



**FORMULATION AND EVALUATION OF TRANSDERMAL PATCHES OF  
METOCLOPRAMIDE HYDROCHLORIDE**

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**ABSTRACT**

The skin can be used as the site for drug administration for continuous transdermal drug infusion into the systemic circulation. For the continuous diffusion/penetration of the drugs through the intact skin surface membrane-moderated systems, matrix dispersion type systems, adhesive diffusion controlled systems and micro reservoir systems have been developed. In the present work, an attempt has been made to develop a matrix-type transdermal therapeutic system comprising of Metoclopramide-HCl with different ratios of hydrophilic and hydrophobic polymeric combinations using solvent evaporation technique. The physicochemical compatibility of the drug and the polymers was studied by infrared spectroscopy. The results obtained showed no physical-chemical incompatibility between the drug and the polymers. The patches were further subjected to various physical evaluations along with the *in-vitro* permeation studies using rat skin. On the basis of results obtained from the *in-vitro* study and physical evaluation of the patches. The drug release study and permeation studies of matrix films showed that cumulative % drug released (% CDR) and cumulative % drug permeation (% CDP) were observed to be increased, on increasing concentration of hydrophilic polymer while decreasing concentration of lipophilic polymer decreased % cumulative drug release and % cumulative drug permeation respectively were obtained. By using lipophilic polymer along with hydrophilic polymer combination, release rate and permeation rate can be achieved in controlled manner for longer time period.

**KEYWORDS:** Metoclopramide, Transdermal Film, Permeation enhancer.

**INTRODUCTION**

Transdermal drug delivery system is a therapeutic system designed to transfer drugs through intact skin for systemic treatment. It offers controlled drug release pattern by a simple application to the skin's surface, eliminating the vagaries influencing the gastrointestinal absorption associated with oral administration and providing for more efficient drug utilization. It offers various advantages such as: avoidance the risk and inconvenience of intravenous therapy (noninvasive), avoidance of first pass hepatic metabolism thus increasing bioavailability and efficacy of drugs, no gastrointestinal degradation (pH, enzymatic activity, drug interaction with food, drink and other orally administered drugs) and substitute for oral administration of medication when that route is unsuitable as with vomiting and diarrhoea.<sup>[1-2]</sup> Patients, particularly pediatric and geriatric patients, have difficulty in swallow in solid dosage forms. These patients are unwilling to take these solid preparations due to a fear of choking. To overcome these difficulties there is a need for the development of new drug delivery system; which will improve the therapeutic efficacy and safety of drugs by more precise (i.e. site specific), spatial and temporal

placement within the body thereby reducing both the size and number of doses. One of the methods most often utilized has been transdermal drug delivery –meaning transport of therapeutic substances through the skin for systemic effect. Closely related is percutaneous delivery, which is transport into target tissues, with an attempt to avoid systemic effects. Metoclopramide hydrochloride a derivative of paraaminobenzoic acid, is a commonly prescribed drug used for the management of gastrointestinal disorders such as gastric stasis, gastroesophageal reflux<sup>[3]</sup> and for the prevention of cancer chemotherapy- induced emesis. In general, emesis is preceded with nausea and in such condition it is difficult to administer drug with a glass of water; hence it is beneficial to administer such drugs as TDDS.<sup>[4]</sup> The objectives of the investigations were to formulate transdermal patches using Carbopol 934P and Ethyl cellulose, evaluate the patches and study the release profile and release mechanisms from patches.

**MATERIALS AND METHODS**

The drug Metoclopramide was obtained as gift sample from JBCPL, Ancleshwer (India). Carbopol 934P and

Ethylcellulose was purchased from Remkem Lab Pvt Ltd. All other chemicals used were of analytical grade.

