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Formulation and evaluation of metoclopramide hydrochloride transdermal patch

Ms.Archana K Gaikwad[1], Mr.M.H. Dehghan[2]

Y.B.Chavan college of pharmacy,

Dept of pharmaceutics, rauza bagh

Maharashtra Aurangabad 431001

Abstract: **The idea of delivering drugs through skin is old, as the use is reported back in 16th century B.C. A skin patch uses a special membrane to control the rate at which the liquid drug contained in the reservoir within the patch can pass through the skin and into the bloodstream. Many drugs that not having desired parameters for penetration their penetration enhanced with incorporation of the penetration enhancers. Metoclopramide hydrochloride which, is used as dopamine receptor antagonist antiemetic. short half-life ,low dose and low melting point, and their respective properties makes Metoclopramide hydrochloride good candidate for the Transdermal drug delivery. The laminated transdermal films of MCP prepared with different grades and ratios of Eudragit RS-100, EugragitRL-100, HPMC-E5 and EC holds potential for transdermal delivery of Metoclopramide hydrochloride and evaluation study has been done. A 3^2 factorial design was applied to prepare transdermal film of Ethyl cellulose Eudragit RL100, Eudragit RS-100 polymer as membrane and incorporation of drug in hydroxyl propyl methyl cellulose film as a matrix and to study its effect on evaluation parameters. In order to understand mechanism of drug release, *in vitro* permeation data were treated to kinetic models and linearity was observed. The correlation coefficient obtained from Korsemeyer Peppas as best fit model, r value was found to be 0.9903(F7), 0.9885(F8) and 0.9948 (F9). The optimized patch F9 the required patch size calculated, 25.10 cm^2 patch is required to get desired concentration of drug.**

According to Design Expert Software formulation F9 was the best formulation having cumulative amount of drug permeated 3.79 mg/cm^2, 99.43 drug content 109.75 Tensile strength and moisture content and moisture uptake 2.24 and 2.47 respectively.

From the formulation F9 formulation is the best formulation with desirability factor 0.678 and drug release is 66.97%

Keywords: **metoclopramide hydrochloride, transdermal patch, permeation enhancer, eudragit RL100, hydroxy propyl methyl cellulose.**

1. INTRODUCTION

The use of transdermal patches for pharmaceuticals has been limited because only a few drugs have proven effective delivered through the skin — typically cardiac drugs such as nitroglycerin and hormones such as estrogen.[1] The idea of delivering drugs through skin is old, as the use is reported back in 16th century B.C. The husk of castor oil plant in water was placed on an aching head[2].Today the transdermal drug delivery is well accepted for delivering drug to systemic circulation. A skin patch uses a special membrane to control the rate at which the liquid drug contained in the reservoir within the patch can pass through the skin and into the bloodstream.[3, 4] The basic components of any transdermal delivery system include the drug(s) dissolved or dispersed in a reservoir or inert polymer matrix; an outer backing film of paper, plastic, or foil; and a pressure-sensitive adhesive that anchors the patch to the skin[5,6]. The adhesive is covered by a release liner, which needs to be peeled off before applying the patch to the skin[7].Nausea and vomiting may occur in a variety of conditions (for examples; motion sicknes, pregnancy , hepatitis) and are always un-pleasant for the patient, it is the nausea

and vomiting produced by many chemo therapeutic agent that demand effective management as uncontrolled vomiting can produce dehydration, profound metabolic imbalances and nutrient depletion[8,9,]

Metoclopramide hydrochloride is used as dopamine receptor antagonist antiemetic. It is available white crystalline powder or crystals which is very soluble in water freely soluble in alcohol and sparingly soluble in methylene chloride.[10] this antiemetic chemically related to procainamide acts predominantly as a dopamine antagonist.

Metoclopramide in its conventional dosage forms like tablets and injections produce many side effects like chills, convulsions, dizziness or fainting, fast or irregular heartbeat, headache, increasing blood pressure, increased swelling itching, skin rash and loss of appetite. Metoclopramide needs to be administered 2-3 times daily, which may lead to patient non-compliance.[11]

These limitations associated with conventional Metoclopramide administration may be overcome by altering drug administration routes and /or by modifying the drug delivery systems. Among the various drug delivery systems available, transdermal drug delivery provides many benefits like extended period of drug action, increased bioavailability and increased patient compliance.[12] Metoclopramide hydrochloride shows hepatic metabolism The drug is antiemetic and thus routes other than oral is preferable It has a molecular weight of 299D therefore within the range Partition coefficient is 1.8 which is also within desirable range Thus Metoclopramide hydrochloride is a favourable candidate for delivery by the transdermal route.

2. MATERIALS AND METHODS

The drug, Metoclopramide Hydrochloride was procured as gift sample from IPCA Ltd, Mumbai, Maharashtra, India. Backing layer Polyester films laminate 3M scotch pak backing-1006 and Release liner: Fluropolymer coated film 3M scotch pak- 1002 as Gift sample form 3M Company, USA. Cellulose acetate membrane (0.22µm) was procured from Millipore, Bangalore; Calcium Chloride: Loba Chemicals, India. Dibutyl phthalate (DBP): Qualingenes Fine Chemical Ethanol from S.D Chemicals Eudragit RL 100 (ERL) and Eudragit RL 100 (ERS) Rohm lab,Germany and Hydroxyl propyl methyl cellulose E-5. Obtained as gift sample form Wockhardt. Mercury and Ethyl cellulose Research fine lab. Menthol: Loba Chemicals, India. The human cadaver skin used for permeation studies was procured from Government Medical College, Aurangabad.

