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Development and *in vitro* evaluation of Eudragit E100 and PVP based matrix films for the transdermal delivery of Repaglinide

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Abstract
The study aims the feasibility of transdermal delivery of an antidiabetic agent Repaglinide for controlled and extended release by formulating as matrix film using Eudragit E100 and polyvinylpyrrolidone (PVP). The films were prepared by solvent evaporation technique and characterized *in vitro* for physico chemical properties, drug release and permeation across synthetic cellulose acetate membrane Effect of plasticizer concentration (20% w/w, 30%w/w and 40%w/w) penetration enhancers (menthol and propylene glycol+oleic acid) on drug release and permeation respectively were studied. Stability studies were conducted at ambient and accelerated conditions. Translucent flexible films of Repaglinide having uniform thickness, weight, folding endurance and drug content were formulated. A 30% w/w concentration of plasticizer in the film had produced higher drug release of 93.26%±0.46% in 14 h and the release was found to follow higuchi kinetics with diffusion mediated mechanism. The formulation Eudragit E100 and PVP (7:3) with 5% menthol as enhancer was chosen as an optimized formulation that effectively penetrated Repaglinide across the cellulose acetate membrane and thus suitable for transdermal delivery. The optimized film was stable at ambient conditions of storage with respect to drug content and release.

Keywords: Repaglinide, Eudragit E100, Polyvinylpyrrolidone, Menthol, Transdermal delivery, *in vitro* evaluation.

1. Introduction
Drug delivery through the skin to achieve a systemic effect of a drug is commonly known as transdermal delivery. Transdermal delivery is widely employed for many therapeutic classes of drugs as it overcomes the disadvantages associated with oral and parenteral administration. It is one of the promising methods for controlled and extended drug administration into the systemic circulation [1]. With the advent of new technologies for improved permeation of drug across the stratum corneum barrier, transdermal delivery has increased potential for many therapeutic agents.

Here the antidiabetic class of drug Repaglinide (RG) was chosen for its delivery across the skin into the systemic circulation. Repaglinide is taken orally in the control of sugar for longer period and it produces gastrointestinal side effects of abdominal pain and swelling, increased flatus, jaundice, diarrhea, loose stools, delay in digestion and absorption of disaccharides, nausea, taste change, etc. The drug undergoes extensive first pass effect with a bioavailability of 56% and it has an extremely short half life of 1 h. Controlled transdermal delivery of RG was attained earlier using Hydroxy propyl methyl cellulose and methocel polymers embedded with solid lipid nanoparticles of the drug to improve the safety and efficacy of RG [2, 3]. The role of plasticizer, penetration enhancer and the stability of the formulations have not been reported in these studies. The use of much sophisticated nanotechnology may increase the cost of medication which is quite difficult in the case of chronic use. However the use of eudragit polymers is found to be more suitable in the development of transdermal films than the hydrophilic polymers. The eudragit polymers are well tolerated by the skin and have a high capacity for loading drugs. Particularly, Eudragit E100 is an adhesive cationic copolymer that provides matrix for controlled drug release. They possess defined swelling capacity and permeability for water and dissolved drug, respectively [4]. Moreover, the matrix systems are more convenient, easy to manufacture, provides uniform dispersion and distribution of drug than the reservoir type of film formulations. Hence, the present work was aimed to develop a matrix transdermal film formulation of RG using Eudragit E100 and polyvinylpyrrolidone

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(PVP) incorporating dibutyl phthalate (DBP) as plasticizer to provide controlled and extended release of drug to enhance its therapeutic efficacy.

DBP miscible easily in the solvents used for dissolving Eudragit E100, it imparts adhesiveness at concentration above 25%w/w and enables solute permeation by reducing polymer crystallinity [5, 6]. Hence the concentration of plasticizer (30%, 20%, 40% w/w) on physico chemical properties of film, drug release were assessed. Further, the penetration enhancing effect of menthol, propylene glycol and oleic acid combinations were tested using a locally fabricated franz type diffusion cell. The stability study was carried out at ambient and at accelerated conditions.

2. Materials and methods
2.1 Materials
RG was obtained from Torrent Pharmaceutical Ltd. (Gujarat, India). Eudragit E100 was gifted from Evonik industries (Mumbai, India). PVP, DBP, ethanol, dichloromethane, potassium chloride, sodium chloride and anhydrous calcium chloride were obtained from Loba chemie pvt. Ltd. (Mumbai, India). Potassium dihydrogen phosphate and sodium hydroxide were obtained from Qualigens Fine Chemicals (Mumbai, India).

