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Formulation and Evaluation of Transdermal Patches of Metoclopramide Hydrochloride

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ABSTRACT

The present research was designed to evaluate matrix type Metoclopramide hydrochloride transdermal patches. Metoclopramide hydrochloride has an average oral bioavailability of about 75% but it appears to vary from 30 and 100%. So, the present work is an attempt to study effect of variation in Methocel E15LV concentration and study effect of hydrophilic and hydrophobic Methocel E15LV – Eudrgit RL100 combination on release profile of Metoclopramide Hydrochloride. All prepared formulations were evaluated for physical and mechanical properties like thickness, moisture uptake, percent flatness, tensile strength, and percent elongation. An attempt was made to get a patch with suitable drug release property as well as physical and mechanical properties. A formulation containing Methocel E15LV 2% has shown good physical, mechanical and in-vitro drug release properties. It also showed good diffusion of Metoclopramide hydrochloride across rat skin.

Key-words:

Transdermal patches; Metoclopramide hydrochloride.

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INTRODUCTION:

Transdermal drug delivery systems have recently developed to achieve the objective of systemic medication through topical application. The transdermal route of drug delivery is becoming popular because large number of drugs can be delivered and various diseases can be treated after transdermal administration[1, 2]. They facilitate more predictable drug absorption due to avoidance of GI tract variables such as pH, motility transit time, food and enzyme activity. It provides suitable alternative when oral dosing is unsuitable. They provide extended therapy with a single application, improving compliance over other dosage forms requiring more frequent dose administration. Multiday therapy can be possible with single application and gives better patient compliance[3-6] Cancer chemotherapy and radiotherapy induced emesis needs continuous release of drug like Metoclopramide hydrochloride. Metoclopramide hydrochloride is given orally 8 mg three time's day. Metoclopramide hydrochloride has about 75% oral bioavailability but bioavailability appears to vary from 30 and 100 %.[7.] Among various antiemetic drugs, Metoclopramide showed maximum flux through rat skin[8]. So, Metoclopramide hydrochloride is a good candidate for transdermal drug delivery**.**

So, transdermal patches containing Metoclopramide hydrochlorides were formulated using various polymers. Effect of variation in Methocel E15LV concentration and Methocel E15LV: Eudragit RL100 combination on transdermal film properties was studied. The physical and mechanical properties like thickness, moisture uptake, percent flatness, and tensile strength and percent elongation were performed. Other evaluations like drug content, weight variation, and area variation were performed. Drug release studies were carried out using USP dissolution apparatus Type V (Disk Over Paddle*).* In vitro permeation of Metoclopramide hydrochloride across rat abdominal skin was investigated.

MATERIALS AND METHODS:

Metoclopramide Hydrochloride was obtained as a gift sample from Shalaks pharmaceutical Ltd Delhi, Hydroxypropyl methylcellulose E15LV was obtained as gift sample from Colorcon Asia, Goa and Eudragit RL100 gift sample from Rohm pharma Polymers Ltd. Dichloromethane and Ethyl alcohol were purchased from Universal Labs, Mumbai and S.D. Fine Chemicals Ltd., Mumbai. Silicone emulsion gift was obtained as a gift sample from Hindustan Antibiotics, Pimpri. Pune.

PREPARATION OF THE PATCHES: -

Formulation of various patches are given in Table no 1

Table no: 1 Formulation of various patches:

Composition	**F1**	**F2**	**F3**	**F4**	**F5**	**F6**	**F7**	**F8**
HPMC E-15LV (mg)	500	750	1000	400	350	300	250	200
Eudragit RL-100(mg)	-	-	-	100	150	200	250	300
Drug (mg)	256	256	256	256	256	256	256	256
Plasticizer PEG-400 30% w/w of polymer.	150	225	300	150	150	150	150	150
Cosolvent Propylene glycol (ml)	0.7	0.7	0.7	0.7	0.7	0.7	0.7	0.7
Solvent (ml) Ethanol: DCM 1: 1	50	50	50	50	50	50	50	50

Preparation of mixture:

The polymer was dissolved in 40 ml of solvent mixture of ethanol: dichloromethane in beaker 'A'. In beaker 'B' propylene glycol, polyethylene glycols 400 were dissolved in 10ml of same solvent mixture (Ethanol : Dichloromethane 1:1) to get a transparent solution. Metoclopramide hydrochloride (256

mg) was added to beaker B and dissolved. Then contents of both beakers were mixed together and stirred well by mechanical stirrer for 20 minutes. The air bubbles were removed with the help of ultrasonicator.