METHODS

Preformulation study

Various tests were carried out on the sample of the drug to establish its identity and purity and the results were compared with specifications reported in literatures, wherever possible. The parameters studied include FTIR analysis Melting point Determination of partition coefficient Polymers and other excipients used in the study were standardized as per USP 2004 NF and Handbook of Pharmaceutical Excipients,for their physiochemical characteristics such as appearance, solubility, pH, melting point and viscosity.[14,15,16]

Formulation development

Formulation of blank transdermal patch

Transdermal patches of polymers Eudragit RS-100, Eudragit RL-100, Ethyl cellulose (EC) and hydroxyl propyl methyl cellulose (HPMC) was prepared in different solvents (5ml) respectively.

In the preliminary study the transdermal patches were prepared by incorporating dibutyl phthalate (20% w/w) and glycerol (30%w/w) as a plasticizer and without any permeation enhancer.

Table 1: Polymeric composition for preparation of blank polymeric film

Polymer composition in ratio for various batches							
Materials	AG1	AG2	AG3	AG4	Ag5	AG6	AG7
ERL100	7	7	8	3	1	1	
ERS100	3		1	7	1	8	
EC		3	1		8	1	
HPMC							10

Formulation of drug loaded transdermal patch

Preparation of Rate-controlling Membrane

Ethyl cellulose, Eudragit RL and Eudragit RS100 are dissolved in ethanol (5 ml).It is stirred continuously until it is completely dissolved, Dibutyl phthalate (20% w/w) is added as plasticizer. The solution was poured on glass rings placed on mercury surface and allowed for controlled drying by putting inverted funnel for 24 hours. The patch was wrapped in aluminium foil and stored over fused calcium chloride in a dessicator at room temperature for further use.[17]

Preparation of matrix patch

Drug i.e. Metoclopramide hydrochloride and hydroxyl propyl methyl cellulose is dissolved in water (5 ml) glycerol (30%w/w) is added as plasticizer The solution was poured on glass rings placed on mercury surface and allowed for controlled drying by putting inverted funnel for 24 hours. The patch was wrapped in aluminium foil and stored over fused calcium chloride in a dessicator at room temperature for further use.[18]

Preparation of laminated patch and Preparation of polymeric films with drug and penetration enhancer

The permeation enhancers (menthol) were used in 18.86% w/w of polymer weight. The Membrane patch (EC+ERL+ERS) is laminated on matrix patch (drug+hpmc). The fabricated patch was wrapped in aluminum foil and stored over fused calcium chloride in a dessicator at room temperature for further use.

A 3^2 factorial design (Table 2 and Table 3) was applied to prepare transdermal film of Ethyl cellulose Eudragit RL100, Eudragit RS-100 polymer as membrane and incorporation of drug in hydroxyl propyl methyl cellulose film as a matrix and to study its effect on evaluation parameters. The amount of polymers added for loaded Transdermal patch as per factorial design (Table 2) was 230 mg while HPMC (200 mg) and drug (8 mg) were kept constant for all the batches.

Table 2. Variables and their levels for factorial design

Variables	**Levels**		
	Lower (-1)	Middle(0)	Upper(+1)
X_1-Concentration ofEthyl cellulose (EC).	25% w/w	30 % w/w	35 % w/w
X_2-Concentration of Eudragit RL-100(ERL).	65% w/w	70 % w/w	75 % w/w

Table 3.Formulation of Drug Loaded transdermal patch

Formulation code	**X_1**	**X_2**
F1	-1	-1
F2	0	-1
F3	+1	-1
F4	-1	0
F5	0	0
F6	+1	0
F7	-1	+1
F8	0	+1
F9	+1	+1

Evaluation of transdermal patch

Separation of human epidermis from human cadaver skin:

The human cadaver skin was obtained from Govt. Medical College and Hospital, Aurangabad. The epidermis was prepared which involves soaking the whole skin in water at 60^0 C for 45 sec. The skin was removed from water, blotted dry and pin with dorsal side down. The intact epidermis was teased off from the dermis with forceps, washed with water and used in the *in-vitro* permeation studies.[19]

Physico-chemical evaluation of medicated films

Thickness

The thickness of the film was measured by micrometer screw gauge (Acculab) at three different places; averages of three values were calculated.[20]

Flatness

Longitudinal strips were cut out from each film, one from the center and two from either side. The length of each strip was measured and the variation in length because of non-uniformity in flatness was measured by determining percent constriction, considering 0% constriction equivalent to 100% flatness.[21]

% constriction =L1 – L2 / L2 × 100.

Where, L1 = initial length, L2 = final length of each strip.

Folding endurance

The folding endurance of the films was determined by repeatedly folding a small strip measuring 2×2 cm^2 size at same place till it breaks.[21]

Moisture content

The films were weighted and kept in desiccator containing calcium chloride for at least 24 hr or more until it showed a constant weight. The percentage moisture content was the difference between the initial and final weight with respect to final weight.[21]

Moisture uptake

A weighted film kept in a desiccator at normal room temperature for 24 hr was taken out and exposed to two different relative humidity of 75% (saturated solution of sodium chloride) and 93% (saturated solution of ammonium hydrogen phosphate) in two different desiccators, at room temperature. Then the weights were measured to constant weight. The percentage of moisture uptake was calculated as the difference between final and initial weight with respect to initial weight.[21]

Water vapour transmission rate (WVTR)

Glass vials of equal diameter were used as transmission cells. These transmission cells were washed thoroughly and dried in an oven. About 1g 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 desiccators containing saturated solution of potassium chloride to maintain a humidity of 84%. The cells were taken out and weighed after 12, 24 h of storage. The percentage of water vapour transmission rate was calculated as the difference between final and initial weight with respect to initial weight.[22]

Tensile strength

Tensile strength at break is the maximum tensile stress sustained by the specimen during the tension test. Stress is the force exerted on a body that tends to deform its shape. It is defined as the ratio of applied force to the cross sectional area.[21]

Tensile strength is calculated as-

Tensile strength = Maximum applied force/ (Minimum cross Sectional area)

= m x g / b x t dynes / cm^2

Where,

m- Mass in grams

g- Acceleration due to gravity 980 cm/ sec^2

b- Breath of specimen in cm

t – Thickness of specimen in cm.

