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Design, Formulation and Evaluation of Transdermal Drug Delivery System of Budesonide

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ABSTRACT

Budesonide is a highly potent synthetic, nonhalogenated corticosteroid. The mechanism of action of corticosteroids in allergic rhinitis remains unknown, but may involve reductions in number of various mediator cells such as basophils, eosinophils, T-helper cells, mast cells, and neutrophils. In the nasal mucosa, nasal reactivity to allergens, and release of inflammatory mediators and proteolytic enzymes. Budesonide is very effective and quikly acting as it is rapidly and almost completely absorbed after oral administration, but has poor systemic availability (about 10%) due to extensive first-pass metabolism in the liver, mainly by the cytochrome P450 isoenzyme CYP3A4. The major metabolites, 6-β-hydroxybudesonide and 16-α-hydroxyprednisolone have less than 1% of the glucocorticoid activity of unchanged drug with a terminal half-life of about 2 - 4 hours. Polymeric films containing Eudragit RL 100: Eudragit RS: drug (7:3:1, 7:2:1) and Ethyl cellulose: PVP: drug (7:3:1, 7:2:1) were selected for transdermal administration based on evaluation studies. These polymeric films were prepared by mercury substrate method employing PEG-400 as plasticizer. Two different penetration enhancers Urea and Dimethyl sulphoxide (DMSO) were employed in the study. The patches in each group were uniform in drug content, thickness. In Vitro drug permeation, moisture absorption and WVTR studies were carried out on these test patches. It was found that at all humidity condition the absorption increases which were linear to the moisture absorbed. In PVA and EUDRAGIT RL 100 patches the water vapor transmission rate was found to be higher at 75% RH, RT conditions. Therefore at both % RH, RT condition the PVA and EUDRAGIT RL 100 patches provide the best resistance to water vapor. Therefore, when applied to animals (in further studies) these patches may provide more occlusion to water vapor loss from skin thus making atmosphere beneath the skin more humid that aid in drug permeation.

Keywords*: *Budesonide*, *Transdermal Drug Delivery

1. Introduction

Corticosteroids and their biologically active synthetic derivatives differ in their metabolic (glucocorticoid) and electrolyte-regulating (mineralocorticoid) activities. These agents are employed at physiological doses for replacement therapy when endogenous production is impaired. In addition, glucocorticoids potently suppress inflammation, and their use in a variety of inflammatory, asthmatic conditions, skin disorders, rhinitis, inflammatory bowel disease, collagenous colitis and autoimmune diseases makes them among the most frequently prescribed classes of drugs [1]. Budesonide is a highly potent synthetic, nonhalogenated corticosteroid. It has high glucocorticoid and weak mineralocorticoid activity [2]. Exact mechanism(s) of action of corticosteroids in allergic rhinitis remains unknown, but may involve reductions in the following: number of mediator cells (basophils, eosinophils, T-helper cells, mast cells, and neutrophils) in the nasal mucosa, nasal reactivity to allergens, and release of inflammatory mediators and proteolytic enzymes [3].

Budesonide is rapidly and almost completely absorbed after oral administration, but has poor systemic availability (about 10%) due to extensive first-pass metabolism in the liver, mainly by the cytochrome P450 isoenzyme CYP3A4 [4]. The major metabolites, 6-β-hydroxybudesonide and 16-α-hydroxyprednisolone have less than 1% of the glucocorticoid activity of unchanged drug with a terminal half-life of about 2 - 4 hours [4-6].

The polymeric film containing Eudragit RL 100: Eudragit RS: drug (7:3:1, 7:2:1) and Ethyl cellulose: PVP:

drug (7:3:1, 7:2:1) were selected for transdermal administration based on evaluation studies [7,8]. The polymeric films were prepared by mercury substrate method employing PEG-400 as plasticizer. Two different penetration enhancers Urea and Dimethyl sulphoxide (DMSO) were employed in the study. The dried polymeric film was evaluated using different parameters including thickness uniformity, drug content of the film, in vitro drug release from films and in vitro skin permeation of drug, prior to their in vivo evaluation [8,9].

2. Materials and Methods

2.1. Materials

Budesonide (gift sample from M/s. Cipla Pharmaceuticals Ltd., Mumbai, India), Eudragit RL-100, Eudragit RS-100 (Röhm GmbH & Co. KG, Pharma Polymers, Darmstadt, Germany), Polyethylene glycol (PEG-400), Cellophane Membrane, Polyvinyl alcohol (PVA), Ethyl cellulose (14 cps), PVP (Mol. Wt. 40,000), Potassium dihydrogenorthophosphate, Potassium carbonate, Potassium nitrate, Sodium chloride, Sodium hydroxide, Urea, Dimethyl sulphoxides (DMSO), Glyceryl triacetate, all other chemicals used were of analytical grade and obtained commercially.

2.2. Animals

The Swiss albino rats (170 - 190 gm) were obtained from National Chemical Labortary, Pune, India, and maintained at 25 ± 1˚C for the study. The animals were housed in stainless metabolic cages and provided with standard diet and water ad libitum. Necessary approvals were obtained from CPCSEA India, for conducting the study.

2.3. Preparation and Evaluation of Polymeric Films

2.3.1. Preparation of Transdermal Patch by Solvent Casting on Mercury Substrate [10,11]

The transdermal patch was prepared by solvent evaporation technique on mercury substrate. Polymer solution was prepared in ethanol (10 ml) and to it budesonide was added. The plasticizer or permeation enhancer or the pore forming agent were added during patch casting. The solution was poured on glass rings placed on mercury surface and allowed to dry in air for 24 hours. Circular patches of 2 cm diameter (3.14 cm^2) were cut from semi-dried patches and placed in desiccator with 0% Relative Humidity (RH).

2.3.2. Evaluation of patch

1) Measurement of thickness [11]

Thickness was measured using micrometer screw gauge. Each patch was measured for thickness at five different points to ascertain thickness uniformity in patch.

2) Drug content [11]

Accurately weighed patches were individually dissolved in minimum quantity of ethanol and volume was made up to 20 ml with pH 7.4 phosphate buffer containing 2.5% ethanol. From this solution, 1 ml was transferred to volumetric flask and volume was made up to 10 ml. The absorbance was recorded at 247 nm. The blank solution was prepared in the similar way except that the patches without drug were used.

3) Moisture absorption studies [12]

The moisture absorption study was carried out at 43, 75, 93% RH, RT at 25 ± 1 °C. The pre-weighed samples of patches were kept under the humidity conditions and weighed after 24 hours. The increase in weight indicates the moisture absorption by samples.

4) Dissolution studies [13,14]

The accurately weighed patches were fixed on glass discs of 2.5 cm diameter using standard glue. This assembly was kept in dissolution vessel such that the patch faced the dissolution media upwards. The dissolution media was 900 ml of pH 7.4 phosphate buffer containing 2.5% ethanol at 32 ± 0.5˚C. The speed of paddle was kept at 50 rpm. Samples were withdrawn at 1 hour interval till 12 hours and replaced with the media. The absorbance was measured at 247 nm against the blank.

5) In vitro skin permeation studies [10]

Cellophane membrane was used. The membrane was mounted between the donor and receptor compartment of Franz diffusion cell. The patch was kept in contact with cellophane membrane. The receptor compartment contained pH 7.4 phosphate buffer containing 2.5% ethanol. The assembly was kept on a magnetic stirrer and stirred at a speed of 200 rpm. The temperature of assembly was kept at 37 ± 1˚C. After each hour, 1ml of sample was withdrawn and replaced with same media up to 24 hours to study.

6) Effect of drugs loading and polymer concentration on film [15]

Films with different drug load and polymer concentration were prepared and studied for their thickness, moisture absorption, and In vitro drug permeation.

7) Effect of penetration enhancers on film

Two penetration enhancers namely urea, dimethylsulphoxide (DMSO) were incorporated in different proportion 5 and 10%. The films were then evaluated for the properties as mentioned earlier.

8) Effect of plasticizers on film

Two plasticizers namely polyethylene glycol-400, glyceryl triacetate were added in different concentration 5 and 10 % of polymer concentration. These films were then evaluated for the properties as mentioned earlier.