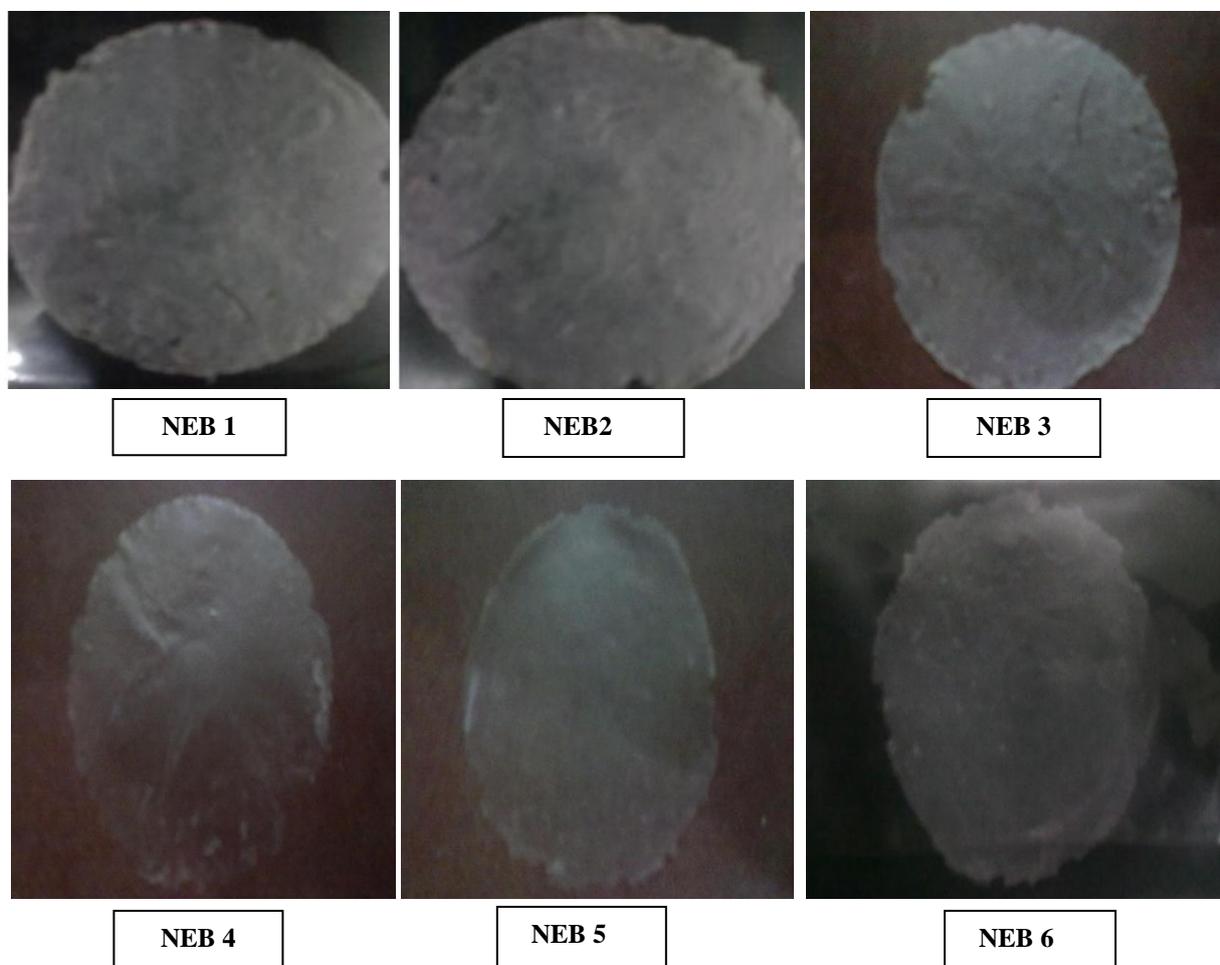
#### Formulation of Metoclopramide Hydrochloride Transdermal Patches

Transdermal patches of Metoclopramide hydrochloride were prepared by solvent evaporation technique. The matrix-type transdermal patches containing Metoclopramide HCl were prepared using different ratios of ethyl cellulose and carbopol 934P. Polymers in different ratios were dissolved in methanol then drug was added slowly to the polymeric solution. To the mixture,