2.2 Preparation of film formulations containing RG
Films were prepared using different ratios of polymers Eudragit E100 and PVP. DBP was added as plasticizer at a concentration of 30%w/w of dry weight polymer. Weighed quantity of Eudragit E100 was dissolved in 5 ml of ethanol with the help of a mechanical stirrer (Remi equipment Pvt. Ltd, Mumbai, India). RG (10 mg) and PVP were added and mixed thoroughly followed by plasticizer with constant stirring at 25 ºC in a closed system. The resultant solution was poured on a disc and placed above an inverted funnel for 24 h for the solvent to evaporate.

2.3 Compatibility
Fourier transform infrared (FTIR) analysis was carried out to observe the compatibility among the film components.

2.4 Weight variation of films
Weight of the films was measured using an electronic balance (Sartorius, Germany) and the standard deviations were calculated.

2.5 Film Thickness
The thickness of films was measured at three different places using a screw gauge (Mitutoyo, Japan) and average thickness was calculated.

2.6 Folding endurance of films
Folding endurance was determined by repeatedly folding the film at the same place until it broke. The maximum number of times the film could be folded at the same place without breaking/cracking gave the value of folding endurance.

2.7 Moisture absorption study
The films were weighed (Initial weight) accurately and placed in a desiccator containing 100 ml of saturated solution of potassium chloride (Relative humidity 79.50%), for 3 days. The films were taken out and weighed (Final weight). The study was performed at room temperature. The percentage moisture absorption was calculated according to the following equation

$$Moisture\ absorption\ (\%) = \frac{Final\ weight - Initial\ weight}{Initial\ weight} \times 100$$
(1)

2.8 Moisture loss study
The films were weighed (Initial weight) and kept in a desiccator containing 1 g of anhydrous calcium chloride. After 3 days, the films were taken out and weighed (Final weight). The moisture loss was calculated according to the following equation

$$Moisture\ loss\ (\%) = \frac{Initial\ weight - Final\ weight}{Initial\ weight} \times 100$$
(2)

2.9 Water vapor transmission rate (WVT)
Glass vials of equal diameter were used as transmission cells. These transmission cells were washed thoroughly and dried in an oven. 1 g of anhydrous calcium chloride was placed in the cells and the respective polymer film was fixed over the brim. The cells were accurately weighed and kept in a closed desiccator containing saturated solution of potassium chloride to maintain a humidity of 84%. The cells were taken out and weighed after 12 h, 24 h of storage. The amount of water vapor transmitted was found using the following formula:

$$WVT = WL/S$$
(3)

WVT– Water Vapor Transmission, W-Water transmitted (mg)/24, L-Thickness of film (cm); S-Surface area of film (cm^2).

2.10 Determination of Drug content in the film
A film of 2 cm^2 area was dissolved and diluted subsequently in methanol. This was then shaken in a mechanical shaker for 24 h to get a homogeneous solution and filtered. The drug content in the filtrate was spectrophotometrically measured (UV-1700-Shimadzu, Japan) against blank at λmax of 281 nm after suitable dilution. The calibration curve was plotted at a concentration range of 5 to 30 µg/ml and the R^2 value of 0.997 was obtained.

2.11 *In vitro* drug release study
The paddle over disc method (USP apparatus V) was employed for the assessment of drug release from the films. Dry films of known thickness was weighed and fixed over a glass plate with an adhesive. The glass plate was then placed in 500 ml of phosphate buffer (pH 7.4) as dissolution medium and the apparatus was equilibrated to 32±0.5 °C. The paddle was then set at a distance of 2.5 cm from the glass plate and operated at a speed of 50 rpm. Samples (5 ml) were withdrawn at appropriate time intervals up to 24 h and the concentration of RG was spectrophotometrically determined at 281 nm (UV-1700-Shimadzu, Japan).

2.12 Effect of plasticizer concentration on drug release
The study was performed to select the optimum concentration of plasticizer. Lower concentration of 20%w/w (F7 to F12) and a higher concentration of 40% w/w plasticizer (F13 to F18) were employed in the formulation. Plasticizer generally relaxes the polymeric network of the film and influences, drug release [7].