Model	Equation
Zero order Kinetics	$Q = Q_0 - K_0t$
First order kinetics	$Q = Q_0 (1 - e^{-Klt})$
Higuchi square root model	$Q_t = K_H \cdot t^{1/2}$
Hixson-Crowell cube root model	$\sqrt[3]{Q_0} - \sqrt[3]{Q_t} = K_{HC}{}^t$
Korsmeyer-peppas model	$Q_t/Q_\infty = K_k \cdot t^n$

where, Qt—amount of drug released at time t; Qo—initial amount of drug. and Ko, K1, KH, KHC and KK are the coefficients of equations.

9) Water vapor transmission rate (WVTR)

The WVTR study was carried out in desiccators main- tained at 43 and 75% RH at 25 ± 1˚C using saturated solution of potassium carbonate and sodium chloride respectively. Patches were placed on the mouth of glass vials containing fused calcium chloride and sealed using silicon wax. These vials were accurately weighed and placed in desiccators at 0% RH. The weight of these vi- als was recorded after 24 hours. The increase in weight was indicative of water transmission across the patch.

10) Study of drug release kinetics [16]

In order to investigate the drug release mechanism from patches, the % cumulative drug release data was analyzed with following mathematical model.

The most appropriate model was selected on the basis of goodness of fit test. The zero order kinetic describes the systems in which the drug release rate is independent of its concentration. The drug releases slowly (assuming that the area does not change and no equilibrium conditions are obtained). The first order kinetics describes the systems in which drug release rate is concentration dependent. Higuchi model describes the release of water-soluble drug from an insoluble matrix as a diffusion process based on the Fick's law and is square root time dependent.

The Hixson-Crowell cube root law describes the drug release from a system depends upon the change in surface area or diameter of particle or system and involves no diffusion mechanism. Korsmeyer-Peppas model describes the fraction of drug release relates exponentially with respect to time. This model is generally used to analyze the release of pharmaceutical polymeric dosage forms, when the release mechanism is not well known or when more than one type of release phenomena could be involved.

11) Skin irritancy study [17,18]

Area on the back of rats was clean shaved 24 hours prior to testing. Optimize patch was applied to the clean area and kept in its place by adhesive tape. After every hour, the patch was removed and observed visually for signs of edema or erythema and scored according to Draize's scoring index. Patch without drug was used as control patch.

3. Results and Discussion

3.1. Table 1. Effect of Drug Loading and Polymer Concentration on Film

The patches in each group are uniform in drug distribution. The thickness and weight increases with the increase in polymer concentration. The films formed are transparent in appearance. (**Tables 1** and **2**)

3.2. Table 2. Characterization of Eudragit RL 100 Patches

3.3. Moisture absorption study

The patches were subjected to different % RH, RT conditions and the absorption of moisture noted the results are shown as under;

3.3.1. Table 3. Moisture Absorption of PVA Patches

Visual examination indicates that, at 43% RH, RT no change was observed in PVA patches on 7th day, while at 75% RH, RT the PVA Patches lost there shape on 7th

Table 1. Effect of drug loading and polymer concentration on film.

PVA	Eudragit RL 100	% Polymer Concentration	Drug	Appearance	Thickness (mm)	Weight (mg)	Content (mg)
P1	U1	5	-	Transparent	0.019	22.1	1.910
P2	U2	6	-	---Do----	0.020	24.4	1.877
P3	U3	7	-	---Do----	0.021	29.1	1.891
P4	U4	8	-	---Do----	0.023	29.5	1.848
V1	Eu1	5	15	---Do----	0.015	18.6	1.040
V2	Eu2	6	15	---Do----	0.017	20.2	1.002
V3	Eu3	7	15	---Do----	0.019	23.9	1.035
V4	Eu4	8	15	---Do----	0.021	26.4	0.988
F1	El1	5	10	---Do----	0.018	16.2	0.137
F2	El2	6	10	---Do----	0.019	22.1	0.146
F3	El3	7	10	---Do----	0.021	25.4	0.170
F4	El4	8	10	---Do----	0.023	29.2	0.212
J1	Eb1	5	5	Transparent	0.019	22.1	1.910
J2	Eb2	6	5	---Do----	0.020	24.4	1.877
J3	Eb3	7	5	---Do----	0.021	29.1	1.891
J4	Eb4	8	5	---Do----	0.023	29.5	1.848

Table 2. Characterization of Eudragit RL 100 patches.

Code	Appearance	Thickness	Weight (Mg)	Content (Mg)
Eu1	Transparent	0.019	21.8	2.671
Eu2	---Do----	0.021	23.8	2.713
Eu3	---Do----	0.023	26.4	2.652
Eu4	---Do----	0.025	29.7	2.661
El1	---Do----	0.017	24.8	1.271
El2	---Do----	0.018	25.6	1.290
El3	---Do----	0.019	29.8	1.281
El4	---Do----	0.022	32.1	1.267
EB1	---Do----	0.015	19.8	0.165
EB2	---Do----	0.017	22.4	0.174
EB3	---Do----	0.020	27.3	0.151
EB4	---Do----	0.023	28.6	0.156

Table 3. Moisture absorption of PVA patches.

CODE	43% RH, RT Pot. Carbonate			75% RH, RT Sod. Chloride			93% RH, RT Pot. nitrate		
	Wt. of patch (mg)	Moist. Absorp. (mg)	% ABS.	Wt. of patch (mg)	Moist. Absorp. (mg)	%ABS	Wt. of patch (mg)	Moist. Absorp. (mg)	% ABS
P1	16.0	1.7	10.62	16.4	2.7	16.46	15.0	5.6	37.33
P2	18.5	1.5	8.10	17.9	2.9	16.20	17.0	6.1	35.88
P3	17.9	0.4	2.23	18.0	3.6	20.00	16.0	8.4	52.50
P4	24.9	1.4	5.62	24.7	3.9	15.78	19.8	9.2	46.46
V1	22.1	10.5	47.51	21.9	13.8	63.01	22.4	17.0	**75.89**
V2	24.4	7.14	29.26	24.6	15.8	64.22	25.2	19.0	75.39
V3	29.1	5.79	19.89	28.2	8.2	29.07	27.4	13.7	50.00
V4	29.5	7.15	24.23	30.4	11.1	36.51	29.6	15.6	52.70
F1	18.6	11.17	60.05	18.8	6.7	35.63	19.4	7.6	39.17
F2	20.2	6.29	31.13	19.9	8.75	43.96	20.9	10.6	51.45
F3	23.9	7.43	31.08	24.2	8.55	35.33	23.6	10.8	45.76
F4	26.4	8.03	30.41	27.0	10.10	37.40	27.2	14.3	52.57
J1	16.2	4.1	25.3	16.5	4.9	29.69	16.9	5.6	33.13
J2	22.1	3.5	15.83	21.4	3.9	18.22	22.6	8.6	38.05
J3	25.4	2.4	9.44	24.3	8.6	35.39	25.9	9.9	38.22
J4	29.2	2.8	9.65	28.2	7.0	24.82	29.6	9.0	30.40

Table 4. Moisture absorption of Eudragit RL 100 patches.

CODE	43% RH, RT Pot. Carbonate			75% RH, RT Sod. Chloride			93% RH, RT Pot. nitrate		
	Wt. of patch (mg)	Moist. Absorp. (mg)	% ABS.	Wt. of patch (mg)	Moist. Absorp. (mg)	%ABS	Wt. of patch (mg)	Moist. Absorp. (mg)	% ABS
U1	15.9	0.3	1.88	15.3	0.3	1.96	15.6	0.6	3.84
U2	17.7	2.0	11.29	17.9	1.4	7.82	17.4	2.0	11.49
U3	18.8	1.5	7.97	18.1	1.3	7.18	18.9	1.2	6.34
U4	20.1	0.8	3.98	20.7	0.5	2.41	20.4	1.6	7.84
EU1	21.8	0.4	1.83	22.2	1.3	5.85	21.3	1.4	6.57
EU2	23.8	2.9	12.18	23.6	0.5	2.11	23.2	3.3	14.22
EU3	26.4	0.7	2.65	27.1	0.8	2.95	26.8	12.5	9.32
EU4	29.7	1.8	6.06	29.9	2.8	9.36	30.1	0.6	1,99
EL1	24.8	1.2	4.83	24.3	0.8	3.29	21.7	2.5	11.52
EL2	25.6	1.4	5.46	25.1	0.6	2.39	26.1	3.5	13.40
EL3	29.8	0.6	2.01	29.3	1.9	6.48	28.6	2.6	9.09
EL4	32.1	1.6	4.98	31.8	1.3	4.08	32.7	2.8	7.95
EB1	19.8	0.9	4.54	19.6	0.4	2.04	20.1	3.0	**14.92**
EB2	22.4	1.0	4.46	21.9	0.6	2.73	22.9	1.4	6.11
EB3	27.3	1.4	5.12	27.8	1.1	3.95	27.0	1.5	5.55
EB4	28.6	0.8	2.79	28.3	0.7	2.47	28.9	1.8	6.22

day, however the patches were found to be less stable at 93% RH, RT on 5th day.