Propylene glycol (0.2 ml) as plasticizer and Span 80 (0.1 ml) as permeation enhancer were added and mixed. The dispersion was poured within a glass bangle in a glass plate previously lubricated with Light liquid paraffin. The plate was kept aside for drying at room temperature for 24 hrs. Inverted funnel was placed over the glass plates to prevent the current of air. After drying, the patches were peeled from glass plates, wrapped in aluminum foil and preserved in desiccator for further studies. Compositions of different formulations NEB1 to NEB6 are represented in Table.1 and photographs are shown below.

**Table 1: Different formulation compositions of Metoclopramide Hydrochloride transdermal patches.**

Formulations	Metoclopramide Hydrochloride (mg)	EC:CP (mg)	Span 80 (ml)	Propylene glycol (ml)
NEB1	11	200:200	0.1	0.2
NEB2	11	133:267	0.1	0.2
NEB3	11	100:300	0.1	0.2
NEB4	11	267:133	0.1	0.2
NEB5	11	300:100	0.1	0.2
NEB6	11	320:80	0.1	0.2



**Fig. 1: Formulated Metoclopramide HCl Transdermal patches.**

## EVALUATION PARAMETERS

### Physical Appearance

All the prepared patches were kept under visual observation for 7 days, it was observed that patches were found to be transparent, clear, soft & smooth. Film appearance showed that the uniform films were formed.<sup>[5]</sup>

### Thickness uniformity

Thickness of the prepared patches were measured in 3 different points by using a vernier caliper and determined the average thickness.<sup>[6]</sup>

**Table 2: Thickness parameters of Metoclopramide hydrochloride transdermal patches.**

Formulation Code	Average Thickness (mm)
NEB1	0.043
NEB2	0.047
NEB3	0.030
NEB4	0.040
NEB5	0.047
NEB6	0.056

### Weight uniformity

For each formulation, three randomly selected patches were used. For weight variation test, 3 films from each

batch were weighed individually by Digital electronic balance and the average weight was calculated.<sup>[7]</sup>

**Table 3: Weight variation parameter of Metoclopramide hydrochloride transdermal patches.**

Formulation Code	Average Weight (gm)
NEB1	0.104
NEB2	0.134
NEB3	0.154
NEB4	0.054
NEB5	0.073
NEB6	0.055

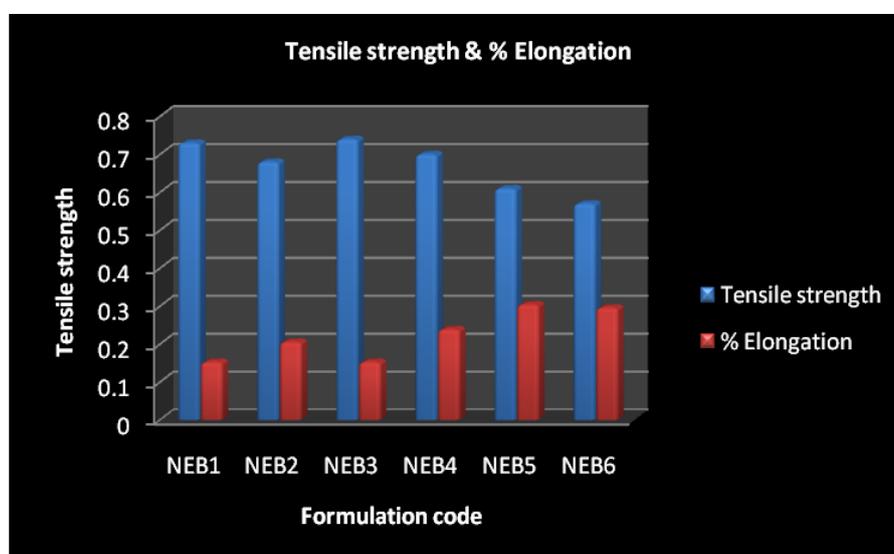
### Tensile Strength

The films were taken in rectangular containers using proportionate quantity of the solution calculated on the basis of area. The films were cut into strips of 1cm width and 15cm length. The films were fixed onto the Tensile strength apparatus in such a way that the length of film between the jaws was initially 10 cm. The trials where the breakage occurred at the jaw were invalid and the result was repeated on another strip.<sup>[7-8]</sup> The Tensile strength was calculated by the formula, Tensile strength = Break force [1 + change in length] / (width) (breadth) [initial length of the film].