Casting and drying of films:
Above mixture was poured into petri dishes, which were pretreated with silicone emulsion. The petridishes were kept in closed box so as to control the evaporation of organic solvents used. The control of evaporation was necessary for uniform drying of films. The drying was carried out at room temperature for at least 8 –12 hours. Then the films were cut into small patches of diameter 2.5 cm. Table no 1 describes various formulations of blank films with Methocel E15LV and combinations of Methocel E15LV with EudragitRL100.

PHYSICAL CHARACTERISTICS OF PREPARED FILMS[9-13]:

PHYSICAL EVALUATIONS

Thickness:
The thickness of films was measured by digital vernier caliper with least count of 0.01mm. The thickness was measured at five different sites and average of five readings was taken.

Percent flatness:
The percent flatness was measured by cutting the film into five strips from center of the film. The strips were cut so that each should have 4cm length and 0.5cm breadth. Each strip was put on the clean surface without applying any additional pressure and measured its length by digital vernier caliper. The percent flatness was calculated by the following formula.

$$\text{Percent flatness} = \frac{(L1 + L2 + L3+L4+L5)/5}{4} \times 100$$

Moisture uptake:

The films casted in petri dish were used for moisture uptake studies. Three desiccators were used for the study, one for drying the films, second for 58% RH and third for 79% RH. Saturated solutions of sodium bromide and aluminum chloride were used for 58% RH and 79% RH respectively.

The films were dried in a desiccators containing anhydrous calcium chloride for 24 hours (room temperature 28°C) and the initial weight was noted. Then the films were kept in desiccators of 58% RH and 79% RH. The films were equilibrated at respective % RH for 48 hours and percent moisture uptake was calculated by using following formula.

$$\text{Percent moisture uptake} = \frac{\text{Final weight} - \text{initial weight}}{\text{Initial weight}} \times 100$$

MECHANICAL PROPERTIES:

Tensile Strength:
Three strips of patch were cut having 4cm length and 0.5cm breadth. The thickness and breadth of strips were noted at three sites and average value was taken for calculation. The strips were marked with ink 2cm apart and 1cm from each end. Each strip was fit in clips in such a way that the markings would be just visible. The rate of change of stress was kept constant with the increment of 10 g per 2 minutes. The elongation was observed and the total weight required for breaking of film was used in calculation. The tensile strength was calculated by using following formula.

$$\text{Tensile strength (S)} = \frac{\text{Applied force}}{\text{Cross sectional area}} = \frac{m \times g}{b \times t}$$

Where, S = tensile stress in dynes/cm^2
m = mass in grams
g = acceleration due to gravity (980 dynes/cm^2)
b = breadth of strip in centimetres.
t = thickness of strip in centimetres.

The strain is change resulting in size of strip after the force was applied to its original size. Therefore, the strain can be given as,

$$\text{Strain (E)} = \frac{\text{Total elongation}}{\text{Original length}} = \frac{L - L_0}{L_0}$$

Where, L = length after force was applied
L_0 = original length

Percent elongation

The percent elongation at break was measured by formula given below.

$$\text{Percent elongation} = \frac{\text{Total elongation}}{\text{Original length}} \times 100 = \frac{L - L_0}{L_0} \times 100$$

Where, L = length after force was applied.
L_0 = original length. (in cm)

Modulus of elasticity

Modulus of elasticity was calculated by the formula,

$$\text{Modulus of elasticity } (M_0E) = \frac{\text{Tensile strength}}{\text{Strain}}$$

The unit of modulus of elasticity is dynes/cm.^{2}

TESTS DONE ON MEDICATED FILMS:

Content uniformity:

2.5cm diameter patch was cut and transferred to 100 ml volumetric flask. 100ml of Phosphate buffer pH 7.4 was added and kept at room temperature. After disintegration of patch, drug and polymer were dissolved. Then 1 ml was withdrawn from the solution and diluted to 10ml. The absorbance of the solution was taken at 273 nm against solvent blank. Concentration was calculated by using calibration curve.