The rate of change in stress was kept constant by increasing the load on the pan at the rate of 100 gm/ 2 min, as stress – strain relationship changes with the rate of change in stress.

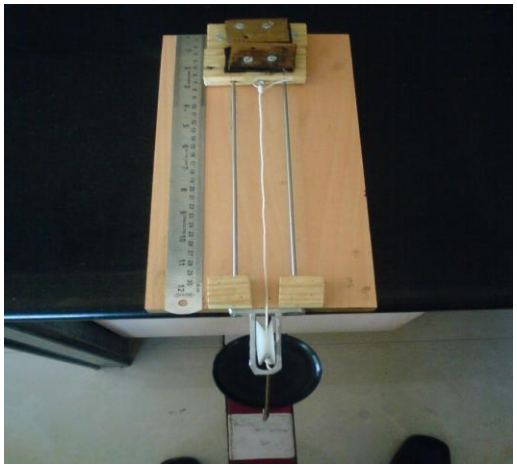

Fig 1: Tensile strength apparatus

Percent elongation at break

It is defined as the elongation at the moment of rupture of the specimen divided by the initial gauge length of the specimen and multiplying by 100 [21]

Percent elongation at break = LB-Lo/ Lo x 100

LB= Length of the specimen in cm where it breaks.

Lo= Original length of specimen.

An instrument and procedure is similar to that used for tensile strength.

Drug content

The 1.25cm X 1.25cm was accurately cut and patches were individually dissolved in 100 ml pH 7.4 phosphate. From this solution, 10 ml was transferred to volumetric flask and volume was made up to 100 ml. The absorbance was recorded at 309 nm. The blank solution was prepared in the similar way except that the patches without drug were used.[23]

***In-vitro* drug permeation study of transdermal films**

A modified Keshary- Chien diffusion cell was used for diffusion studies. The donor phase was consisting of 1.56 cm^2 patch containing approximately 10 mg drug. The receptor compartment was consisting of 20 ml of pH 7.4 phosphate buffer .The whole assembly was maintained at 37 ± 2º C. The solution in the receptor compartment was continuously stirred at 100 rpm by means of Teflon coated magnetic bead, in order to avoid diffusion layer effects. One ml of sample was withdrawn from receptor compartment and replaced with same amount fresh medium. The withdrawn samples were suitably diluted and assayed spectrophotometrically at 309 nm. The study was carried out for 24 hr. The aliquots were taken after period of 1 hr up to 12 hr .[23]

Studies on drug release kinetics

The Metoclopramide hydrochloride concentration was corrected for sampling effects according to the equation described by Hyton and Chien.[18]

$$C^1_n = C_n (V_T/V_T-V_S) (C^1_{n-1}/ C_{n-1})$$

Where,

C^1_n is the corrected concentration of the n^{th} sample.

C_n is the measured concentration of Metoclopramide hydrochloride in the n^{th} sample.

C^1_{n-1} is the measured concentration of Metoclopramide hydrochloride in the $(n-1)^{th}$

Sample.

V_T is the total volume of the receiver fluid and VS is the volume of the sample drawn.

The cumulative amount of Metoclopramide hydrochloride permeated per unit skin surface was plotted against time and the slope of the linear portion of the plot was estimated as steady state flux (µg/cm^2/h).[24]

The permeability coefficient K_p was calculated by using the following equation.[24]

$$K_p = J_{ss} / C_V$$

Where, J_{ss} is the steady state flux and C_V is the initial concentration of Metoclopramide hydrochloride in donor compartment.

The penetration enhancing effect of the solvent system was calculated in term of enhancement ratio (ER) using the following equation, [24]

$$ER = Kp_{\text{with solvent system}} / Kp_{\text{with water}}$$

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

Model	Equation
Zero order kinetics	$Qt = Q_o - K_o t$
First order kinetics	$Qt = Q_o (1 - e^{-K1t})$
Higuchi square root model	$Qt = K_H t^{½}$
Hixson-Crowell cube root model 3	$\sqrt[3]{Qo} - \sqrt[3]{Qt} = K_{HC}{}^t$

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.

Statistical analysis

Statistical tools such as descriptive statistics, one way ANOVA, probability values were determined for various parameters evaluated.[25]

Multiple regression analysis of 3^2 factorial batches

The responses obtained from 3^2 factorial batches were subjected to multiple regression analysis. The polynomial equations were determined using the form[25]

$$Yi = b_0 + b_1X_1 + b_2X_2 + b_{11}X_1^2 + b_{22}X_2^2 + b_{12}X_1X_2 + b_{12}X_1X_2^2 + b_{12}X_1^2X_2 + b_{12}X_1^2X_2^2$$

Where Yi is the dependent variable, b_0 is the arithmetic mean response of the 9 runs, and b_1 is the estimated coefficient for the factor X_1. The main effects (X_1 and X_2) represents the average results of changing one factor at a time from its low to high value.