% Elongation = [Final length - Initial length] / Initial length \* 100.

**Table 4: Tensile strength & % elongation parameter of Metoclopramide hydrochloride transdermal patches**

Formulation code	Tensile strength	% Elongation
NEB1	0.73	15.24%
NEB2	0.68	20.53%
NEB3	0.74	15.24%
NEB4	0.70	23.86%
NEB5	0.61	30.4%
NEB6	0.57	29.56%



**Fig 2: Comparative Tensile strength & % Elongation studies of all Metoclopramide hydrochloride matrix transdermal patch formulations.**

**Folding endurance**

A strip of specific area (2×2 cm<sup>2</sup>) was cut evenly and repeatedly folded at same place till it was broken. The number of times the films could be folded without breaking/ cracking gives the value of the folding endurance, and if the film shows any crack it was taken as end point.<sup>[8]</sup>

**Table 5: Folding endurance studies of Metoclopramide hydrochloride transdermal patch formulations.**

Formulation Code	Average Folding endurance
NEB1	133.6
NEB2	145.6
NEB3	157.6
NEB4	111.6
NEB5	93.6
NEB6	82

**Percentage Moisture Absorption Studies**

The physicochemical studies like moisture absorption (uptake) provide information regarding the stability of the formulations.<sup>[8]</sup> The accurately weighed films were kept in desiccators at room temperature for 24 hours, containing saturated solution of potassium chloride in order to maintain 80-90% RH. After 24 hours the films were taken out and reweighed. After 72 hours films are again weighed. The percentage moisture uptake was calculated from the formula mentioned below.

$$\text{Percentage Moisture Uptake} = \left[ \frac{\text{Final weight} - \text{Initial weight}}{\text{Initial weight}} \right] \times 100$$

**Table 6: Percentage moisture uptake studies of Metoclopramide hydrochloride matrix transdermal patch formulations for 24 hours at 80-90% RH.**

Formulation Code	% Moisture Absorption
NEB1	7.071
NEB2	9.231
NEB3	13.54
NEB4	5.56
NEB5	2.89
NEB6	1.818

**Percentage Moisture Loss Determination**

The moisture loss studies provide information regarding the stability of formulations. The prepared films are to be weighed individually and to be kept in desiccators containing fused calcium chloride at room temperature for 72 hours. After 72 hours the films are taken out and reweighed.<sup>[8]</sup> The percentage moisture loss was calculated from the formula mentioned below.

$$\% \text{ Moisture Loss} = \left[ \frac{\text{Initial weight} - \text{Final weight}}{\text{Final weight}} \right] \times 100$$

**Table 7: Percentage moisture loss studies of Metoclopramide hydrochloride matrix transdermal patch formulations for 24 hours at 80-90% RH.**

Formulation Code	% Moisture Loss
NEB1	10.23
NEB2	10.16
NEB3	12.85
NEB4	6.25
NEB5	5.79
NEB6	5.35

**Water Vapour Transmission Rate (WVTR) Determination**

WVTR is defined as the quantity of moisture transmitted through unit area of the film in unit time.<sup>[9]</sup> This is expressed as gm/hr cm<sup>2</sup>. Glass vials of 5 ml capacity were washed, dried to a constant weight in oven. 1 gram of fused calcium chloride was taken in the vials and the polymer films of 2.25 cm<sup>2</sup> was fixed over a brim of each vials separately with the help of adhesive tape. Then the vials were weighed and stored in a humidity chamber of 80-90% RH condition for a period of 24 hours and 72 hours. Each vials were then removed and reweighed after 24 hours and 72 hours of the storage and weight gain was noted. Transmission rate was calculated by using formula given below.

$$\text{Water Vapour Transmission rate} = W \times L / S$$

Where, W= gram of water transmitted, L= thickness of the film in centimeter, S= exposed surface area of the film in cm<sup>2</sup>.