In case of combination of Methocel E15LV and Eudragit RL, 2.5 cm was cut and transferred to 100 ml volumetric flask. 100 ml of Phosphate buffer pH 7.4 was added and kept on magnetic stirrer at 37 ^{0}C. After disintegration of patch, drug and polymer were dissolved. Then 1 ml was withdrawn from the solution and diluted to 10 ml. The absorbance of the solution was taken at 273 nm against solvent blank. Concentration was calculated by using calibration curve.

Weight variation

The three disks of diameter 2.5 cm. were cut and weighed on electronic balance for weight variation test. The test was done to check the uniformity of weight among patch.

Area variation

The change in area would change the drug content of the patch. The error in cutting was checked by measuring the area of the films. Three disks (same disks used for weight variation tests) were taken for accurate measurement of area of films. Diameter of patch was measured at five different points using digital vernier calliper. Average diameter was used for calculation of area.

Folding endurance

The disintegration test apparatus was modified for the determination of folding endurance of polymeric films. The apparatus was equipped with two clamps for holding the film firmly. Out of these two clamps, one was fixed while another clamp was moving. The moving clamp was able to move 2.5cm distance from another at speed of 30 rpm. The film was clamped in such a way that when clamps were at maximum distance, the film will be slightly stretched and at minimum distance the film will get folded. The apparatus was put on and allowed to run until film broke into two pieces. Number of folds the films withstand without breaking was noted.

DRUG RELEASE STUDIES:

Dissolution studies[14, 15]:

The *USP Dissolution Apparatus Type V (Paddle Over Disk)* was used for the determination of release rate of drug Metoclopramide from films. The test was carried out at 50 rpm. The distance between paddle and disk was 25.5 mm (Standard 25 ± 2mm). 900ml of phosphate buffer pH 7.4 was used as a dissolution medium and the temperature of dissolution medium was maintained at 32± 1°C. 10ml of aliquots of samples were collected after every hour and was replaced with the same quantity of fresh dissolution medium and was analyzed at 273 nm using Shimadzu 1700 double beam UV-Visible spectrophotometer without any further dilution.

Diffusion studies[16]:

Preparation of skin:

For diffusion study rat abdominal skin was excised from abdominal portion of rat and the skin was washed with water. The fatty tissue layer was removed. The outer portion with hair was applied with depilatory and allowed to dry. With the help of wet cotton the hair were scrubbed and washed with normal saline solution. The skin was kept in normal saline solution in refrigerator (4-8^{0}C) until skin was used for diffusion study.

Prior to use, the skin was washed with water and allowed to equilibrate with room temperature for 30 minutes. Then, skin was mounted between donor and receptor compartment of cell and allowed to get saturated with diffusion medium phosphate buffer pH 7.4. Keshary Chien (K-C) type diffusion cell of 27ml capacity was used**.** 1 ml sample was withdrawn every hour and replaced with same quantity of fresh diffusion medium. The aliquot was diluted up to 5ml and was analysed at 273 nm using Shimadzu 1700 double beam UV-Visible spectrophotometer.