2.13 *In vitro* permeation study

The fabricated film was placed above the cellulose acetate membrane [8] (pore size 0.45 µm) that has been clamped between the receptor and donor compartment of a vertical franz diffusion cell with an effective diffusion area of 3.14 cm² (fig. 1) [9].

Fig 1: Franz Diffusion Cell

The transdermal film was applied to the hydrophilic side of the membrane and then mounted in the diffusion cell with lipophillic side in contact with the receptor fluid. The receptor compartment was maintained at a temperature of 32±5 °C and was continuously stirred at 500 rpm using a small magnetic bead rotated with the help of a magnetic stirrer (Remi, India). The receptor compartment was filled with 50 ml of saline phosphate buffer (pH 7.4). The samples were withdrawn at different time intervals and an equal volume of fresh buffer

was immediately replaced after each sampling. The sample of RG was determined spectrophotometrically at 281 nm. The cumulative amount of drug permeated was calculated and plotted against time.

The films were added with menthol (5% w/w), [10] oleic acid (OA) (1%w/w) and propylene glycol (PG) (30% w/w) at a ratio of 1:30 (OA:PG) as penetration enhancers [11] for the permeation studies. These films were coded as F1(M) to F6(M) for menthol and F1 (PO) to F6 (PO) for PG and OA.

2.14 Stability study

Stability of the film formulations F1 to F6 were assessed after storing the samples at ambient temperature and at an accelerated temperature (40±0.5 ºC and 75%±5% RH) for 6 months. The samples were withdrawn at 0, 15, 30, 45, 60 and 90 days and analyzed for drug content and drug release [12].

2.15 Statistical analysis

The results are expressed as mean±S.D of at least three experiments. Analysis of variance (ANOVA) was used to test the statistical significance of differences among the formulations.

3. Results

The FTIR spectra of RG, Eudragit E100, PVP and their physical mixture are shown in Figure 2. The principal peaks of the drug such as 3941.92 cm⁻¹, 3833.66 cm⁻¹, 3307.14 cm⁻¹, 2946.45 cm⁻¹, 2568.60 cm⁻¹, 1694.39 cm⁻¹, 1213.22 cm⁻¹, 756.06 cm⁻¹, 540.49 cm⁻¹ were found to be present in the physical mixture. In the structure of RG the bands at 2932.39 cm-1 is due to alkyl C-H stretching, 2575.76 cm-1 is due to carboxylic acid O-H stretching and 3301.31 cm-1 is due to alcohol O-H stretching.
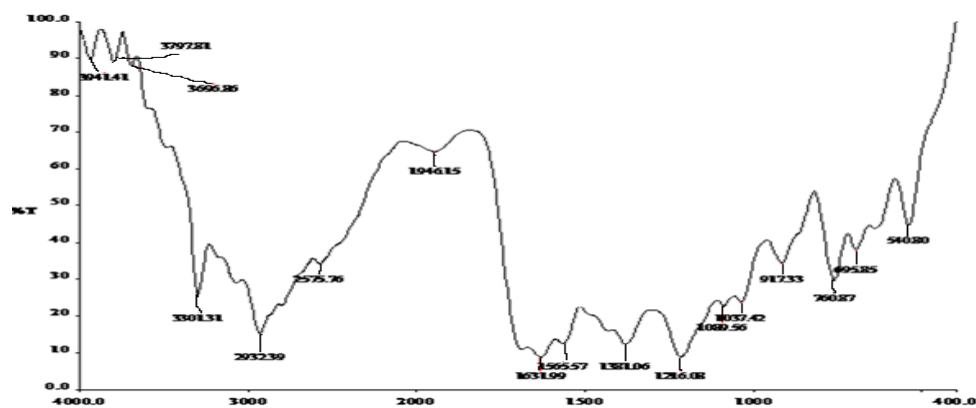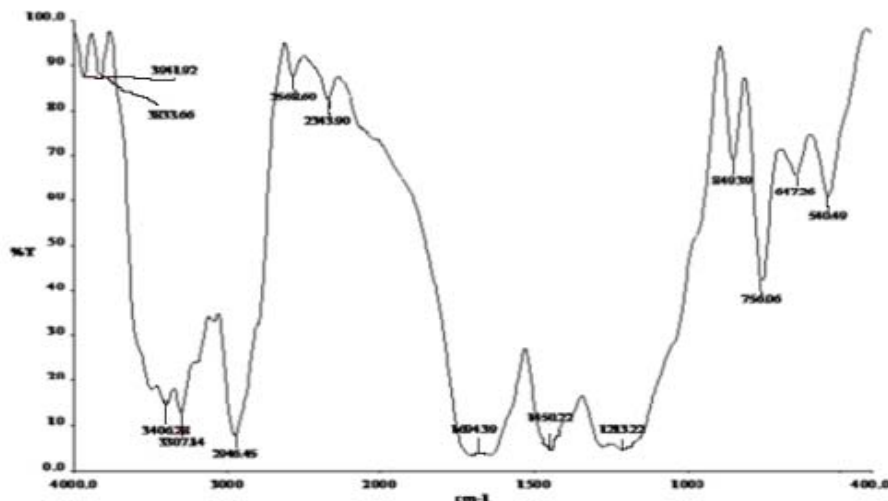

