395%. As the % RSD of RH is within the acceptable limits (% RSD shall be less than 2.0%). It reveals that the drug RH was found to be stable in the receptor medium (PBS pH 7.4) up to 48 h at room temperature.

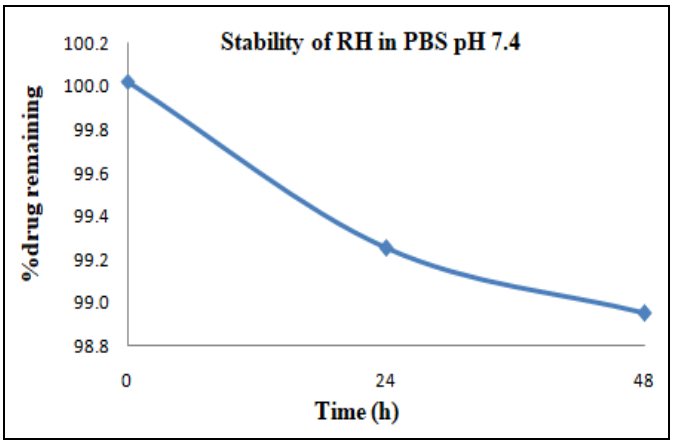

FIG. 1: STABILITY OF RH IN pH 7.4 PHOSPHATE BUFFERED SALINE (PBS). (Each point represents the MEAN ± SD, n = 3).

Apparent Partition Coefficient: The partition coefficient values for RH in n-octanol and PBS pH 7.4 system was found to be -0.468 ± 0.97. The reported value is within the limits of -1 to 4 as required for the transdermal permeation [17]. The obtained value suggested that the drug possesses enough lipophilic property, which meets the requirements to formulate it into a transdermal formulation.

FTIR: The FTIR spectra of RH **Fig. 2** exhibited sharp characteristic peaks at 3367 cm^{-1} due to secondary amino group (N-H) stretching, 3068 cm^{-1} due to aliphatic (C-H) stretching, 1712 cm^{-1} due to C=O stretching, 1456 cm^{-1} due to aromatic C=C stretching, 1313 cm^{-1} due to CH_3 bending and at 1242 cm^{-1} due to C-N stretching. All these characteristic peaks were also found in the working standard and available data in standard literature [18, 19], it was clear that all peaks are a coincidence.

DSC: The DSC thermogram of RH **Fig. 3** showed a sharp endothermic peak at 250.88 °C. The DSC thermogram of RH peak value determined was concurrent with standard literature value [19].