3.3.2. Table 4. Moisture Absorption of Eudragit RL 100 Patches

For Eudragit RL100 patches at 43% RH, RT the Patches lost their shape on 7th day, while at 75% RH, RT the Patches lost their shape on 5th day and at 93% RH, RT patch were still more unstable and lost their shape at 4th day.

Since the absorption pattern is not uniform in both the cases therefore no conclusion can be drawn regarding the stability of patch from the above data. At every % RH, RT condition the Eudragit RL 100 patches absorb less moisture than PVA patches, but PVA patches were found to be more stable than the Eudragit RL 100 patches.

3.4. *In Vitro* Drug Permeation through Cellophane Membrane

The *in-vitro* permeation of PVA patches was studied by using cellophane membrane, results obtained are as shown under;

3.4.1. Table 5. Drug Permeation from PVA Patches (15 mg)

3.4.2. Table 6. Drug Permeation from PVA Patches (10 mg)

3.4.3. Table 7. Drug Permeation from PVA Patches (5 mg)

3.4.4. Figure 1. Effect of PVA Concentration with Constant Drug Concentration (15 mg) on Drug Permeation

Table 5. Drug permeation from PVA patches (15 mg).

CODE	(%) Percent permeated Time in (hrs.)							
	1	2	3	4	5	6	12	24
V1	4.11	4.98	6.21	7.53	8.85	10.33	11.39	12.98
V2	4.39	5.30	6.54	7.79	9.06	10.72	11.94	13.48
V3	4.99	6.16	7.48	8.73	10.15	11.58	12.97	15.05
V4	4.19	5.14	6.36	7.64	8.98	10.26	11.37	12.89

Table 6. Drug permeation from PVA patches (10 mg).

CODE	(%) Percent permeated Time in (hrs.)							
	1	2	3	4	5	6	12	24
F1	3.82	5.22	6.27	7.31	8.29	9.26	10.72	12.06
F2	4.19	5.61	7.19	8.32	9.54	10.70	12.14	13.43
F3	4.79	5.88	7.56	8.94	10.18	11.71	13.14	**14.86**
F4	3.63	5.11	5.93	7.14	8.16	9.36	11.06	12.41

Table 7. Drug permeation from PVA patches (5 mg).

CODE	(%) Percent permeated Time in (hrs.)							
	1	2	3	4	5	6	12	24
J1	3.42	4.81	5.83	6.85	7.82	8.77	10.21	11.53
J2	3.79	5.20	6.76	7.87	9.07	10.21	11.63	12.91
J3	4.40	5.46	7.13	8.49	9.71	11.21	12.63	**14.32**
J4	3.23	4.71	5.48	6.68	8.48	9.84	11.34	12.57

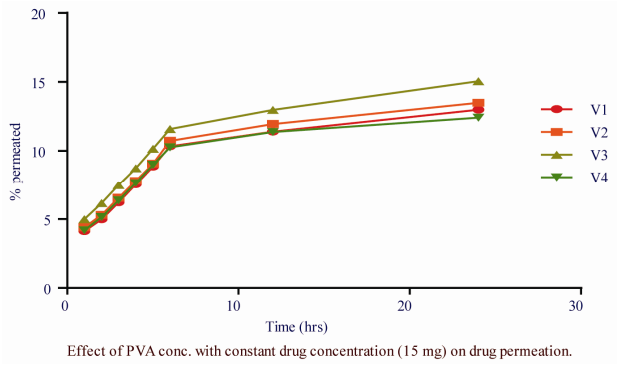


Figure 1. Effect of PVA concentration with constant drug concentration (15 mg) on drug permeation.

3.4.5. Figure 2. Effect of PVA Concentration with Constant Drug Concentration (10 mg) on Drug Permeation

3.4.6. Figure 3. Effect of PVA Concentration with Constant Drug Concentration (5 mg) on Drug Permeation

The *in vitro* drug permeation in all the cases increase up to 7% w/w polymer concentration while at 8% it decreases with constant drug load, the permeation of drug increases with increase in polymer content up to 7% w/w and thereafter it decrease. With constant polymer concentration, higher drug load gives higher permeation of drug. Thus the maximum percent permeation in V, F, and J series was observed with 7% w/w polymer concentration and it was 15.05%, 14.86%, 14.32% respectively as represented by Figure 1, 2 and 3 for PVA concentration.

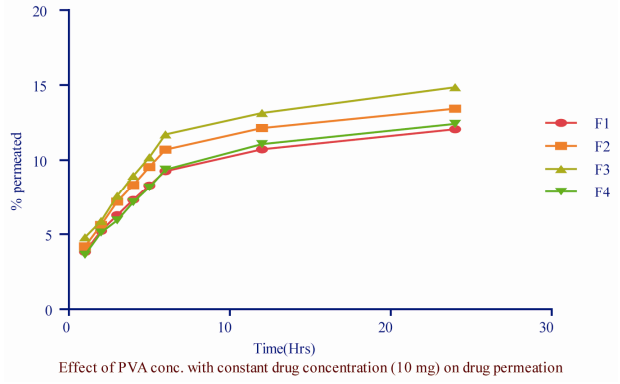


Figure 2. Effect of PVA concentration with constant drug concentration (10 mg) on drug permeation.

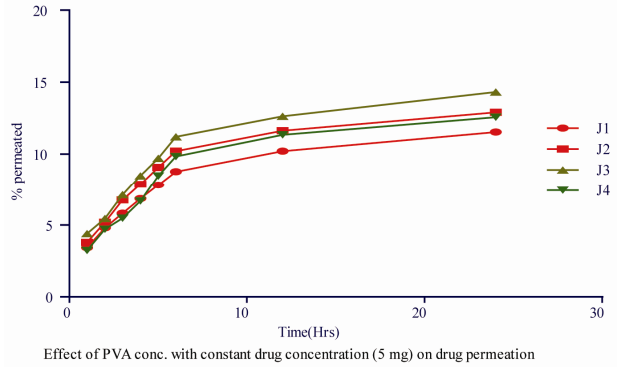


Figure 3. Effect of PVA concentration with constant drug concentration (5 mg) on drug permeation.

3.5. *In Vitro* Drug Permeation through Cellophane Membrane

The drug permeation through cellophane membrane was studied, results obtained are as shown under;

3.5.1. Table 8. Drug Permeation from EUDRAGIT RL 100 Patches (15 mg)

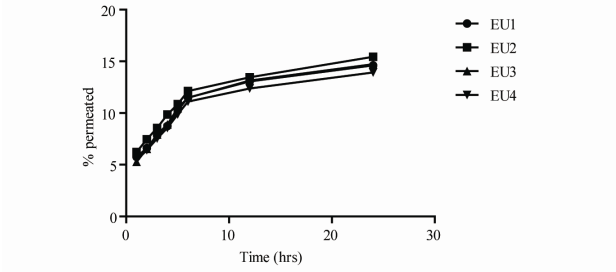
3.5.2. Figure 4. Effect of EUDRAGIT RL 100 conc. with Constant Drug Concentration (15 mg) on Drug Permeation

3.5.3. Table 9. Drug Permeation from EUDRAGIT RL 100 Patches (10 mg)

3.5.4. Figure 5. Effect of EUDRAGIT RL 100 conc. with Constant Drug Concentration (10 mg) on Drug Permeation

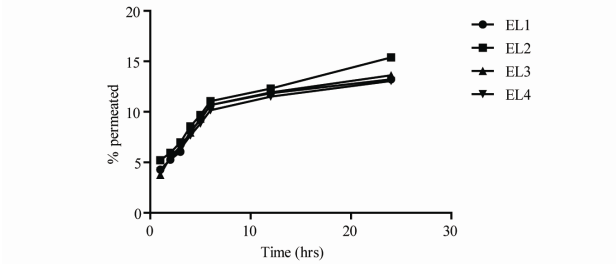
Table 8. Drug permeation from EUDRAGIT RL 100 patches (15 mg).