(A)
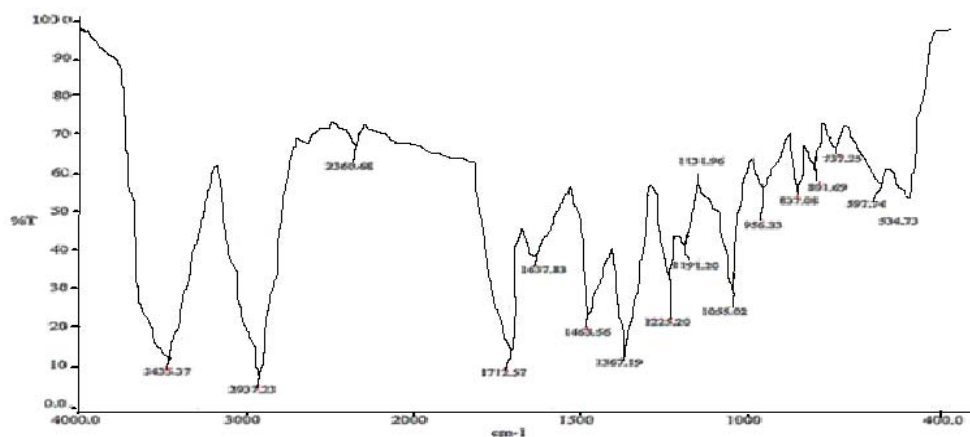
(B)
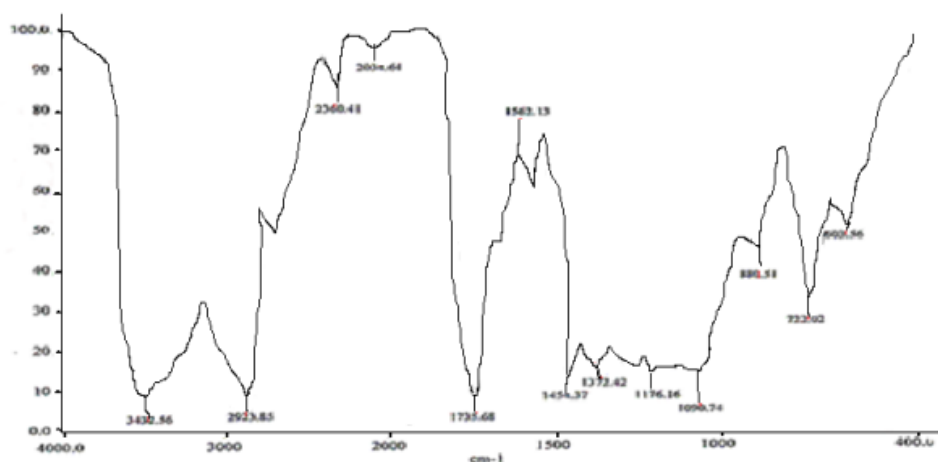
(C)

(D)

Fig 2: FTIR Spectra of Repaglinide (A), Eudragit E100 (B), PVP(C) and Physical Mixture of Repaglinide, Eudragit E100 and PVP (D)

Polymeric film formulations having an area of 28.28 cm^2 containing various ratios of Eudragit E100: PVP, loaded with 10 mg of RG were prepared and their physicochemical properties (Table 1) such as weight, thickness, folding endurance, moisture absorption, moisture loss, water vapor transmission rate were examined in the presence and absence of penetration enhancers. There were no significant (P< 0.5) weight variations and thickness found between the film formulations. The values of folding endurance indicates their integrity and that they can be handled easily without any

breakage. The moisture absorption and moisture loss gets increased with an increase in the ratio of PVP in the film. The enhancer added films possess the high moisture absorption capacity and no much difference was found between the enhancers. Estimation of drug content ranged from 9.946 mg±0.03 mg to 9.888 mg±0.028 mg which indicates the uniform distribution of RG in the matrix film.