**Table 8: Water vapour transmission rate studies of Metoclopramide hydrochloride matrix transdermal patch formulations for 24 & 72 hours at 80-90% RH.**

Formulation Codes	WVTR in gm/ hr cm <sup>2</sup>	
	After 24 hrs	After 72 hrs
NEB1	0.00293	0.00389
NEB2	0.00264	0.00373
NEB3	0.0032	0.0046
NEB4	0.0039	0.0051
NEB5	0.0042	0.0071
NEB6	0.0048	0.00843

**Drug content**

Drug content of the prepared transdermal patch was determined by the procedure reported by Pullakandam *et al* (2009) with slight modification.<sup>[10]</sup> Specified area of patch (1cm<sup>2</sup>) were cut and dissolved in 10 ml of methanol then volume was made up to 100 ml with phosphate buffer saline of pH 7.4. The medium was stirred with magnetic bead. The content were filtered using whatmann filter paper and the filtrate was examined for the drug content against the reference solution consisting of plaNEBo films (containing no

drug) with the UV spectrophotometer (Shimadzu 1700) at  $\lambda_{\max}$  273 nm and average was calculated.

**Table 9: Percentage drug content profiles of Metoclopramide hydrochloride transdermal patch formulations by using phosphate buffer pH 7.4.**

Formulation Code	% Drug content
NEB1	92.8
NEB2	98.182
NEB3	96.184
NEB4	89.09
NEB5	85.45
NEB6	80

#### ***In vitro* drug release studies**

*In vitro* drug release studies were performed as per procedure reported by (Shivaraj *et al* 2010) with slight modification.<sup>[11-12]</sup> By using Franz diffusion cell with receptor compartment of capacity of 20 ml and by

mounting the synthetic cellophane membrane between the donor & receptor compartment of the diffusion cell, *in vitro* drug release studies was performed. The formulated patches were cut into size of 1cm<sup>2</sup> and placed over the drug releasing membrane and the receptor compartment of the diffusion cell was filled with phosphate buffer pH 7.4. The whole assembly was fixed on magnetic stirrer and the solution in the receptor compartment was constantly and continuously stirred using magnetic bead at 50 rpm; the temperature was maintained at 37°C then sample of 5 ml was withdrawn at the time interval of 0, 0.25, 0.75, 1, 2, 3, 4 and 24 hours and analysed for the drug content spectrophotometrically at  $\lambda_{\max}$  273 nm against blank solution. The receptor compartment (phase) was replenished with an equal volume of phosphate buffer pH 7.4 at each time of the sample withdrawal. The cumulative amount of drug released per square centimeter of the patches was plotted against time.

**Table 10: *In vitro* drug release studies of Metoclopramide hydrochloride matrix transdermal patch formulation NEB 1.**

Time (hours)	$\sqrt{T}$	Absorbance	Amount of drug (mg)	% Cumulative drug released	Log % Cumulative drug remaining to be released
0	0	0	0	0	2
0.25	0.5	0.020	0.0254	5.48	1.975
0.5	0.707	0.032	0.0472	10.172	1.953
0.75	0.866	0.044	0.069	14.89	1.929
1	1	0.063	0.1036	22.328	1.890
2	1.414	0.082	0.138	29.78	1.846
3	1.732	0.105	0.18	38.79	1.786
4	2	0.129	0.22	48.198	1.714
24	4.898	0.221	0.391	84.26	1.197