CODE	(%) Percent permeated Time in (hrs)							
	1	**2**	**3**	**4**	**5**	**6**	**12**	**24**
EU1	5.76	6.61	7.83	8.74	10.25	11.49	13.06	14.60
EU2	6.23	7.46	8.55	9.85	10.85	12.13	13.46	**15.44**
EU3	5.28	6.54	7.92	8.89	10.48	11.48	13.15	14.72
EU4	5.45	6.41	7.54	8.56	9.87	11.11	12.37	13.92



Effect of EUDRAGIT RL 100 conc. with constant drug concentration (15 mg) on drug permeation.

Figure 4. Effect of EUDRAGIT RL 100 conc. with constant drug concentration (15 mg) on drug permeation.



Effect of EUDRAGIT RL 100 conc. with constant drug concentration (10 mg) on drug permeation.

Figure 5. Effect of EUDRAGIT RL 100 conc. with constant drug concentration (10 mg) on drug permeation.

Table 9. Drug permeation from EUDRAGIT RL 100 patches (10 mg).

CODE	(%) Percent permeated Time in (hrs)							
	1	**2**	**3**	**4**	**5**	**6**	**12**	**24**
EL1	4.28	5.25	6.44	8.05	9.21	10.68	11.84	13.22
EL2	5.21	5.94	6.97	8.56	9.69	11.05	12.3	**15.39**
EL3	3.76	5.54	6.56	7.94	9.32	10.67	11.92	13.63
EL4	4.09	5.32	6.33	7.65	8.84	10.16	11.50	13.06

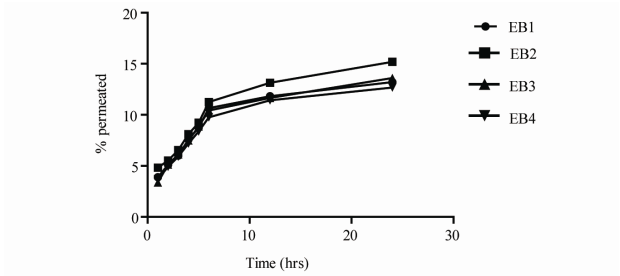
3.5.5. Table 10. Drug Permeation from EUDRAGIT RL 100 (5 mg)

3.5.6. Figure 6. Effect of EUDRAGIT RL 100 conc. with Constant Drug Concentration (5 mg) on Drug Permeation

The *in vitro* drug permeation in all the cases increase upto 6% w/w polymer concentration & there after it decreases. Higher drug load gives higher permeation of drug. thus the maximum percent permeation in EU2, EL2, EB2 series was observed with 6% w/w polymer

Table 10. Drug Permeation from EUDRAGIT RL 100 (5 mg).

CODE	(%) Percent permeated Time in (hrs)							
	1	**2**	**3**	**4**	**5**	**6**	**12**	**24**
EB1	3.89	5.11	6.01	7.60	8.74	10.66	11.82	13.21
EB2	4.82	5.53	6.54	8.11	9.22	11.26	13.15	**15.20**
EB3	3.37	5.13	6.13	7.49	8.86	10.42	11.66	13.60
EB4	3.70	4.91	5.90	7.20	8.37	9.76	11.42	12.67



Effect of EUDRAGIT RL 100 conc. with constant drug concentration (5 mg) on drug permeation

Figure 6. Effect of EUDRAGIT RL 100 conc. with constant drug concentration (5 mg) on drug permeation.

concentration and it was 15.05%, 14.86%, 14.32% respectively after 24 hrs. PVA 7% w/w gives maximum drug permeation while EUDRAGIT RL 100 at 6% w/w gives maximum permeation of drug. The maximum % permeation with PVA was 15.05 while with EUDRAGIT RL 100 it was 15.44%. For same drug content, the permeation through EUDRAGIT RL100 was better and higher than with PVA. Also with constant polymer concentration the drug permeation by EUDRAGIT RL100 was higher than PVA.

Therefore, with EUDRAGIT RL 100 better permeation may be obtained with less polymer requirement in *in-vitro* studies, therefore, EUDRAGIT RL 100 was better polymer than PVA.

3.6. Effect of Penetration Enhancer on Film

The compositions of various films and patches obtained were examined and characterized for the parameter are shown as below;

3.6.1. Table 11. Compositions of Patches with Different Penetration Enhancers.

3.6.2. Table 12. Characterization of PVA & EUDRAGIT RL 100 with Different Penetration Enhancers

In both the cases the patches formed are uniform with respect to drug content also with increase in the amount of penetration enhancer the weight of the patch also increase linearly .The thickness was also to be uniform throughout the patch.

Table 11. Compositions of patches with different penetration enhancers.

CODE	Polymer (mg)	Drug (mg)	Urea (mg)	DMSO (mg)
S1/M1	PVA/Eudragit RL100 - 700	5	35	--
S2/M2	PVA/Eudragit RL100 - 700	5	70	--
T1/R1	PVA/Eudragit RL100 - 700	5	--	35
T2/R2	PVA/Eudragit RL100 - 700	5	--	70

Table 12. Characterization of PVA & EUDRAGIT RL 100 with different penetration enhancers.

CODE	Appearance	Thickness (mm)	Weight (mg)	Drug content (mg)
S1	Transparent	0.018	26.3	0.302
M1	Transparent	0.017	24.3	0.472
S2	Transparent	0.020	29.1	0.453
M2	Transparent	0.018	27.9	0.879
T1	Transparent	0.017	28.2	0.226
R1	Transparent	0.019	26.2	0.335
T2	Transparent	0.019	32.1	0.430
R2	Transparent	0.021	29.4	0.789

Table 13. Moisture Absorption by PVA and EUDRAGIT RL 100 Patches with Different Penetration Enhancers.

CODE	43% RH, RT			75% RH, RT			93% RH, RT		
	Wt. of Patch (Mg)	Moist. Absor. (Mg)	% Absorption	Wt. of Patch (Mg)	Moist. Absor. (Mg)	%Absorption	Wt. of Patch (Mg)	Moist. Absor. (Mg)	% Absorption
S1	26.1	4.5	17.24	27.2	11.9	43.75	28.0	15.0	53.57
S2	28.7	6.2	21.60	28.5	14.1	49.47	28.3	16.8	59.36
T1	28.0	3.1	11.07	28.3	7.4	26.14	27.9	11.2	40.14
T2	31.7	7.1	22.39	31.6	11.8	37.34	32.0	14.6	**45.62**
M1	24.6	2.1	8.53	24.8	3.9	15.72	24.2	4.8	19.83
M2	27.4	3.6	13.13	27.8	5.4	19.42	27.9	6.7	24.01
R1	26.4	1.8	6.8	26.6	2.6	9.77	26.8	3.5	13.05
R2	29.2	2.9	9.93	29.4	3.7	12.58	29.5	5.1	17.22

3.7. Moisture Absorption

3.7.1. Table 13. Moisture Absorption by PVA and EUDRAGIT RL 100 Patches with Different Penetration Enhancers

At 43% RH, RT, the moisture absorption by PVA patches is comparable with patch without the enhancers *i.e.* J3. The moisture absorption increases with increase in enhancer content. DMSO 10% w/w gives greater absorption than other *i.e.* 22.39%. It is found that 75% RH, RT the absorption pattern is higher than at 43% RH, RT. At 75% RH, RT maximum absorption is shown by urea 10% w/w with 49.47% absorption & at 95% RH, RT with 59.36%. All humidity condition the absorption increases with increase in enhancer content. As the humidity increases, there increase in moisture absorption and this increase linear. However, at 43% RH, RT all the patches retain their shape at the end of 7th day, At 75% RH, RT the urea patches lose their shape on 7th day, while DMSO patches a little sticky to touch. At 95% RH, RT the urea patches lose their shape on 4th day while DMSO patches still sticky & lose their shape on 6th day.