Table 1: Physicochemical properties of Repaglinide film formulations

Enhancer	Eudragit E100:PVP	Weight ±SD(mg)	Thickness ±SD(mm)	Folding endurance (no. of folds)	MA(%)±SD	ML(%)±SD	WVT±SD (mg/cm^2,24h) × 10^{-5}
No enhancer	8:2 (F1)	783±1.52	0.10±0.015	296±3.02	2.245±0.002	1.614±0.002	2.65±0.015
	7:3(F2)	781±1.01	0.13±0.031	276±2.08	2.431±0.001	1.706±0.002	5.83±0.047
	6:4(F3)	786±1.52	0.11±0.014	286±2.00	2.733±0.001	1.850±0.002	6.47±0.034
	5:5(F4)	802±1.15	0.12±0.023	283±1.52	4.661±0.002	2.875±0.003	4.86±0.012
	4:6(F5)	785±0.57	0.09±0.015	292±1.52	5.233±0.001	3.171±0.001	5.78±0.042
	10:0(F6)	804±1.01	0.12±0.017	296±3.00	1.362±0.002	0.878±0.002	3.62±0.031
Menthol	8:2 (F1M)	794±1.23	0.11±0.012	292±2.13	2.276±0.001	1.746±0.003	2.56±0.025
	7:3(F2M)	802±0.86	0.10±0.037	286±2.08	2.543±0.002	2.218±0.008	5.53±0.065
	6:4(F3M)	782±1.14	0.09±0.023	278±1.64	2.871±0.003	3.156±0.011	6.23±0.014
	5:5(F4M)	815±1.57	0.14±0.021	285±1.52	5.213±0.002	3.321±0.021	4.36±0.022
	4:6(F5M)	812±0.69	0.17±0.011	292±2.00	6.246±0.002	3.665±0.002	5.58±0.052
	10:0(F6M)	789±1.25	0.10±0.042	296±3.00	1.381±0.012	0.981±0.001	3.32±0.081
Propylene glycol + oleic acid	8:2 (F1PO)	801±1.34	0.12±0.014	289±2.87	2.262±0.002	1.243±0.004	2.56±0.025
	7:3(F2PO)	816±0.57	0.14±0.009	284±3.02	2.483±0.003	2.201±0.013	5.53±0.065
	6:4(F3PO)	789±1.12	0.09±0.022	298±1.58	2.842±0.011	3.002±0.001	6.23±0.014
	5:5(F4PO)	822±0.96	0.11±0.017	294±3.03	4.983±0.004	3.311±0.002	4.36±0.022
	4:6(F5PO)	821±1.21	0.15±0.012	278±2.01	5.239±0.001	3.886±0.034	5.58±0.052
	10:0(F6PO)	815±1.41	0.12±0.031	287±1.52	1.347±0.002	1.212±0.002	3.32±0.081

Values are expressed as mean ± SD (n=6) [MA, ML, WVT, M, PO means Moisture Absorption, Moisture Loss, Water Vapor Transmission , Menthol and Propylene glycol + Oleic acid respectively.]
Loaded amount of RG was 10mg. Concentration of enhancer menthol was 5%w/w, oleic acid 1%w/w and propylene glycol 30%w/w
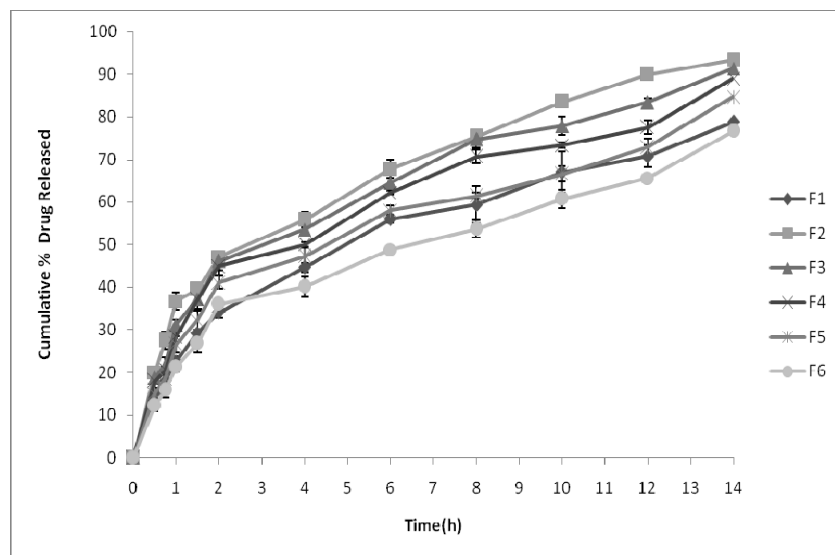
Fig 3: *In vitro* Repaglinide release from films F1, F2, F3, F4, F5 and F6 containing 30%w/w of plasticizer.