**Table 11: *In vitro* drug release studies of Metoclopramide hydrochloride matrix transdermal patch formulation NEB 2**

Time (hours)	$\sqrt{T}$	Absorbance	Amount of drug (mg)	% Cumulative drug released	Log % Cumulative drug remaining to be released
0	0	0	0	0	2
0.25	0.5	0.016	0.0182	3.71	1.984
0.5	0.707	0.026	0.0364	7.42	1.966
0.75	0.866	0.037	0.0564	11.5	1.947
1	1	0.051	0.0818	16.69	1.921
2	1.414	0.079	0.133	27.14	1.862
3	1.732	0.098	0.167	34.08	1.819
4	2	0.131	0.227	46.32	1.729
24	4.898	0.246	0.436	89	1.041

**Table 12: *In vitro* drug release studies of Metoclopramide hydrochloride matrix transdermal patch formulation NEB 3**

Time (hours)	$\sqrt{T}$	Absorbance	Amount of drug (mg)	% Cumulative drug released	Log % Cumulative drug remaining to be released
0	0	0	0	0	2
0.25	0.5	0.013	0.0254	5.48	1.976
0.5	0.707	0.022	0.0472	10.172	1.953
0.75	0.866	0.046	0.0728	15.69	1.926
1	1	0.084	0.1418	30.56	1.842
2	1.414	0.126	0.218	47.026	1.724
3	1.732	0.179	0.315	67.888	1.506
4	2	0.243	0.430	92.86	0.854
24	4.898	0.003	-	-	-

**Table 13: *In vitro* drug release studies of Metoclopramide hydrochloride matrix transdermal patch formulation NEB 4.**

Time (hours)	$\sqrt{T}$	Absorbance	Amount of drug (mg)	% Cumulative drug released	Log % Cumulative drug remaining to be released
0	0	0	0	0	2
0.25	0.5	0.014	0.0146	3.146	1.986
0.5	0.707	0.025	0.0345	7.75	1.965
0.75	0.866	0.045	0.071	15.95	1.925
1	1	0.057	0.0928	20.85	1.898
2	1.414	0.084	0.1418	31.86	1.833
3	1.732	0.107	0.184	41.35	1.768
4	2	0.131	0.227	51.01	1.690
24	4.898	0.207	0.365	82.124	1.252

**Table 14: *In vitro* drug release studies of Metoclopramide hydrochloride matrix transdermal patch formulation NEB 5.**

Time (hours)	$\sqrt{T}$	Absorbance	Amount of drug (mg)	% Cumulative drug released	Log % Cumulative drug remaining to be released
0	0	0	0	0	2
0.25	0.5	0.012	0.0109	2.535	1.989
0.5	0.707	0.019	0.0236	5.527	1.975
0.75	0.866	0.034	0.0509	11.92	1.945
1	1	0.050	0.08	18.73	1.909
2	1.414	0.070	0.116	27.166	1.862
3	1.732	0.091	0.155	36.3	1.804
4	2	0.123	0.213	49.88	1.700
24	4.898	0.190	0.335	78.45	1.333

**Table 15: *In vitro* drug release studies of Metoclopramide hydrochloride matrix transdermal patch formulation NEB 6.**

Time (hours)	$\sqrt{T}$	Absorbance	Amount of drug (mg)	% Cumulative drug released	Log % Cumulative drug remaining to be released
0	0	0	0	0	2
0.25	0.5	0.011	0.0091	2.27	1.990
0.5	0.707	0.016	0.0182	4.55	1.979
0.75	0.866	0.023	0.031	7.72	1.965
1	1	0.044	0.069	17.27	1.918
2	1.414	0.061	0.1	25	1.875
3	1.732	0.082	0.138	34.54	1.816
4	2	0.098	0.167	41.75	1.765
24	4.898	0.154	0.269	67.25	1.515