It is found that around 43% RH, RT, the moisture absorption by EUDRAGIT RL 100 patches is comparable with patch without the enhancers *i.e.* EB3 urea 10% w/w absorb moisture more than any other. When the conditions were of 75% RH, RT and at 95% RH, RT the absorption pattern was found to be higher than at 43% RH, RT At 75% RH, RT maximum absorption is shown by urea 10% w/w with 19.42% absorption & at 95% RH, RT with 24.015. Around all the humidity condition the absorption increases with increase in enhancer content. As the humidity increases, there increase in moisture absorption and this increase linear.

At 43% RH, RT all the patches retain their shape at the end of 7th day, At 75% RH, RT the urea patches lose their shape on 6th day, while DMSO patches a little sticky to touch. At 95% RH, RT the urea patches lose their shape on 3rd day while DMSO patches still sticky & lose their shape on 6th day.

Therefore amongst the enhancers, the patches of UREA & DMSO are stable for 7 days under different humidity condition.

3.8. *In Vitro* Drug Permeation through Cellophane Membrane

The patches were then subjected to in vitro drug permeation through cellophane membrane and the results obtained are indicated as below;

3.8.1. Table 14. Drug Permeation from PVA Patches 5 (Mg) with Different Urea Concentration

3.8.2. Figure 7. Effect on Drug Permeation from PVA Patches 5 (Mg) with Different Urea Concentration

3.8.3. Table 15. Drug Permeation from PVA Patches 5 (Mg) with Different DMSO Concentration

3.8.4. Figure 8. Effect on Drug Permeation from PVA Patches 5 (Mg) with Different DMSO Concentration

The result obtained is compared with patches without

Table 14. Drug permeation from PVA patches 5 (Mg) with different urea concentration.

CODE	Percent Permeated Time (Hrs)								Enhancement
	1	2	3	4	5	6	12	24	Ratio
S1	4.45	5.42	7.50	9.07	11.02	13.71.	15.38	18.09	1.263
S2	6.65	8.29	10.61	13.06	16.08	18.24	21.64	25.92	1.810

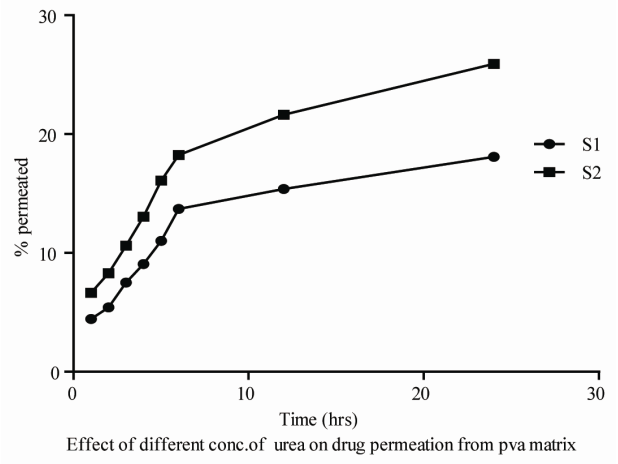


Figure 7. Effect on drug permeation from PVA patches 5 (Mg) with different urea concentration.

Table 15. Drug Permeation from PVA Patches 5 (Mg) with Different DMSO Concentration

CODE	Percent Permeated Time (Hrs)								Enhancement
	1	2	3	4	5	6	12	24	Ratio
T1	2.35	3.91	5.74	7.93	9.18	11.28	13.73	16.34	1.141
T2	3.19	5.40	7.11	8.99	10.85	13.81	16.29	19.89	1.388

penetration enhancers *i.e.* J3. Amongst the different proportion of urea used, urea at 10% w/w concentration gives maximum drug permeation i.e. of 25.92% with the enhancement ratio of 1.810. DMSO also increases the permeation at all concentration. it gives 16.34% , 19.89% of drug permeation for 5% w/w and 10% w/w of DMSO respectively with the enhancement ratio of 1.141 & 1.388 respectively. Therefore amongst the various penetration enhancers used in different proportions urea at 10% w/w concentration gives maximum drug permeation *i.e.* of 25.92% with the enhancement ratio of 1.810. Therefore for budesonide in PVA matrix urea 10% w/w is the best

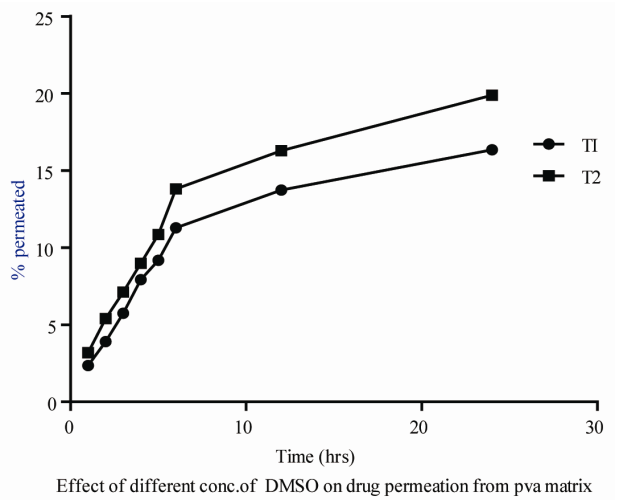


Figure 8. Effect on drug permeation from PVA patches 5 (Mg) with different DMSO concentration.

penetration enhancer.

3.8.5. Table 16. Drug Permeation from EUDRAGIT RL 100 Patches 5 (Mg) with Different Urea Concentration

3.8.6. Figure 9. Effect of Different Urea Concentration on Drug Permeation from EUDRAGIT RL 100 Patches 5 (Mg)

3.8.7. Table 17. Drug Permeation from EUDRAGIT RL 100 Patches 5 (Mg) with Different DMSO Concentration

3.8.8. Figure 10. Effect of Different DMSO Concentration on Drug Permeation from EUDRAGIT RL 100 Patches 5 (Mg)

The result obtained is compared with patches without penetration enhancers *i.e.* EB3. Amongst the different proportion of urea used, urea at 10% w/w concentration gives maximum drug permeation *i.e.* of 27.38 % with the enhancement ratio of 2.01. DMSO also increases the permeation at all concentration. It gives 18.53%, & 24.10% of drug permeation for 5% w/w and 10% w/w of DMSO respectively with the enhancement ratio of 1.362 & 1.772 respectively. Therefore amongst the various

Table 16. Drug permeation from EUDRAGIT RL 100 patches 5 (Mg) with different urea concentration.

CODE	Percent Permeated Time (Hrs)								Enhancement
	1	2	3	4	5	6	12	24	Ratio
M1	4.92	6.94	9.42	11.22	13.51	15.93	18.07	20.65	1.515
M2	5.43	6.96	9.59	12.33	14.90	17.76	21.90	27.38	2.013

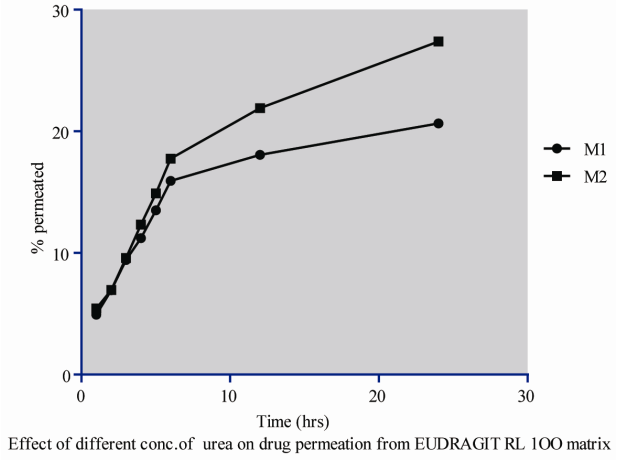


Figure 9. Effect of different urea concentration on drug permeation from EUDRAGIT RL 100 patches 5 (Mg).

Table 17. Drug permeation from EUDRAGIT RL 100 patches 5 (Mg) with different DMSO concentration.