Figure 4 represents the cumulative percentage of RG released in a time period of 14h from film preparations containing 30%w/w, 20%w/w (F7 to F12) and 40%w/w (F13 to F18) of plasticizer DBP. Comparatively higher drug release was obtained for the film containing 30%w/w of plasticizer than other two concentrations. Among all the formulations, F2, F3,F4, F8 and F14 produced significantly higher release of RG and were subjected to kinetic analysis of zero order, first order, higuchi, peppas, Hixson-crowell and the co-efficient of correlation (R^2) and "n" values were calculated (P<0.05)

(Table 2). Higuchi model acquired the highest R^2 value which is statistically different (P<0.05) from other models. Hence, the higuchi model, where the cumulative amount of released drug per unit area is proportional to the square root of time is found to be the most suitable model to describe the release kinetics of RG in the present study. Further, the mechanism of drug release was assessed by determining the "n" value (Table 2) from the korsmeyer peppas model. The value of "n" obtained was less than 0.5 except for F8 indicates that the process of drug release followed ficikian diffusion mechanism.
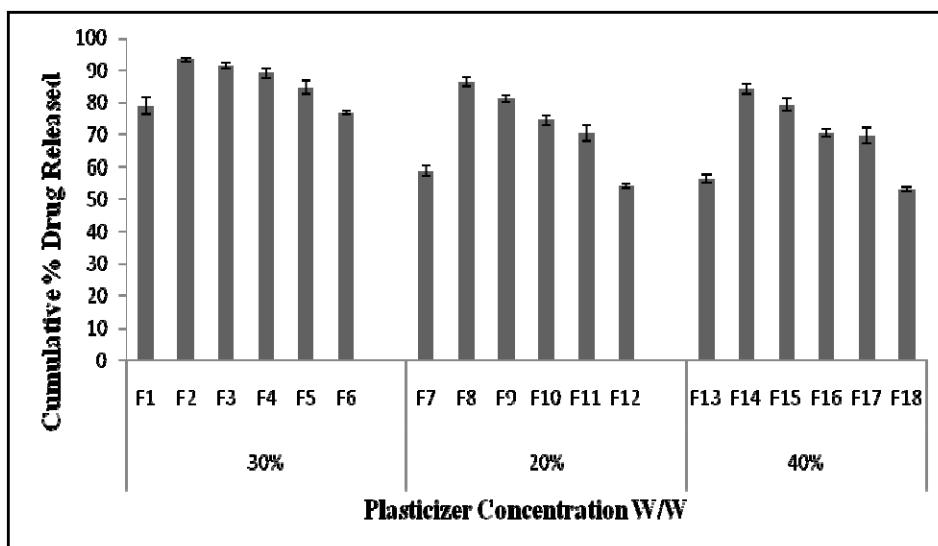
Fig 4: Effect of plasticizer concentration on Repaglinide release

**Table 2:** Regression (R^2) & n values for the film formulations (F2, F3, F4, F8, and F14)

Formulation	R^2 values of Release kinetic models				
	Zero order	First order	Higuchi	Hixson crowell	Kosermeyer (n)
F2	0.8838	0.4143	0.9847	0.9768	0.365
F3	0.8663	0.3994	0.9857	0.9652	0.392
F4	0.8536	0.6742	0.9765	0.9434	0.388
F8	0.9677	0.5334	0.9849	0.9678	0.560
F14	0.9482	0.4848	0.9760	0.9607	0.478

In vitro skin permeation was performed for F2, F3, F4, and F8 & F14 on the basis of higher drug release and the results are shown in Fig. 5a & 5b. Slow and steady permeation was obtained and the film F2 i.e. Eudragit E100: PVP (7:3) produced a highest RG permeation among other preparations. Hence F2 has been selected to evaluate the effect of enhancers.