RESULTS:

Table No 2. Physical evaluations of Medicated films containing various concentrations of Methocel E15LV and different proportions of Methocel E15LV and Eudragit RL100 combination.
**Average ± S.D. (n=5)*

Formulation	Thickness* (mm)	Percent Flatness	Moisture uptake % (w/w)	
			58 % RH	79 % RH
F1	0.10± 0.005	100	2.39 ±0.564	5.81 ±0.74
F2	0.13± 0.005	99.91	3.66 ±0.222	8.39 ±0.26
F3	0.16 ±0 .005	100	6.38 ±0.728	14.2 ±0.40
F4	0.07±0.005	99.86	4.65 ±0.343	6.15 ±0.52
F5	0.05± 0.008	99.95	3.31 ±0.48	5.44 ±0.58
F6	0.04± 0.004	99.88	2.92 ±0.33	5.15 ±0.82
F7	0.04± 0.008	99.77	2.67 ±0.40	4.58 ±0.60
F8	0.04± 0.048	100.	1.94 ±0.40	3.07 ±0.53

*Table No: 3. Mechanical properties of Medicated films containing various concentrations of Methocel E15LV and different proportions of Methocel E15LV and Eudragit RL100. * Average ± S.D. (n=3)*

Formulation	Parameter			
	Tensile strength* (dynes/cm2)	Percent elongation*	Modulus of elasticity*	Folding endurance
F1	32.46× 106 ± 1.7	10.3±0.5	314.1 × 106 ± 0.5	> 500
F2	32.5× 106 ± 1.2	15.3±0.5	211.6× 106± 0.6	> 500
F3	33.0× 106 ± 0.8	20.3± 0.5	162.3× 106 ± 1.4	> 500
F4	74.2× 106 ± 0.5	59.6± 0.5	124.3× 106 ± 0.3	> 500
F5	72.4× 106 ± 0.5	54.6 ± 0.5	132.4 × 106 ± 0.5	> 500
F6	71.6× 106 ±1.6	51.0± 1.73	140.4× 106 ± 1.5	> 500
F7	69.2× 106 ± 1.6	51.0± 1.7	135.8× 106 ± 1.5	> 500
F8	60.9× 106 ± 0.4	45.3± 0.5	134.4× 106 ± 0.6	> 500

*Table No: 4. Weight variation, area variation and drug content of Medicated films containing Methocel E15LV and different proportions of Methocel E15LV and Eudragit RL100. *Average ± S.D. (n=3)*

Formulation	Parameter		
	Weight variation*	Area variation**	Drug content***
F1	48.52±0.21	4.9 ±0.01	95.6 ± 0.27
F2	48.64±0.11	4.90±0.01	95.6 ± 0.23
F3	47.9±0.15	4.9 ±0.013	95.0 ± 0.09
F4	44.7±0.18	4.92±0.012	90.6 ± 0.15
F5	45.3±0.14	4.89 ±0.008	90.6 ± 0.311
F6	44.4±0.10	4.91 ±0.008	90.0 ± 0.188
F7	43.3±0.28	4.89 ±0.011	91.2 ± 0.491
F8	45.2±0.11	4.90 ±0.013	91.8 ± 0.317

DRUG RELEASE STUDIES:

Dissolution studies:

Figure no 1: Average cumulative % drug release from medicated films with various concentrations of Methocel E15LV in phosphate buffer 7.4 as dissolution medium. (F1, F2, F3).