CODE	Percent Permeated Time (Hrs)								Enhancement
	1	2	3	4	5	6	12	24	Ratio
R1	4.22	5.87	7.84	9.75	11.22	13.68	15.44	18.53	1.362
R2	5.01	6.90	9.00	12.04	15.59	17.64	20.61	24.10	1.772

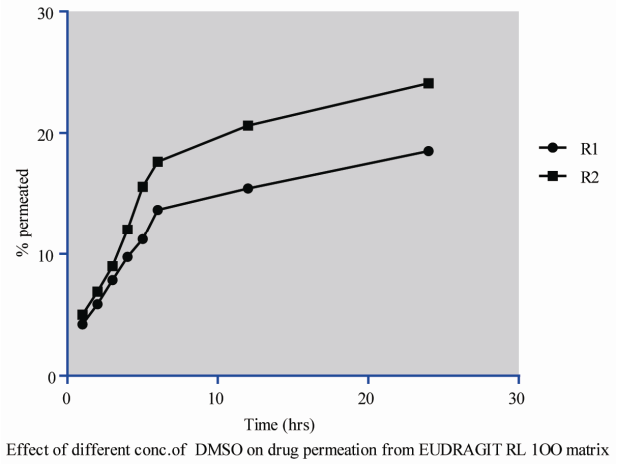


Figure 10. Effect of different DMSO concentration on drug permeation from EUDRAGIT RL 100 patches 5 (Mg).

penetration enhancers used in different proportions urea at 10% w/w concentration gives maximum drug permeation *i.e.* of 27.38% with the enhancement ratio of 2.01. Therefore for budesonide in EUDRAGIT RL 1OO matrix urea 10% w/w is the best penetration enhancer. For both PVA & EUDRAGIT RL 100 patches urea is the best penetration enhancers than DMSO.

3.9. Effect of Plasticizers on Films

The compositions of various films are shown as follows;

3.9.1. Table 18. Compositions of Patches with Different Plasticizers

The patches obtained were examined and characterized for the parameter as shown below

3.9.2. Table 19. Characterization of PVA & Eudragit RL 100 Patches with Different Plasticizers

In both the cases the patches formed are uniform with respect to drug content also with increase in the amount of plasticizers the weight of the patch also increase linearly. The thickness was also to be uniform throughout the patch.

3.10. Moisture Absorption

3.10.1. Table 20. Moisture Absorption Study of PVA and EUDRAGIT RL 100 Patches with Different Plasticizers

At 43% RH, RT, the moisture absorption by PVA patches is comparable with patch without the enhancers *i.e.* J3. The moisture absorption increases with increase in plasticizer content. PEG-400 10% w/w gives greater absorption than other *i.e.* 59.87%. Around 75% RH, RT the absorption pattern is higher than at 43% RH, RT. At 75% RH, RT maximum absorption is shown by PEG-400 10% w/w with 50.75% absorption & at 95% RH, RT with 59.87%. In all humidity condition the absorption increases with increase in plasticizer content. As the hu-

Table 18. Compositions of patches with different plasticizeers.

CODE	Polymer - mg	Drug (mg)	PEG 400 (mg)	Glyceryl triacetate (mg)
PE1/SO1	PVA/Eudragit RL 100 - 700	5	35	--
PE2/SO2	PVA/Eudragit RL 100 - 700	5	70	--
GL1/LO1	PVA/Eudragit RL 100 - 700	5	--	35
GL2/LO2	PVA/Eudragit RL 100 - 700	5	--	70

Table 19. Characterization of PVA & Eudragit RL 100 patches with different plasticizers.

CODE	Appearance	Thickness (mm)	Weight (mg)	Drug content (mg)
PE1	Slightly hazy	0.020	28.5	0.302
PE2	Slightly hazy	0.024	31.9	0.472
GL1	Very Slightly sticky	0.021	31.0	0.453
GL2	Very Slightly sticky	0.026	34.60	0.879
SO1	Transparent	0.018	26.5	0.226
SO2	Transparent	0.020	29.2	0.335
LO1	Transparent	0.019	28.1	0.430
LO2	Transparent	0.022	30.3	0.789

Table 20. Moisture absorption study of PVA and EUDRAGIT RL 100 patches with different plasticizers.

CODE	43% RH, RT			75% RH, RT			93% RH, RT		
	Wt. of Patch (mg)	Moist. Absorb. (mg)	% absorp-tion	Wt. of Patch (mg)	Moist. Absorb. (mg)	% absorp-tion	Wt. of Patch (mg)	Moist. Absorb. (mg)	% absorp-tion
PE1	28.7	5.1	17.77	28.9	12.8	44.29	28.5	15.4	54.03
PE2	32.4	7.4	22.83	33.1	16.8	50.75	32.9	19.7	59.87
GL1	31.4	4.1	13.05	30.8	8.2	26.62	30.9	13.2	42.71
GL2	34.6	7.2	20.80	34.3	13.5	39.35	34.1	17.2	50.43
SO1	26.2	2.2	8.39	26.7	3.4	12.37	26.5	6.9	26.03
SO2	29.8	3.5	11.74	29.1	6.8	23.36	29.7	9.7	32.65
LO1	28.4	3.5	12.32	29.1	6.9	23.71	28.6	10.8	37.76
LO2	30.2	4.8	15.89	29.8	7.6	25.50	30.6	11.2	36.60

midity increases, there increase in moisture absorption and this increase linear.

At 43% RH, RT all the patches retain their shape at the end of 7th day, At 75% RH, RT the PEG-400 patches lose their shape on 7th day, while glyceryl triacetate patches a little sticky to touch. At 95% RH, RT the PEG-400 patches lose their shape on 5th day while glyceryl triacetate patches still sticky & lose their shape on 6th day. At 43% RH, RT, the moisture absorption by EUDRAGIT RL 100 patches is comparable with patch without the enhancers *i.e.* EB3. Glyceryl triacetate 10% w/w absorbs moisture more than any other. At 75% RH, RT and at 95% RH, RT the absorption pattern is higher than at 43% RH, RT At 75% RH, RT maximum absorption is shown by glyceryl triacetate 10% w/w with 25.50% absorption & at 95% RH, RT with 36.60%. At all humidity condition the absorption increases with increase in enhancer content. As the humidity increases, there increase in moisture absorption and this increase linear. At 43% RH, RT all the PEG-400 patches retain their shape at the end of 7th day, while glyceryl triacetate patches lost their shape on 6th day. At 75% RH, RT the PEG-400 patches lose their shape on 6th day, while glyceryl triacetate patches lost their shape on 5th day. At 95% RH, RT the PEG-400 patches lose their shape on 4th day while glyceryl triacetate patches still sticky & lose their shape on 3rd day. Therefore amongst the plasticizers, the patches of PEG-400 & glyceryl triacetate are stable for 7 days under different humidity condition, and selected for final formulation of EUDRAGIT RL 100 & PVA respectively.

3.11. *In Vitro* Drug Permeation

3.11.1. Table 21. Drug Permeation from PVA Patches with Different PEG-400 and Glyceryl Triacetate Concentration

3.11.2. Table 22. Drug Permeation from Eudragit RL 100 Patches with Different PEG-400 and Glyceryl Triacetate Concentration

3.11.3. Figure 11. Effect of Different Conc. of PEG-400 on Drug Permeation from PVA Matrix

3.11.4. Figure 12. Effect of Different Conc. of Glyceryl Triacetate on Drug Permeation from PVA Matrix

3.11.5. Figure 13. Effect of Different Conc. of PEG-400 on Drug Permeation from EUDRAGIT RL 100 Matrix

3.11.6. Figure 14. Effect of Different Conc. of Glyceryl Triacetate on Drug Permeation from EUDRAGIT RL 100 Matrix

The results are compared with patches without plasticizers *i.e.* J3. The PVA patches with 5% & 10% w/w of PEG-400, the permeation increased from 16.50% to 19.96%. Similarly with glyceryl triacetate the permeation increased from 17.56% to 23.76 % respectively thus the glyceryl triacetate with 10% gives maximum permeation hence it is selected for final formulation.

The results are compared with patches without plasticizers *i.e.* EB3. The EUDRAGIT RL 100 patches with

Table 21. Drug permeation from PVA patches with different PEG-400 and Glyceryl triacetate concentration.