The term X_1^2 and X_2^2 indicate curve linear relationship. The interaction X_1X_2 shows how the dependent variable changes when two or more factors are simultaneously changed. The targeted response parameters were statistically analyzed by applying one-way analysis of variance (ANOVA) at 0.05 levels in Design-Expert 8.1.1 version software (Stat-Ease Inc., Minneapolis, MN).

3. RESULT AND DISCUSSION

FTIR spectrum of Metoclopramide hydrochloride:

FTIR absorption spectrum of Metoclopramide hydrochloride was taken and the spectral assignments for major bands were in consistent with the structure of Metoclopramide hydrochloride The FTIR spectra of Metoclopramide Hydrochloride shown in Fig. 2

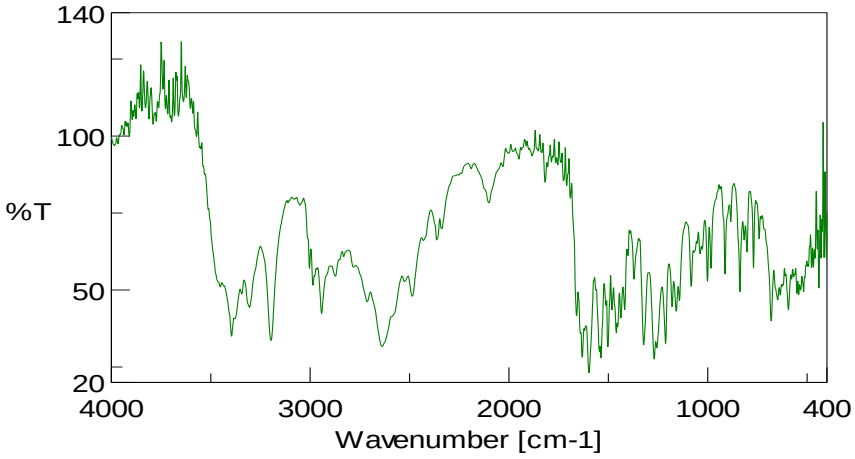

Fig 2: FTIR spectra of Metoclopramide hydrochloride

Table 4: Spectral assignment of metoclopramide hydrochloride

Sr. No.	Functional Group	Frequency (cm^{-1})
1	C=O	1600
2	O-H, N-H	3200, 3300, 3340, 3400, 3460
4	NH (Amide)	1540
5	C-O	1270
6	C-Cl	700

DSC analysis

DSC of Metoclopramide Hydrochloride

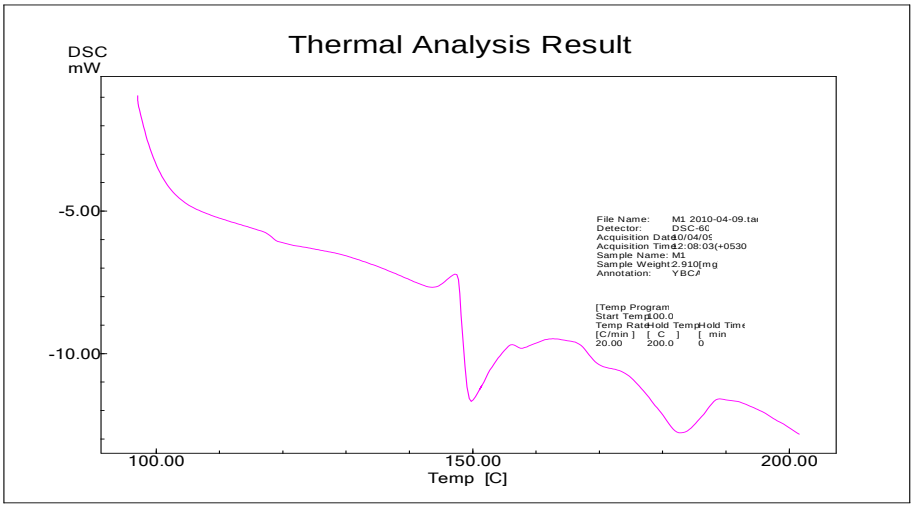

Fig.3: DSC thermogram of Metoclopramide Hydrochloride

Method of drug analysis

Solubility of drug was found to be 10 mg/ml , Partition coefficient of the metoclopramide hydrochloride in n-octanol /phosphate buffer was found to be 1.4**.** Calibration curve of Metoclopramide hydrochloride was taken at λmax 309 nm in phosphate buffer pH 7.4

Formulation Development

Fig.4 .Transdermal Film.

Fig 5: Transdermal patch of Metoclopramide hydrochloride.

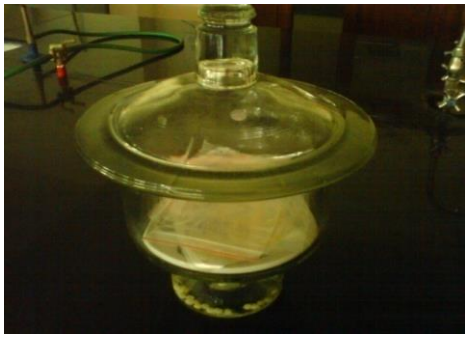

Fig 6: Storage of the prepared patch at dry condition.

Evaluation of blank transdermal patch

Table 5: Evaluation of blank transdermal film.