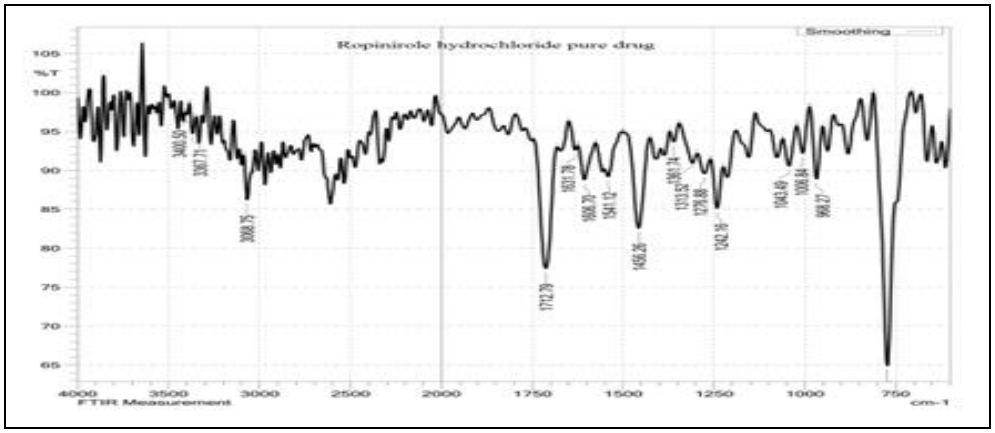

FIG. 2: FT-IR SPECTRA OF RH

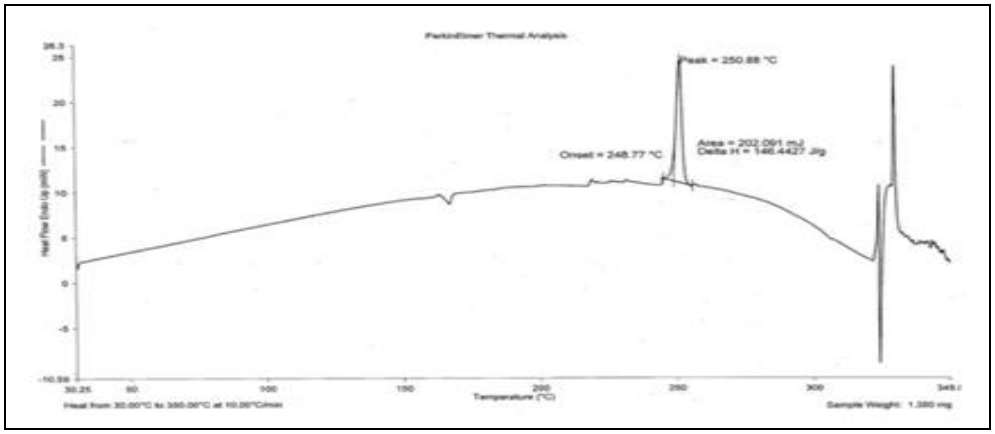

FIG. 3: DSC THERMOGRAM OF RH

PXRD: The powder X-ray diffraction spectrum of RH pure drug exhibited the prominent diffraction peaks at 2θ scale of 7.37°, 11.42°, 13.41°,16.41°, 18.37°, 19.20°, 20.23°, 21.24°, 22.19°, 23.62°, 24.64°, and 26.71°, 27.60°, and 28.61° **Fig. 4** confirms that it had crystalline nature, that coincided with those reported previously [19, 20].

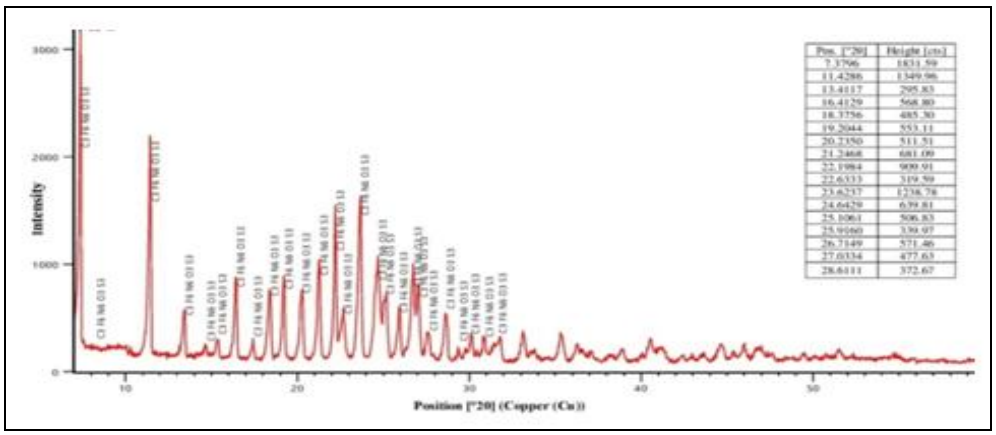

FIG. 4: PXRD SPECTRA OF RH

Based on the above results obtained from the thermal analysis (melting point and DSC), FTIR, and PXRD techniques, it is clearly indicated that the received pure drug was authentified as RH.

HPLC Analysis: The purity of RH in the received pure drug was found to be 99.84% on the dried basis, its purity at par with supplier COA value and USP limits [21] (NLT 98.0% and NMT 102.0% of RH, calculated on the dried basis).

A typical HPLC chromatograph of RH (20 µg/ml), is shown in **Fig. 5**.