CODE	Percent permeated Time in (hrs.)							
	1	2	3	4	5	6	12	24
PE1	2.39	4.52	5.96	8.20	9.75	11.21	13.81	16.50
PE2	3.14	5.12	6.82	9.15	11.30	14.38	17.07	19.96
GL1	3.28	4.94	6.91	8.87	10.49	12.64	14.78	17.56
GL2	5.01	7.13	9.02	11.26	13.78	16.40	19.78	**23.76**

Table 22. Drug permeation from Eudragit RL 100 patches with different PEG-400 and Glyceryl triacetate concentration.

CODE	Percent permeated Time in (hrs.)							
	1	2	3	4	5	6	12	24
SO1	4.22	6.06	8.46	10.68	12.71	15.05	17.53	20.94
SO2	5.01	6.29	8.79	11.07	13.72	16.39	20.19	**24.33**
LO1	4.17	5.64	7.83	9.41	11.38	13.89	16.65	19.42
LO2	4.82	6.56	9.07	10.99	13.46	16.30	18.97	22.54

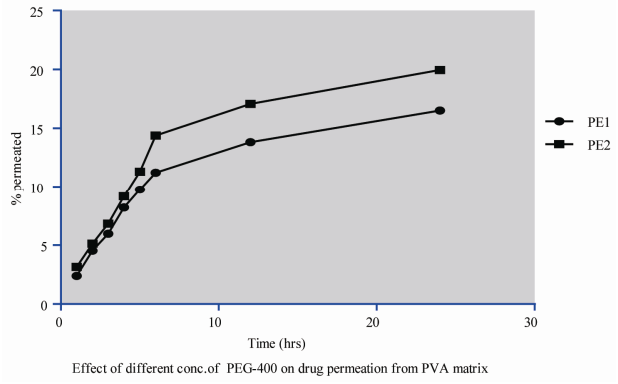


Figure 11. Effect of different Conc. of PEG-400 on drug permeation from PVA matrix.

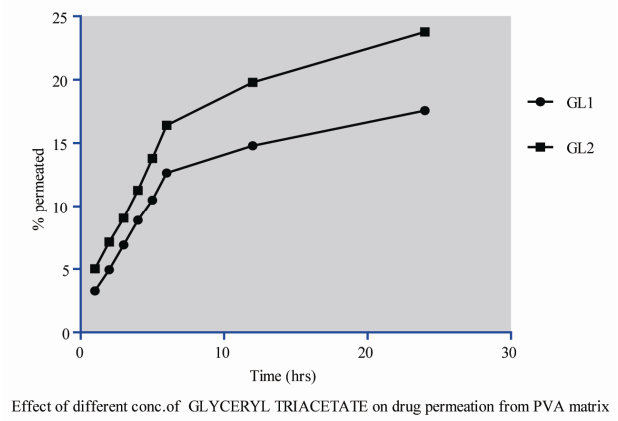


Figure 12. Effect of different Conc. of Glyceryl Triacetate on drug permeation from PVA matrix.

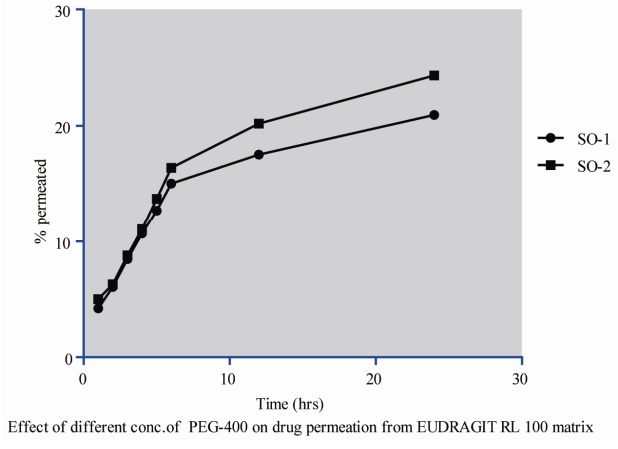


Figure 13. Effect of different Conc. of PEG-400 on drug permeation from EUDRAGIT RL 100 matrix.

5% & 10% w/w of PEG-400, the permeation increased from 20.94% to 24.33% .Similarly with glyceryl triacetate the permeation increased from 19.42% to 22.54% resp. thus the PEG-400 with 10% gives maximum permeation

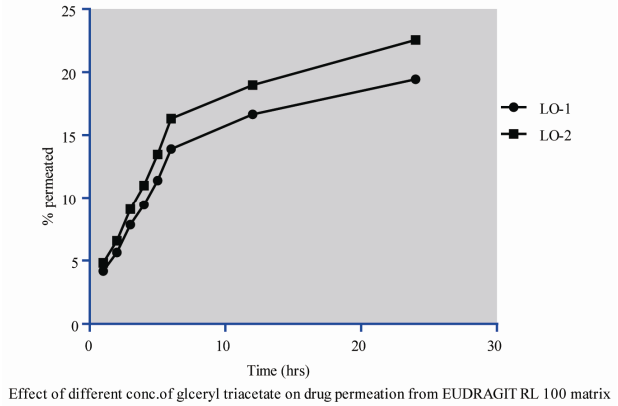


Figure 14. Effect of different Conc. of GLYCERYL TRI-ACETATE on drug permeation from EUDRAGIT RL 100 Matrix.

hence it is selected for final formulation.

3.12. Final Preparation

3.12.1. Preparation and Evaluation of Patch Using Optimum Concentration

Composition of various film prepared is shown in **Table 23**.

3.12.1.1. Table 23. Composition of Films of PVA and EUDRAGIT RL 100

The patch obtained was studied and their characterization was done and is listed in following **Table 24**.

3.12.1.2. Table 24. Characterization of PVA and EUDRAGIT RL 100 Patch

The patch in each group is uniform in drug content and thickness through the patch. And further In Vitro drug permeation, moisture absorption and WVTR studies were carried out.

3.12.2. Moisture Absorption: Table 25. Moisture Absorption Study of Final PVA and EUDRAGIT RL 100

Table 23. Composition of films of PVA and EUDRAGIT RL 100.

CODE	POLYMER (mg)	DRUG (Mg)	PLASTISIZER (Mg)	ENHANCER (Mg)
FP-1	PVA-700	5	GLY.TRI-70	UREA-70
FE-1	EUDRAGIT RL 100 - 700	5	PEG400- 70	UREA-70

Table 24. Characterization of PVA and EUDRAGIT RL 100 patch.

CODE	APPEARANCE	THICKNESS	WEIGHT (Mg)	DRUG CON-TENT (Mg)
FP-1	Transparent	0.019	33.4	1.971
FE-1	Transparent	0.018	31.6	2.174

Table 25. Moisture absorption study of final PVA and EUDRAGIT RL 100.

CODE	43% RH, RT			75% RH, RT			93% RH, RT		
	Wt. of Patch (mg)	Moist. Absorb. (mg)	% absorp-tion	Wt. of Patch (mg)	Moist. Absorb. (mg)	% absorp-tion	Wt. of Patch (mg)	Moist. Absorb. (mg)	% absorp-tion
FP-1	34.4	9.8	28.48	34.9	17.9	51.28	34.1	21.3	62.46
FE-1	31.9	6.7	21.01	31.7	12.8	40.37	32.1	15.9	49.53

Table 26. WVTR of PVA and Eudragit RL-100 patches.

CODE	43% RH, RT			75% RH, RT		
	Wt. of Patch (mg)	Moist. Absorb. (mg)	% absorption	Wt. of Patch (mg)	Moist. Absorb. (mg)	% absorption
FP-1	0.0021	0.020	0.217	0.0151	0.022	0.882
FE-1	0.0391	0.017	12.76	0.145	0.018	18.86

3.12.3. Water Vapor Transmission Rate Study (WVTR): Table 26. WVTR of PVA and Eudragit RL-100 Patches

At all humidity condition the absorption increases. As At all humidity condition the absorption increases. As the humidity increases, there is a increase in moisture absorption and this increases linearly. The patch FP-1 gives maximum absorption at 93% RH, RT *i.e.* 62.46 than any other. At 43% RH, RT the PVA patches retain their shape at the end of 7th day, At 75% RH, RT the PVA patches lose their shape on 7th day, At 95% RH, RT the PVA patches lose their shape on 5th day.