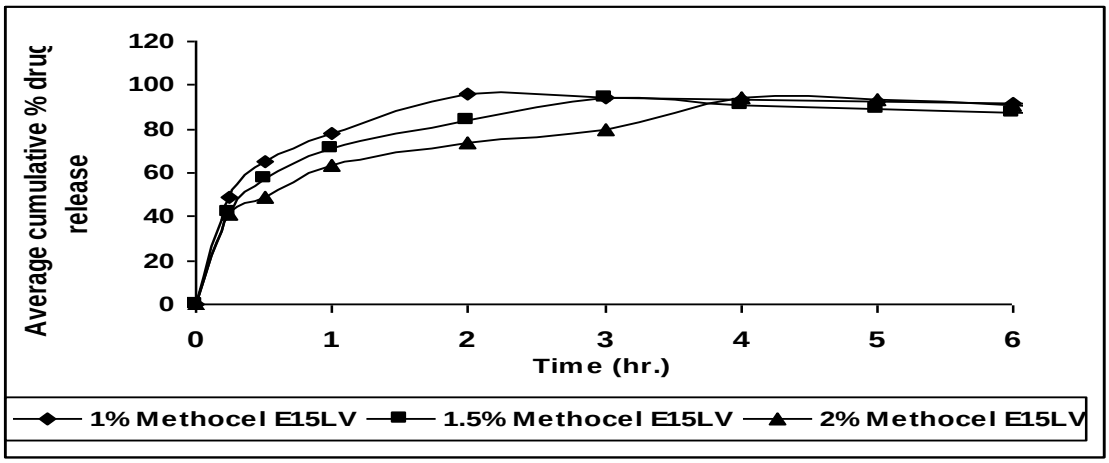
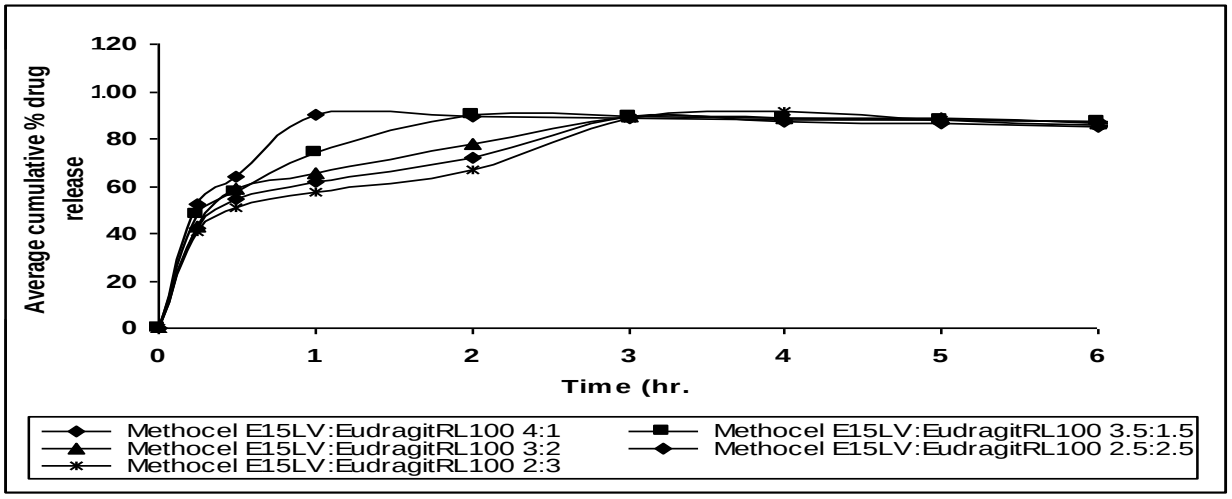


Figure no 2: Average cumulative % drug released from medicated films with different proportions of Methocel E15LV and EudragitRL100 in phosphate buffer 7.4 as dissolution medium. (F4, F5, F6, F7, F8).



Diffusion studies:

Figure no 3: Average cumulative % drug diffused from medicated films with various concentrations of Methocel E15LV in phosphate buffer 7.4 as dissolution medium.