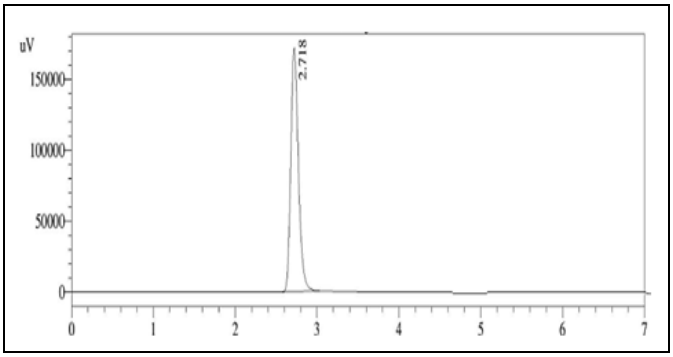

FIG. 5: HPLC CHROMATOGRAPH OF RH

***Ex-vivo* Permeation Kinetics Study:** The *ex-vivo* skin permeation studies of the RH alone and with permeation enhancers were carried out in modified Franz diffusion cell through rat abdominal skin as a barrier. The steady-state flux, permeability coefficient, and enhancement ratio are summarized in **Table 1**. The steady-state flux and permeability coefficient of the pure drug was found to be 5.510 ± 0.453 µg/cm^2/h and 1.102 ± 0.090 cm/h. The enhancement effect of some permeation enhancers on RH was found in the increasing order as follows: of IPM > DMSO > groundnut oil > ethanol > β-cyclodextrin > oleic acid > tween 80 > hyaluronidase. The results of the cumulative amount of drug permeated up to 12 h **Fig. 6** and the enhancement ratio of drug with and without enhancers **Fig. 7** suggested that the addition of permeation enhancers have increased the rate of skin permeation compared to pure drug. During the research study, eight different permeation enhancers were chosen, and each belonged to different classes, and they had a different mechanism for enhancement of permeation. The results of the present study suggested that among the eight permeation enhancers, IPM as more permeation enhancing activity with the highest permeation steady-state flux of 22.846 ± 0.549 µg/cm^2/h and permeation enhancement rate was 4.16 folds higher than the control (no enhancer). The reason for this could be due to its intermediate polaric nature thereby it modifies the polar pathways in the stratum corneum by interacting with the intracellular proteins [2, 11], the selected drug for the study was RH belonged to BCS class III having high solubility with low permeability and polaric in nature, this could be the major mechanism for permeation enhancing activity. Apart from this IPM as an ability to disrupt highly ordered lipid structure of the skin, thereby it enhances the permeability of the skin [22]. DMSO as a permeation enhancing agent it causes a swelling in the stratum corneum due to this; the diffusional channels were with decreased diffusional resistance [23]. The other permeation enhancers like groundnut oil, ethanol, β-cyclodextrin, oleic acid, and tween 80 having similar enhancement ratio suggested that the mechanism through which they enhance the permeation of RH was not predominant as compared to IPM. Among all the permeation enhancing agent, hyaluronidase belonging to the class of enzyme category [24] has less enhancement ratio compared to the other seven permeation enhancers.

The mechanism of hyaluronidase as a permeation enhancer was by acting as a spreading factor due to its decomposition into hyaluronic acid [25], lipophilic domains in hyaluronic acid react with stratum corneum to concert α-helical structure to a β-sheet of keratin in the stratum corneum thereby disordering the lipid bilayers, and it decreasing the viscosity of the body fluids thereby increasing the permeability of the connective tissue [26,] and these mechanisms were not predominant over the mechanism of IPM. Hence, IPM was considered to be the best permeation enhancer for transdermal delivery of RH.

TABLE 1: EFFECT OF PERMEATION ENHANCERS ON THE PERMEATION PARAMETERS OF RH THROUGH RAT ABDOMINAL SKIN

Permeation Enhancer	Steady State Flux (µg/cm^2/h) ± SD *	Permeability Coefficient (cm/h) 10^{-2} ± SD	Enhancement Ratio
Pure drug (RH)	5.510 ± 0.453	1.102 ± 0.090	1.00
RH + IPM	22.846 ± 0.549	4.583 ± 0.121	4.16
RH + DMSO	20.857 ± 0.972	4.171 ± 0.194	3.79
RH + Groundnut oil	19.168 ± 1.384	3.835 ± 0.276	3.48
RH + Ethanol	18.240 ± 0.359	3.648 ± 0.072	3.31
RH + β-cyclodextrin	17.798 ± 0.416	3.559 ± 0.083	3.23
RH + Oleic acid	17.645 ± 0.295	3.529 ± 0.059	3.20
RH + Tween 80	15.974 ± 1.877	3.175 ± 0.378	2.88
RH + Hyaluronidase	11.573 ± 0.431	2.321 ± 0.087	2.11