**Table 16: Summary of using various release kinetic models.**

Formulation Codes	ZERO ORDER MODEL		FIRST ORDER MODEL		HIGUCHI MODEL		CONCLUSION
	SLOPE	$R_1^2$	SLOPE	$R_2^2$	SLOPE	$R_3^2$	
NEB1	3.061	0.795	-0.031	0.957	17.92	0.955	Follow First order kinetic
NEB2	3.378	0.851	-0.039	0.985	19.29	0.973	Follow First order kinetic
NEB3	23.02	0.992	-0.255	0.893	48.05	0.920	Follow Zero order kinetic
NEB4	2.995	0.739	-0.029	0.931	17.85	0.922	Follow First order kinetic
NEB5	2.929	0.752	-0.026	0.932	17.32	0.922	Follow First order kinetic
NEB6	2.506	0.732	-0.019	0.864	14.92	0.910	Follow Higuchi model

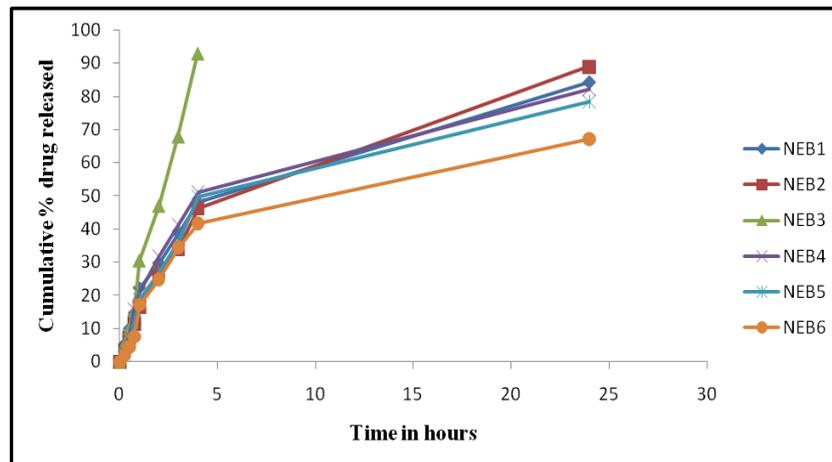


Fig 3: Comparative in vitro drug release studies of various Metoclopramide hydrochloride transdermal patches, for Zero order release kinetic model.

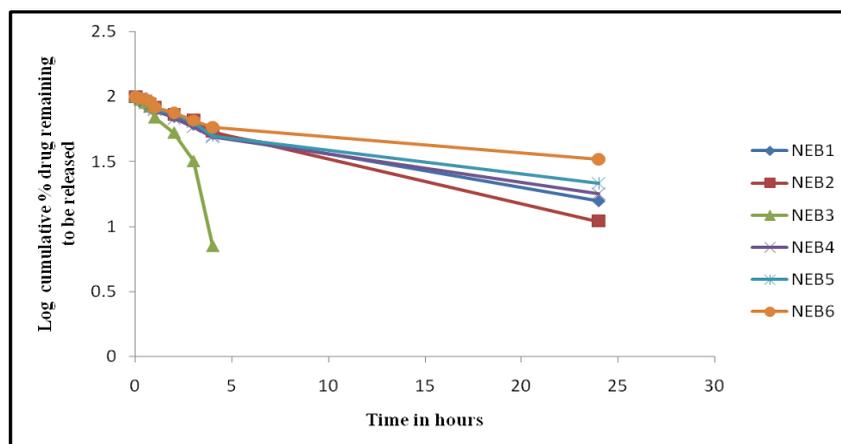


Fig 4: Comparative in vitro drug release studies of various Metoclopramide hydrochloride transdermal patches, for First order release kinetic model.