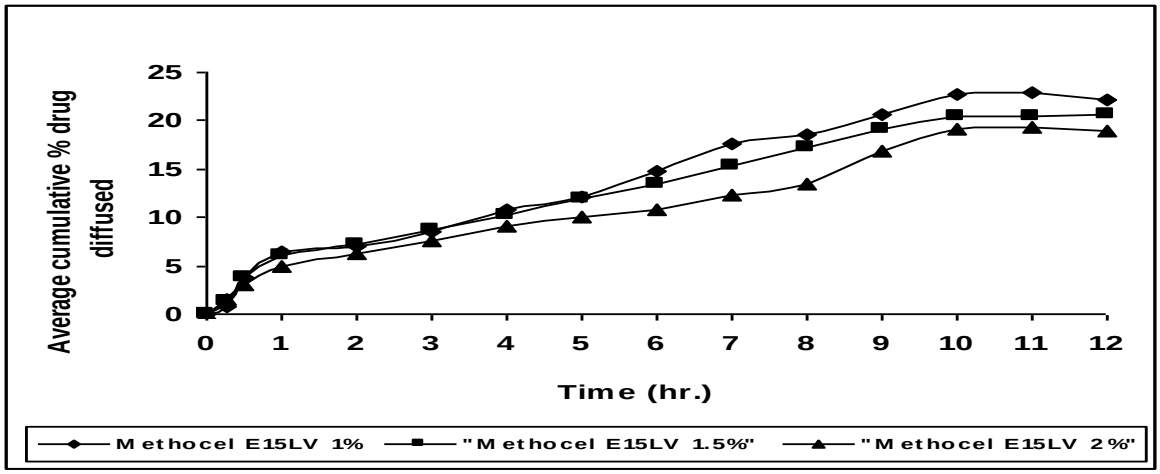
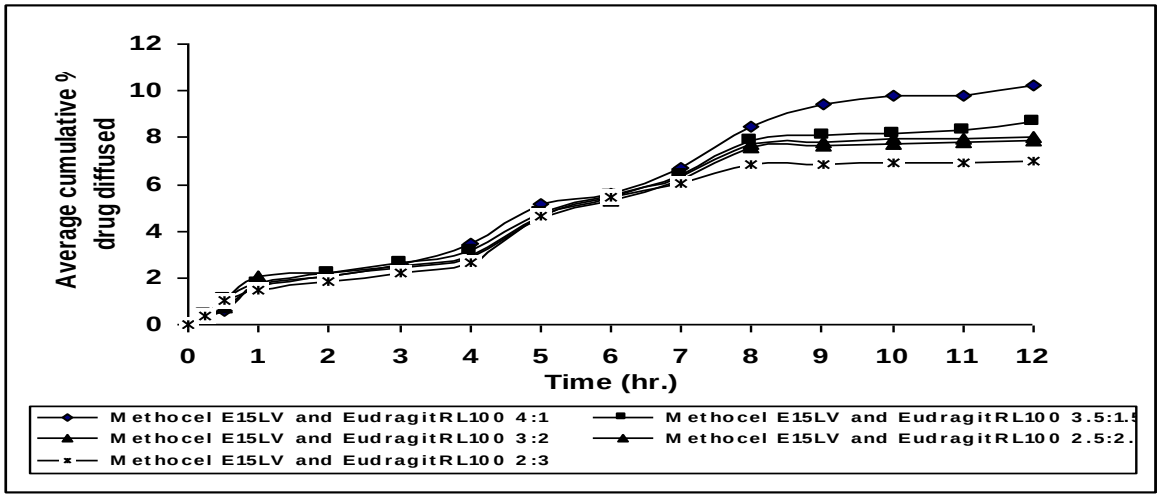


Figure no 4: Average cumulative % drug diffused from medicated films with different proportion of Methocel E15LV and EudragitRL100 in phosphate buffer 7.4 as dissolution medium.



DISCUSSIONS:

As shown in **Table no 2.** For films containing 1%, 1.5%, and 2% Methocel E15LV (F1, F2 and F3) uniform thickness was observed for individual groups of films and a increase in film thickness was observed with increase in polymer concentration. All films with Methocel E15LV showed % flatness close to 100%.

At 58% RH, moisture uptake increased from 2 to 6 % with increase in concentration of Methocel E15LV and PEG-400.At 79% RH moisture uptake increased from 5 to 14 % with increase in concentration of Methocel E15LV and PEG-400. This behaviour may be due to hydrophilic and hygroscopic character of both Methocel E15LV and PEG-400.

The polymer combination of Methocel E15LV and Eudragit RL100 (F4, F5, F6, F7, F8) were used to prepare films in 4:1, 3.5:1.5, 3:2, 2.5:2.5, and 2: 3 ratios. Thickness for individual combination film was found uniform. Film thickness observed was between 0.04 mm to 0.07 mm. But these variations did not show any co-relation with variation in ratio of polymers. The combinations showed percent flatness varying from 99.86 to 100.