Sr.No.	Formulation	MC	MU	WVTR	Folding endurance	Flatness
1	AG1	1.2	1.45	0.038	75	100
2	AG2	1.01	1.08	0.068	88	100
3	AG3	1.23	1.34	0.057	85	100
4	AG4	0.89	1.01	0.036	60	100
5	AG5	0.55	0.88	0.066	87	100
6	AG6	1.01	1.03	0.056	88	100
7	AG7	1.09	1.13	0.076	69	100

Evaluation of Laminated Transdermal film

Thickness, Voidness, Flatness and folding endurance, Moisture content, Moisture uptake, water-vapour transmission rate of laminated transdermal film

Table 6: Thickness, Voidness, Flatness and folding endurance, Moisture content, Moisture uptake, water-vapour transmission rate

Formu-lation code	Thickness (cm)	%Voidness	Flatness	Folding endurance	Moisture content at 25°C± 2°C	Moisture uptake AT 75% RH at 25°C± 2°C	WVTR AT 75% RH at 25°C± 2°C
F1	0.0522± 0.001	0	100	132±2.40	1.92±0.1039	2.33±0.190	0.0636±0.0009
F2	0.0530± 0.003	0	100	135±2.51	2.21±0.17	2.49±0.165	0.0514±0.0027
F3	0.0518± 0.002	0	100	140±1.52	2.61±0.2020	2.83±0.17	0.518±0.0050
F4	0.0520± 0.001	2	98	122±1	0.334±0.168	0.998±0.165	0.0848±0.0027
F5	0.0520± 0.003	2	98	140±1.21	0.840±0.169	1.66±0.09	0.0842±0.0036
F6	0.0519± 0.002	0	100	152±0.57	1.75±0.265	2±0.17	0.0826±0.0115
F7	0.0522± 0.001	2	98	158±0.57	2.79±0.103	2.83±0.17	0.0496±0.0027
F8	0.0530± 0.002	0	100	165±1.15	2.97±0.103	3.11±0.19	0.0421±0.0017
F9	0.0535± 0.002	0	100	173±1.55	3.15±0.103	3.16±0.19	0.0176±0.0050

All values are (Mean±SD), n=3

Tensile strength and percent elongation at break and drug content.

Table 7: Tensile strength, % elongation at break and drug content of all formulation

Sr.No.	Formulation code	Tensile strength	%Elongation at Break	Drug content (±SD) n=3
1	F1	62.87×10^5	52.5	98.89±0.64
2	F2	98.61×10^5	42.5	99.31±0.37
3	F3	100.90×10^5	32.5	99.34±0.95
4	F4	62.92×10^5	50	98.62±0.72
5	F5	75.38×10^5	45	98.86±0.95
6	F6	100.77×10^5	37.5	99.20±0.80
7	F7	75.09×10^5	47.5	99.55±1.40
8	F8	110.94×10^5	22.5	99.58±1.14
9	F9	109.97×10^5	25	99.82±0.2

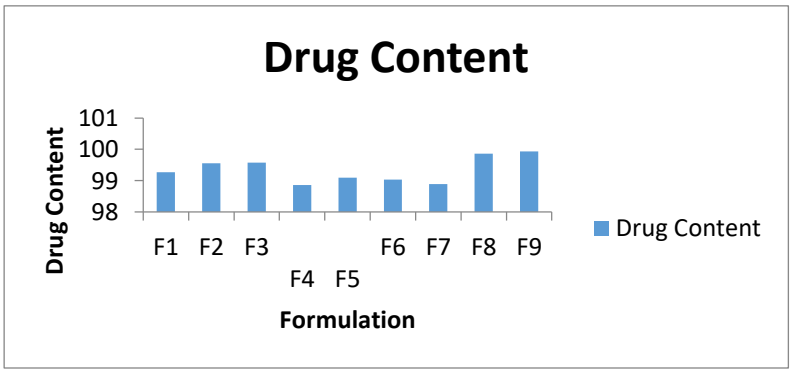

Fig 7: drug content of all formulation (all values are mean±SD, n=3)

In-vitro Drug Release

Table 8. Percentage of Drug release (mean ±SD) n=3 of formulation F1 to F9.

Time	In vitro %Drug release of laminated film (mean± SD) n=3								
	F1	**F2**	**F3**	**F4**	**F5**	**F6**	**F7**	**F8**	**F9**
60	4.24± 0.55	0.8±0 .54	4.24±0. 54	1.7±0.2 7	4.24± 0.55	3.72±0. 48	1.86±0. 89	5.48±0.2 9	4.27±0. 23
120	11.35 ±1.01	3.3±0 .35	5.69±0. 78	6.9±0.3 4	8.12± 0.27	6.63±0. 34	4.44±0. 79	11.86±0. 34	10.01± 0.29
180	11.56 ±0.35	4.6±0 .78	8.12±1. 012	10.72± 0.56	13.63 ±1.07	11.21± 1.09	8.84±1. 29	11.81±0. 789	12.97± 0.27
240	20.63 ±1.01	7.06± 1.07	13.64± 1.68	13.56± 0.67	16.59 ±0.78	13.89± 0.27	14.94± 0.67	22.88±0. 30	16.98± 0.20
300	24.19 ±1.89	15.45 ±0.45	16.59± 1.09	17.78± 1.07	22.12 ±0.39	19.17± 0.27	19.46± 0.89	26.73±0. 39	23.56± 1.30
360	27.01 ±0.90	24.96 ±1.67	22.21± 0.89	18.7±0. 36	32.68 ±0.46	21.11± 1.09	28.12± 1.20	34.56±1. 89	28.25± 0.68
420	32.95 ±1.56	30.47 ±1.08 7	32.39± 1.01	23.58± 0.76	41.1± 1.01	30.03± 1.27	34.7±0. 35	39.4±0.2 5	39.16± 1.89
480	40.61 ±1.01	40.86 ±1.78	41.1±1. 78	34.02± 0.58	46.29 ±1.07	37.58± 1.07	44.24± 0.78	48.33±0. 83	50.09± 0.49
540	46.24 ±0.54	46.24 ±0.96	46.24± 0.87	38.56± 1.05	46.86 ±1.02	45.73± 1.00	51.22± 1.68	58.14±1. 89	62.58± 1.67
600	49.41 ±0.99	49.19 ±1.35	49.41± 1.45	43.79± 1.05	51.53 ±1.01	52.96± 1.03	55.46± 0.69	68.02±1. 67	71.55± 1.69
660	58.62 ±1.29	56.96 ±1.45	60.1±1. 67	47.61± 1.09	59.72 ±1.89	69.87± 1.78	71.76± 1.08	77.76±1. 24	80.36± 1.09
720	72.26 ±1.54	77.92 ±0.54	78.59± 1.50	67.24± 1.34	77.37 ±1.07 8	82.72± 1.33	87.87± 1.10	90.15±1. 23	92.07± 1.29