The film containing menthol (F2 (M)) as an enhancer, has yielded a more permeation percentage than F2 (PO). This was further evidenced by calculating the flux and permeability coefficient values. Approximately 0.3mg/cm^2 of RG was contained in the film.
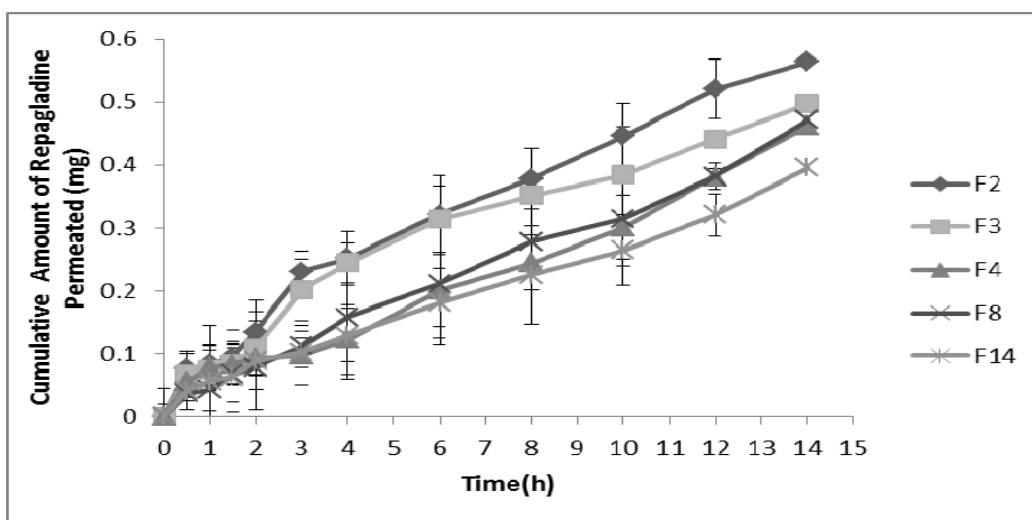
(a)
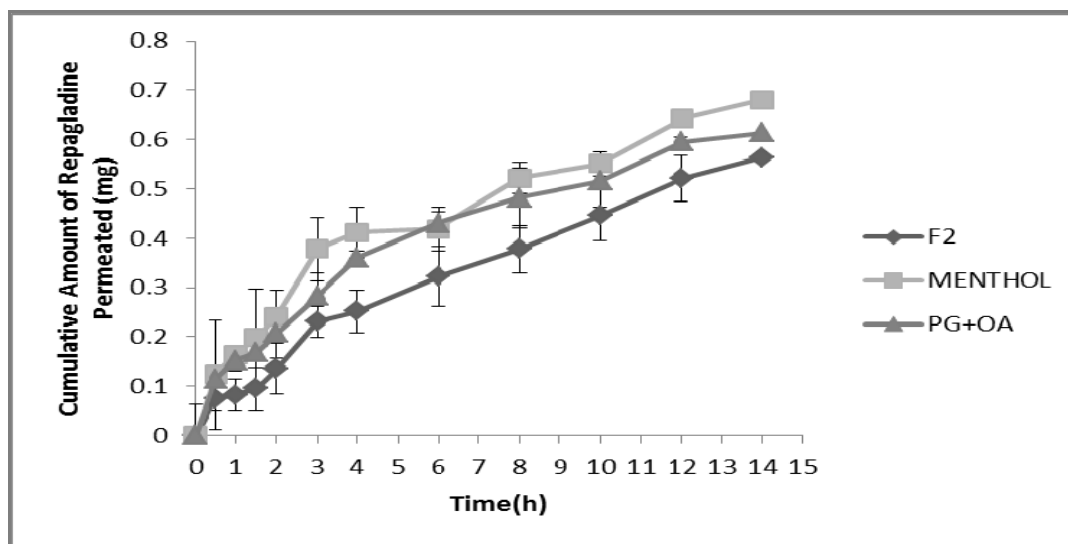
(b)

Fig 5: *In vitro* permeation profile of Repaglinide Transdermal films (F2, F3, F4, F8, F14) without enhancer (a) and F2 with enhancer (b)