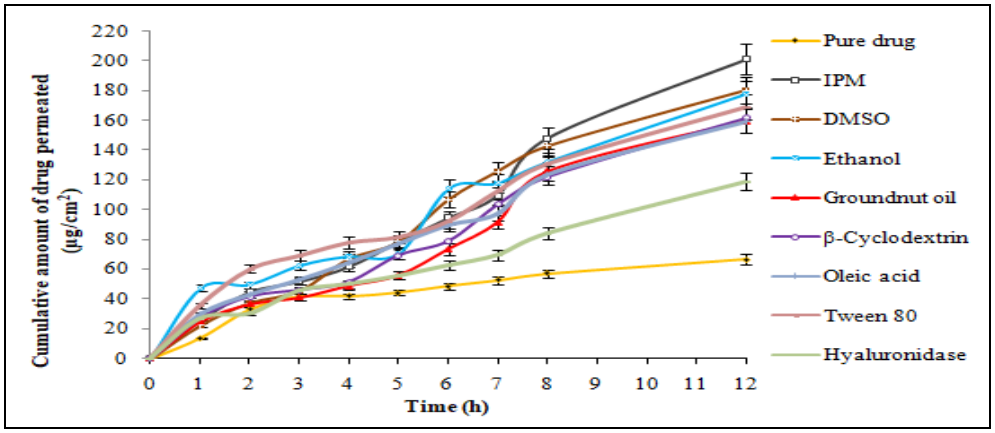

FIG. 6: CUMULATIVE AMOUNT OF DRUG PERMEATED ALONE AND WITH SOME PERMEATION ENHANCERS, MEAN ± SD, n=3

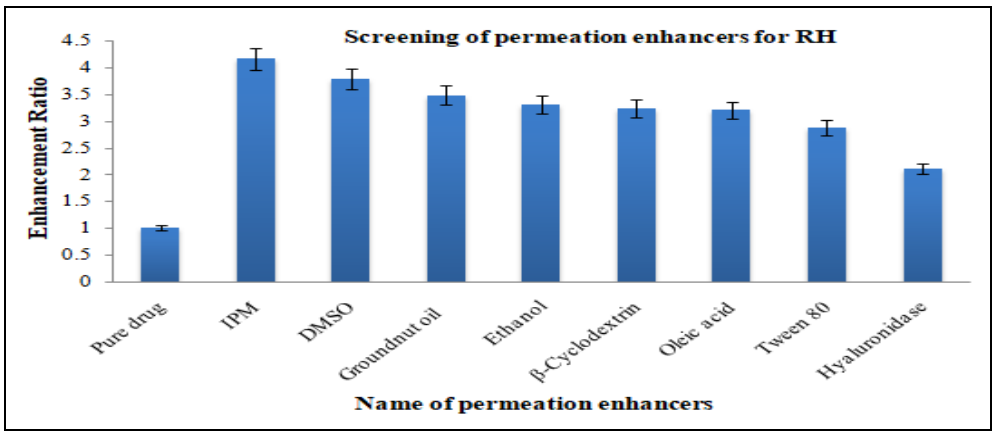

FIG. 7: ENHANCEMENT RATIO OF RH ALONE AND WITH SOME PERMEATION ENHANCERS, MEAN ± SD, n=3

CONCLUSION: The present research study comprises of evaluation of various permeation enhancers, which would be used for the preparation of transdermal delivery of RH. The received pure drug was identified, and its purity was determined and is at par with the standard published literature and official pharmacopeial limits. The e*x-vivo* skin permeation experiments were performed with pure drug alone and along with the individual permeation enhancers to obtain steady-state flux, which interim gives permeability coefficient, enhancement ratio, and the cumulative amount of drug permeated at 12 h. The results reveal that the permeation enhancing activity of permeation enhancers included in the study were in the order: IPM > DMSO > groundnut oil > ethanol > β-cyclodextrin > oleic acid > tween80 > hyaluronidase. Among the tested permeation enhancers, IPM would be the best permeation enhancing agent used to develop a novel transdermal drug delivery of RH.

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CONFLICTS OF INTEREST: Authors declare no conflict of interest.

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