In vitro skin permeation study

Cumulative amount of drug diffuse through the human cadaver skin of all formulation without PE.

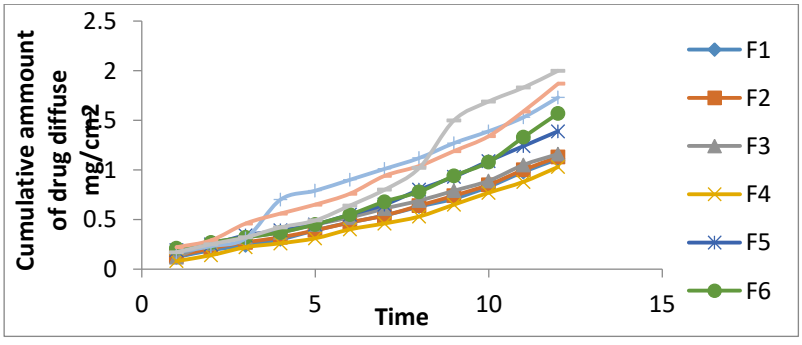

Fig.8: Plot of Cumulative amount of drug diffuse vs. Time of formulation F1to F9

In vitro skin permeation study with permeation enhancer

Cumulative amount of drug permeated through the human cadaver skin of all formulation with PE.

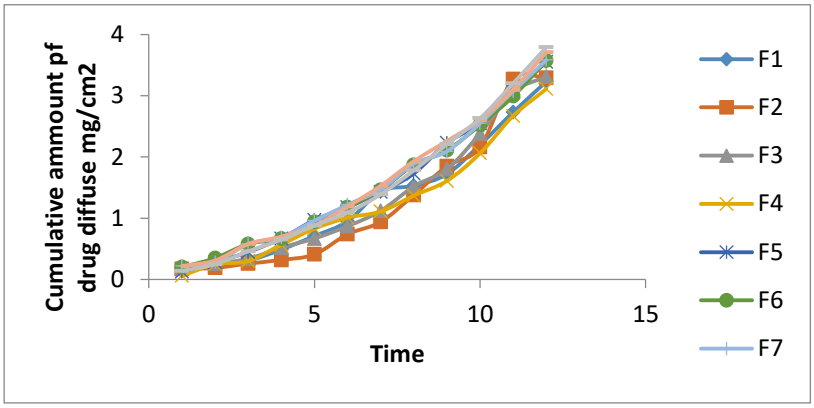

Fig. 9: Plot of Cumulative amount of drug diffuse vs. Time of formulation F1to F9

Table 9: Permeation kinetics with PE

Formu-lation code	R value					Best fit model	Parameters for Korsemeyer Peppas equation	
	Zero order	First order	Matrix	Peppas	Hixson Crowell		K	n
MC1	0.9759	0.9291	0.8543	0.9711	0.9481	**Zero order**	0.03	1.12
MC2	0.9402	0.8800	0.8992	0.9397	0.9028	**Zero order**	0.02	1.13
MC3	0.9640	0.8995	0.8378	0.9710	0.9243	**Peppas**	0.05	1.07
MC4	0.9780	0.9257	0.8627	0.9933	0.9468	**Peppas**	0.02	1.32
MC5	0.9881	0.9262	0.8785	0.9986	0.9532	**Peppas**	0.02	1.19
MC6	0.9914	0.9284	0.8912	0.9942	0.9586	**Peppas**	0.08	1.03
MC7	0.9903	0.9272	0.8886	0.9673	0.9557	**Zero order**	0.07	1.03
MC8	0.9813	0.9180	0.8850	0.9885	0.8505	**Peppas**	0.08	1.03
MC9	0.9799	0.8976	0.8615	0.9948	0.9329	**Peppas**	0.02	1.19

Drug release parameters of transdermal patch in *ex-vivo* permeation study

Table 10: Drug release parameters of laminated transdermal patch in *ex-vivo* permeation study

Sr.No.	Formulation	Jss (ug/cm^2/hr)		Kp (cm/hr)		Enhancement Ratio
		Without PE	With PE	Without PE	With PE	
1	F1	17.02	63.89	1.07	2.68	2.90
2	F2	16.62	60.89	1	2.67	2.89
3	F3	15.58	64.13	0.98	2.65	2.85
4	F4	16.17	63.40	1.42	7.66	3.01
5	F5	19.53	55.69	0.80	3.29	2.55
6	F6	26.67	61.66	0.97	2.41	2.27
7	F7	19.33	63.12	0.84	2.20	2.06
8	F8	28.80	61.31	0.99	2.14	1.98
9	F9	21.11	66.97	0.92	3.59	1.89