As the amount of Eudragit RL100 in the combination was increased, the moisture uptake declined significantly. Eudragit RL100 has hydrophobic nature; the decreased moisture uptake may be due to increased hydrophobicity of resulting films.

As shown in **Table no: 3** (F1, F2, F3) films showed tensile strength ranging from 32.46 × 10^6 to 33× 10^6 dynes/cm^2. It was observed that as Methocel E15LV concentration was increased; there was slight increase in tensile strength. Percent elongation at breaking point increased from 10% to 20 % with increase in concentration of Methocel E15LV**.**

The tensile strength decreased as the proportion of Eudragit RL100 in combinations was increased (F4, F5, F6, F7 and F8). Tensile strength varied in the range of 74.2 × 10^6 to 60.96 × 10^6

dynes/cm^2. The combinations showed percent elongation varying from 45% to 59% Percent elongation at breaking point has also decreased with increase in proportion of Eudragit RL 100.

As shown in **Table no: 4** films obtained from formulations F1to F8 showed less weight variation, less area variation and good content uniformity.

As Shown in Figure no: 1 average cumulative percent release from films (F1, F2 and F3) containing 1% Methocel E15LV, 1.5% Methocel E15LV and 2% Methocel E15LV was different. As concentration of Methocel E15LV increased from 1% to 2%, average cumulative percent release from films decreased. This may be due to increase in thickness of film from 0.10 to 0.16 mm as concentration of Methocel E15LV was increased from 1% to 2%.

Data was analyzed for all models by using PCP disso software, out of which Peppas Korsmeyer and Matrix models were found to be closely fitted. As per Peppas Korsmeyer model parameters for formulation F1, were R=0.93, K= 20.48, n= 0.31, for formulation F2, parameters were R= 0.95, K= 15.26, n= 0.35 and for formulation F3 were R= 0.97, K= 15.91, n = 0.31. For F1, F2 and F3.As n observed was less than 0.5, release mechanism may be diffusion controlled and this may be due to swelling nature of Methocel.[17]

As Shown in **Figure no: 2** average cumulative percent drug releases from different formulations is different from each other. As concentration Eudragit RL100 increased, average cumulative percent release decreased in first 2 hours. The decrease in average cumulative percent release may be due to increased concentration of Eudragit RL100 in combinations, which is hydrophobic in nature. In all formulations, more than 90 % of release was observed in 3 hours.

Data was analyzed for all models by using PCP disso software, out of which Peppas Korsmeyer and Matrix models were found to be closely fitted. As per Peppas Korsmeyer model parameters for formulation F4, parameters were R=0.85, K= 26.91, N= 0.24, formulation F5, parameters were R=0.95, K=19.35, n=0.31 and for formulation F6, parameters were R=0.94, K=18.17, n=0.30. For formulation F7, parameters were R=0.96, K=16.68, n=0.31. For formulation F8, parameters were R= 0.96, K= 14.70, n= 0.33. As n observed was less than 0.5, release mechanism may be diffusion controlled and this may be due to swelling nature of Methocel.[17]

As Shown in **Figure no: 3** average cumulative percent drug diffused from films containing 1% Methocel E15LV, 1.5%Methocel E15LV and 2 % Methocel E15LV was different. As concentration of Methocel E15LV increased from 1% to 2%, average cumulative percent drug diffused at 12 hours was deceased from 22% to 19 %. This may be due to increase in concentration of Methocel E15LV from 1% to 2% which offers more resistance for drug release from matrices which may control release of drug from formulation.

As Shown in **Figure no: 4** as proportion of Eudragit RL100 (in combination) increased, average cumulative percent drug diffused decrease. The decreased in average cumulative percent drug diffused may be due to hydrophobic nature of Eudragit RL100.

Conclusion:

From this it can be reasonably concluded that Metoclopramide hydrochloride can be formulated into transdermal polymeric films. A formulation containing Methocel E15LV 2% has shown good physical, mechanical and *in-vitro* drug release properties. It also showed good diffusion of Metoclopramide hydrochloride across rat skin.

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