Table 3: Flux & Permeability Coefficient Values for Formulation F2, F2(M) & F2(PO)

Formulation	Flux (mg/cm²/h)	Permeability coefficient (cm/h)
F2	0.013	0.014
F2(M)	0.019	0.020
F2(PO)	0.015	0.016

To assess the stability of film formulations, samples having an area of 1 cm² was cut and analyzed for RG content and *In vitro* RG release at the end of 15 days, 30 days, 45 days, 60 days and 90 days. Average of triplicate readings was taken. The loss of RG content in the film was found to be significantly less ($P > 0.5$) under the conditions of storage upto three months. The cumulative percentage of released RG was also similar to that observed initially.

4. Discussion
RG films were developed using Eudragit E100 and PVP in different proportions in order to produce a film with desirable physicochemical properties. Here the rigid nature of eudragit was reduced by the incorporation of PVP, a hydrophilic polymer that makes the film resilient, smooth and flexible enough. The FTIR analysis revealed the compatibility of formulation ingredients with the drug. Transparent films of RG having a small uniform thickness is reflected in their low standard deviation values. The film moisture absorption characteristics are due to PVP which could absorb water readily than the hydrophobic polymer Eudragit E100 [10]. However, a small percentage of moisture loss may help the films to remain stable, not brittle and free from complete drying. There was no significant effect of enhancers on film physicochemical properties except a slight increase in moisture absorption of films containing 5%w/w menthol as enhancer. The uniformity in drug content indicates the homogeneous distribution of RG in the polymer matrix.

The film F6 had produced a lowest RG release which might be due to hydrophobicity and low moisture absorption capacity of Eudragit E100 that resists drug release. Whereas, the film F2 (Eud E100: PVP; 7:3) has been found to increase RG release due to the addition of a hydrophilic substance PVP. PVP acts as a crystallization inhibitor and thus enhances the solubility of drug substances [13]. An initial burst release followed by a slow and steady release has been observed. The steady state was maintained up to 14 h. The burst effect might be attributed to the rapid dissolution of PVP upon contact with the dissolution medium which creates pores and cause the initial rapid drug release from the film. The slow release might be due to the eudragit polymeric network that restricts the diffusion of the dug molecules out of the film. The plasticizer DBP influences RG release by binding with the polymer chains and thus relaxes the polymeric network, enabling diffusion of the drug across the matrix. The concentration of such plasticizer is important in controlling the drug release. A 30%w/w of plasticizer had produced higher drug release when compared with 40%w/w and 20%w/w. Hence, 30%w/w was chosen as an optimum plasticizer concentration. Higuchi's model, where the cumulative amount of released drug is proportional to the square root of time, was found to be the most suitable model to describe the release kinetics of RG and the mechanism was fickian diffusion mediated as the obtained n value was less than 0.5. This shows the uniform diffusion of RG across the eudragit film than the HPMC films in which case the diffusion was non fickian [2].

Incorporation of permeation enhancers is essential to increase the permeation of RG across the membrane. Among the several enhancers focused by the researchers, menthol [14] and PG+OA were selected in our study since they are potent and safe. Further, the combination of PG and OA were reported to exhibit synergistic action [15, 16]. The addition of enhancers had significantly increased ($P < 0.5$) the permeation of RG which has been reflected in their flux and permeability coefficient values. The permeation effect of F2 (M) containing 5%(w/w) menthol was higher than F2 (PO). This might be ascribed to the property of menthol forming a eutectic mixture with the drug [17]. The permeation of solid lipid nanoparticles of RG from a methocel K100M has been found to be effective [3], but the effect of these particles on physicochemical properties of film, stability studies have not been reported. Moreover, the use of such expensive technology may raise the problem of

reproducibility, scale up the difficulty, cost effectiveness, etc. Stability studies conducted for the present formulations revealed no significant change with respect to drug content and drug release. The films were also stable with respect to their physical appearance. The results of the stability studies indicate that the films had retained their properties for longer periods, hence stable at the storage conditions studied.

5. Conclusion
In view of the results obtained, it has been proposed that RG can be formulated as a matrix type transdermal film using eudragit E100 and PVP which could provide extended release and effective permeation of RG. This study may be useful for the development of RG transdermal film, however, *in vivo* animal studies are need to be carried out to confirm their biological efficacy.

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