Multiple regression analysis for 3^2 factorial designs

Table 11: Multiple regression analysis for 3^2 factorial designs

Source	Degree of freedom	Sum square	Mean square	F-value	Prob>F
Y_1= Diffusion study					
Model	2	0.36	0.18	14.05	0.0054
X_1	1	0.27	0.27	20.84	0.0038
X_2	1	0.094	0.094	7.27	0.0358
	R^2=0.8241	AdjR^2=0.7655	PredR^2=0.6246	SD=0.11	CV=3.28
Equation	**$Y_1=3.46+0.21X_1+0.12X_2$**				
Y_2=Drug content					

Model	5	1.17	0.23	13.95	0.0274
X_1	1	0.33	0.33	19.82	0.0211
X_2	1	0.28	0.28	16.85	0.0262
X_1X_2	1	8.100E-003	8.100E-003	0.48	0.5364
X_1^2	1	0.54	0.54	32.56	0.0107
X_2^2	1	3.556E-004	3.556E-004	0.021	0.8933
	R^2=0.9588	Adj R^2=0.8900	Pred R^2=0.5129	SD=0.13	CV=0.13
Equation	**Y_2= 98.90+0.24 X_1+0.22X_2-0.045X_1X_2+0.52 X_1^2-0.013 X_2^2**				
Y_3=Tensile strength					
Model	2	2233.01	1116.51	8.36	0.0184
X_1	1	*188.38*	*188.38*	*1.41*	*0.2798*
X_2	1	*2044.63*	*2044.63*	*15.31*	*0.0079*
	R^2=0.7360	Adj R^2=0.6480	Pred R^2=0.5262	SD=0.56	CV=13.04
Equation	**Y_3= 88.61+5.60X_1+18.46X_2**				

Source	**Degree of freedom**	**Sum square**	**Mean square**	**F-value**	**Prob>F**
Y_4= Moisture content					
Model	5	7.18	1.44	15.59	0.0234
X_1	1	0.79	0.79	8.60	0.0609
X_2	1	1.02	1.02	11.09	0.0447
X_1X_2	1	0.029	0.029	0.31	0.6145
X_1^2	1	5.33	5.33	57.81	0.0047
X_2^2	1	0.014	0.014	0.15	0.7217
	R^2=0.9629	AdjR^2=0.9011	PredR^2=0.5571	SD=0.30	CV=14.72
Equation	**Y_4=2.91-0.63X_1-0.41X_2-0.18X_1X_2-1.36X_1^2+0.084X_2^2**				
Y_5=Moisture uptake					
Model	5	3.99	0.80	17.29	0.0202
X_1	1	0.35	0.35	7.58	0.0705
X_2	1	0.56	0.56	12.10	0.0401
X_1X_2	1	7.225E-003	7.225E-003	0.16	0.7190
X_1^2	1	3.07	3.07	66.42	0.0039
X_2^2	1	7.688E-003	7.688E-003	0.17	0.7108
	R^2=0.9588	Adj R^2=0.8900	Pred R^2=0.5129	SD=0.13	CV=0.13
Equation	**Y_5= 1.59+0.24 X_1+0.31X_2-0.042X_1X_2+1.24 X_1^2-0.062 X_2^2**				

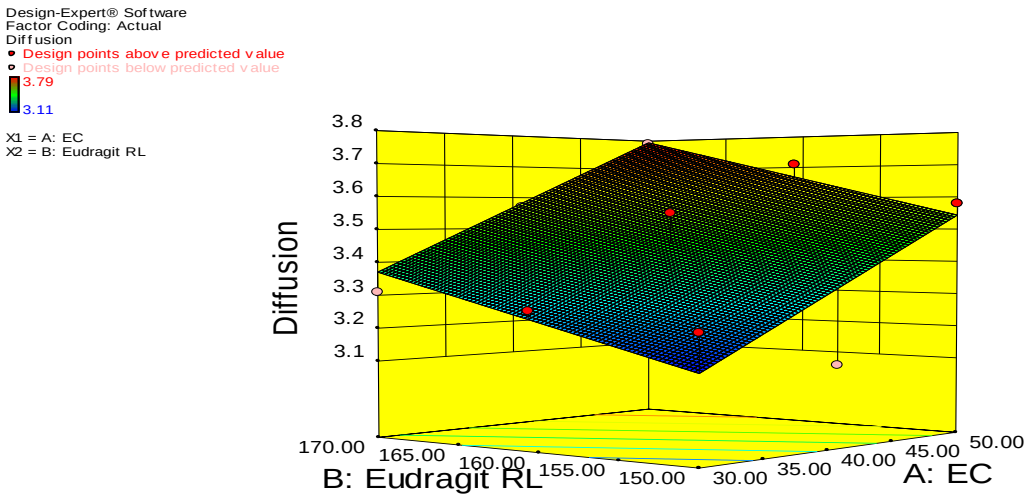

Fig 10: Response Surface Plot showing effect of variables on Cumulative amount of drug diffuse at t_{12}Hr of transdermal patch

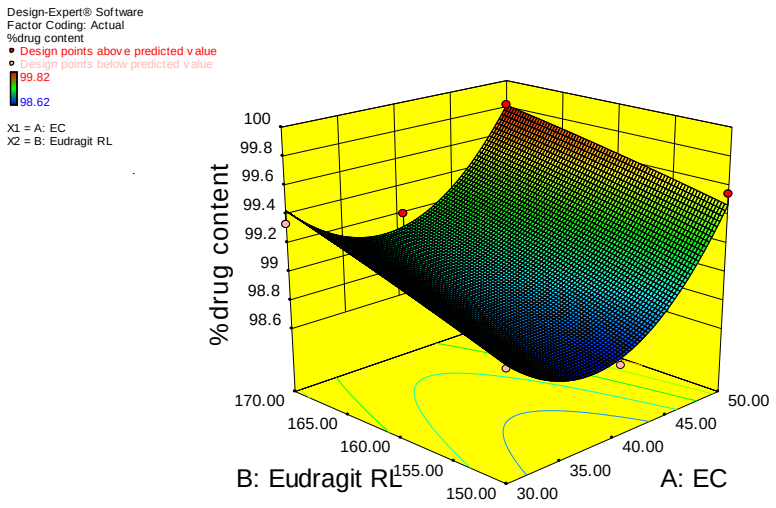

Fig. 11: Response Surface Plot showing effect of variables on Drug content of transdermal patch.