3.12.4. Drug Permeation through Cellophane Membrane

3.12.4.1. Table 27. *In-Vitro* Drug Permeation from EUDRAGIT RL 100 Patches

3.12.4.2. Table 28. *In-Vivo* Drug Permeation from EUDRAGIT RL 100 Patches

3.12.4.3. Figure 15. Drug Permeation of Patch FP-1

3.12.4.4. Figure16. Drug Permeation of Patch Fe-1

At all humidity condition the absorption increases. As the humidity increases, there increase in moisture absorption and this increase linearly. The patch FE-1 gives maximum absorption at 93% RH, RT *i.e.* 49.53% than any other. At 43% RH, RT the EUDRAGIT RL 100

Table 27. *In-Vitro* drug permeation from EUDRAGIT RL 100 patches.

CODE	Percent permeated							
	Time (hrs)							
	1	2	3	4	5	6	12	24
FE-1	10.94	14.25	17.60	20.85	24.26	27.71	32.07	37.25

Table 28. *In-Vivo* drug permeation from EUDRAGIT RL 100 patches.

CODE	Percent permeated							
	Time (hrs)							
	1	2	3	4	5	6	12	24
FE-1	10.94	14.25	17.60	20.85	24.26	27.71	32.07	37.25

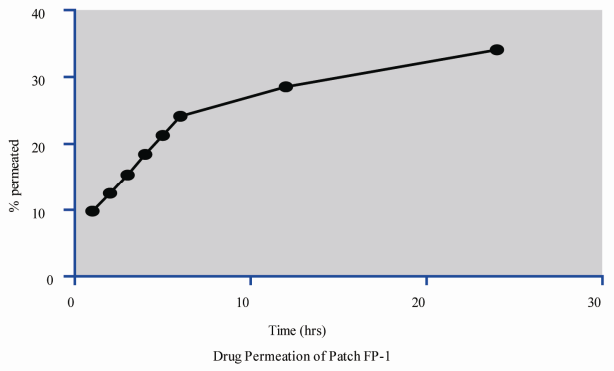


Figure 15. Drug Permeation of Patch FP-1.

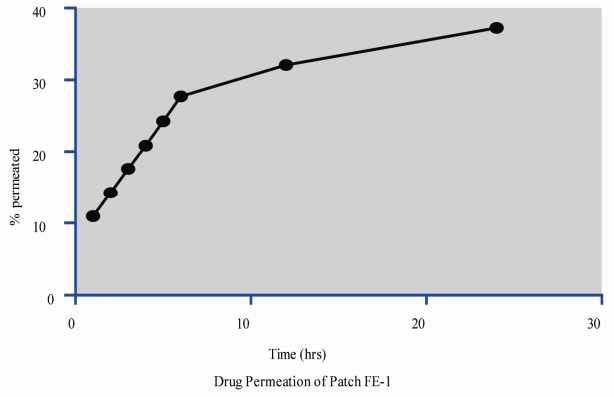


Figure 16. Drug Permeation of Patch Fe-1.

patches lost their shape at the end of 7th day, At 75% RH, RT the EUDRAGIT RL 100 patches lose their shape on 6th day, At 95% RH, RT the EUDRAGIT RL 100 patches lose their shape on 4th day. In PVA and EUDRAGIT RL 100 patches the water vapor transmission rate was found to be higher at 75% RH, RT conditions. Therefore at both % RH, RT condition the PVA and EUDRAGIT RL 100 patches provides the best resistance to water vapor. Therefore, when applied to animals (in further studies) these patches may provide more occlusion to water vapor loss from skin thus making atmosphere beneath the skin more humid that aid in drug permeation.

4. References

[1] B. J. Unde, "Pharmacotherapy of Asthma," In: L. L. Brunton, J. S. Lazo and K. L. Parker, Eds., *Goodman & Gilman's*, *The Pharmacological Basis of Therapeutics*, Mcgraw-Hill Medical Publishing Division, New York, 2006, pp. 897-934.

[2] C. M. Spencer and D. McTavish, "Budesonide: A Review of Its Pharmacological Properties and Therapeutic Efficacy in Inflammatory Bowel Disease," *Drugs*, Vol. 50, No. 5, 1995, pp. 854-872. doi:10.2165/00003495-199550050-00006

[3] R. N. Brogden and D. McTavish, "Budesonide: An Updated Review of Its Pharmacological Properties, and Therapeutic Efficacy in Asthma and Rhinitis," *Drugs*, Vol. 44, 1998, pp. 375-407. doi:10.2165/00003495-199244030-00007

[4] G. Jeffrey, *et al.*, "Have Done Budesonide Enema for the Treatment of Active, Distal Ulcerative Colitis and Proctitis: A Dose Ranging Study," *Current Therapy*, Vol. 22, 2005, pp. 23-27.

[5] N. Mygind and T. J. H. Clark, "Topical Steroid Treatment for Asthma and Rhinitis," B. Tindall Inc., London, 1980, pp. 89, 91,152,159,172.

[6] K. Masuyama, *et al.*, "Glucocorticosteroid (Fluticasone propionate) Inhibits Cells Expressing Cytokine mRNA for Interleukin-4 in the Nasal Mucosa in Allergen-Induced Rhinitis," *Immunology*, Vol. 82, 1994, pp. 192-199.

[7] N. S. Chandrashekar and R. H. S. Rani, "Design, Fabrication and Calibration of Modified Franz Diffusion Cell for Transdermal Diffusion Studies," *International Journal of Pharmaceutical Excipients*, October-Novem- ber 2005, pp. 104-106.

[8] J. Eliassaf, "Detection of Small Quantity of Poly(Vinyl Alcohol) in Poly(Vinyl Chloride) Resins," *Polymer Letters,* Vol. 16, 1972, pp. 225-235.

[9] S. P. Gupta and S. K. Jain, "Development of Matrix-Membrane Transdermal Drug Delivery System for Atenolol," *Drug Delivery*, Vol. 11, No. 5, 2004, pp. 281-286. doi:10.1080/10717540490493943

[10] P. R. P. Verma and S. S. Iyer, "Transdermal Delivery of Propranolol Using Mixed Grades of Eudragit: Design and *in Vitro* and *in Vivo* Evaluation," *Drug Development and Industrial Pharmacy*, Vol. 26, No. 4, 2000, pp. 471-476. doi:10.1081/DDC-100101257

[11] R. Krishna and J. K. Pandit, "Transdermal Delivery of Propranolol," *Industrial Pharmacy*, Vol. 20, No. 15, 1994, pp. 2459- 2465.

[12] P. Arora and B. Mukherjee, "Design, Development, Physicochemical and *in Vitro* and *in Vivo* Evaluation of Transdermal Patches Containing Diclofenac Diethylammonium Salt," *Journal of Pharmaceutical Sciences*, Vol. 91, 2002, pp. 2076-2089. doi:10.1002/jps.10200

[13] United States Pharmacopoeia, "Physical Tests <711> Dissolution," Vol. 24, 2000, pp. 1941.

[14] M. Siewert, J. Dressman, C. K. Brown and V. P. Shah, "FIP/AAPS Guidelines to Dissolution/*in Vitro* Release Testing of Novel/Special Dosage Forms," *AAP Spharmscitech*, Vol. 4, No. 1, 2003, pp. 1-10.

[15] C. Valenta and B. G. Auner, "The Use of Polymers for Dermal and Transdermal Delivery," *European Journal of Pharmaceutical Sciences*, Vol. 58, No. 2, 2004, pp. 279-289.

[16] P. Costa, "Modeling and Comparison of Dissolution Profiles," *European Journal of Pharmaceutical Sciences*, Vol. 13, No. 2, 2001, pp. 123-133. doi:10.1016/S0928-0987(01)00095-1

[17] J. Singh and H. I. Maibach, "Irritancy of Topical Chemicals and Transdermal Delivery Systems," *Drug Pharmaceutical Sciences*, Vol. 1, 2001, pp. 281-296.

[18] A. C. Calpena, E. Escribano and H. San Martin, "Influence of Formulation on the *in Vitro* Transdermal Penetration of Sodium Diclofenac," *Arzneimittle Forschung Drug Research*, Vol. 49, No. 11, 1999, pp. 1012-1017.