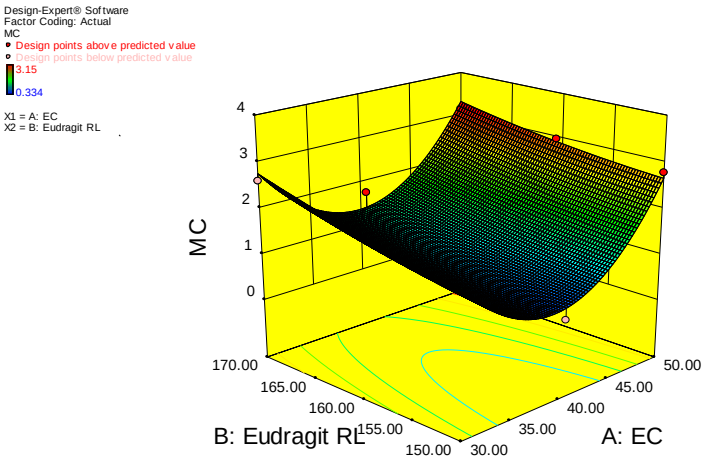

Fig. 12: Response Surface Plot showing effect of variables on Moisture content of transdermal patch.

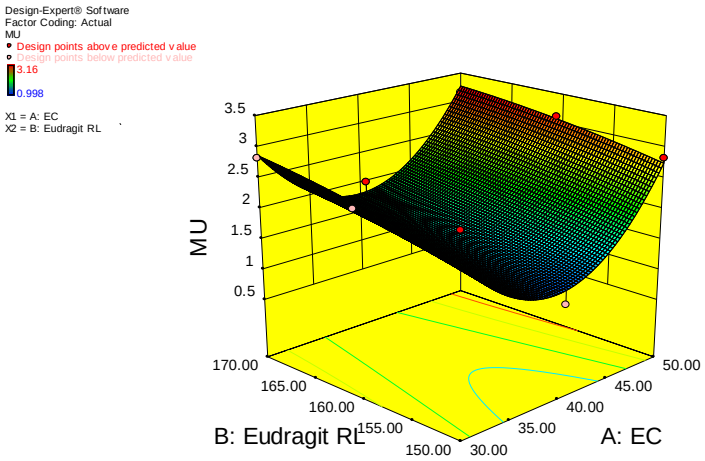

Fig. 13: Response Surface Plot showing effect of variables on Moisture uptake of transdermal patch

Optimization

Constraints:

Table 12: Constraints for optimization as per Design Expert Software

Name	Goal	Lower Limit	Upper Limit
Ethyl cellulose	In range	30	50
Eudragit RL100	In range	150	170
In vitro drug release at t_{12}Hr	Target- 3.75	3.11	3.79
Drug content	Target- 99.80	99.62	99.82
Tensile strength	Target- 109.70	62.87	110.94
Moisture content	Target- 0.334	0.334	3.15
Moisture uptake	Target- 0.334	0.998	3.16

Solution:

Table 13: Solution for optimization as per Design Expert Software.

No.	Ethyl cellulose	Eudragit RL 100	In vitro drug release at t_{12}Hr	Drug content	Tensile strength	Moisture content	Moisture uptake
1	49.70	169.5	3.71	99.43	109.75	2.24	2.47

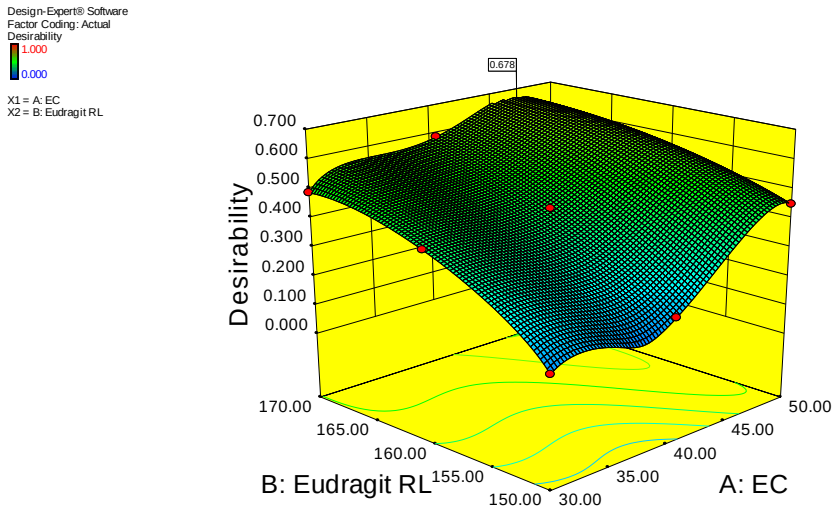

Fig. 14: Response Surface Plot showing Desirability for optimized formulation.

From the solution for optimization as per Design Expert Software it can be concluded as **F9 formulation** is the best formulation with desirability factor **0.678.**

4. CONCLUSION

The metoclopramide hydrochloride transdermal patch was prepared successfully using differeent concentration of eudragit RL And ethyl cellulose and shown good promising results for all evaluated parameters .

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