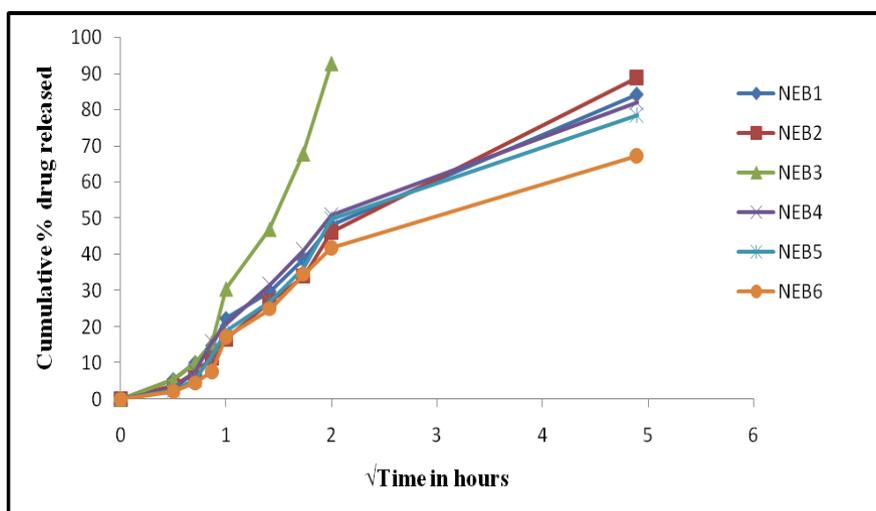


Fig 5: Comparative in vitro drug release studies of various Metoclopramide hydrochloride transdermal patches, for Higuchi release kinetic model.

## RESULTS AND DISCUSSION

The prepared films were smooth, flexible and uniform. The thickness of the patches was varied from 0.030 mm to 0.056 mm. The film shows increase in thickness was linear with polymer concentration. The results are

tabulated in Table 2. The weight of the patches was varied from 54 mg to 154 mg. The results were tabulated in Table 3. The tensile strength & % elongation were determined and results was tabulated in table 4. The folding endurance was measured manually, the result

showed that folding endurance was found to be maximum for formulation NEB3 (157.6 folds) whereas, minimum for formulation NEB6 (82 folds) was observed. The result was tabulated in table 5. The result showed that moisture uptake was found to be maximum for formulation NEB3 (13.54) whereas moisture uptake observed to be minimum for formulation NEB6 (1.818). The result are recorded in Table 6. The result showed that percentage moisture content was found to be maximum for formulation NEB3 (12.85) whereas, minimum for formulation NEB6 (5.35) was observed. The result are recorded in Table 7. The result showed after 24 hours that water vapour transmission rate was found to be maximum for formulation NEB6 (0.0048) whereas, minimum for formulation NEB2 (0.00264) was observed. Similar results were obtained after 72 hours. The result are recorded in Table 8. The results showed that the drug content of the Metoclopramide hydrochloride transdermal patches was ranging between 80% to 98.182%. The results showed that the drug content was found to be maximum for formulation NEB2 (98.182%) whereas drug content observed to be minimum for formulation NEB6 (80%). The results were recorded in Table 9. The results showed that *in vitro* drug release of Metoclopramide hydrochloride transdermal patches was found to be maximum for formulation NEB3 (92.86%) in 4 hours and for formulation NEB2 (89 %) in 24 hours respectively whereas, after 24 hours *in vitro* drug release observed to be minimum for formulation NEB6 (67.25 %). The results are recorded in Table 10-16 and shown graphically in figure 3-5. Different release kinetics (zero order, first order & Higuchi order) mechanism were tabulated in Table 6.15 showed zero order release kinetics for formulation NEB3 having  $R^2 = 0.992$  & slope = 23.02, as compared to the formulation NEB1, NEB2, NEB4, NEB5 showed first order release kinetic mechanism because *in vitro* drug release kinetics varies from  $R^2 = 0.931$  to 0.985 and NEB6 showed Higuchi model having  $R^2 = 0.910$  & slope = 14.92 were shown in graphically figure 3-5.

## CONCLUSION

Metoclopramide HCl is an anti-nauseated and antiemetic agent indicated for the prevention of nausea and vomiting associated with moderately-emetogenic cancer chemotherapy and for the prevention of postoperative nausea and vomiting. The chemotherapeutic agents produce nausea and vomiting by releasing serotonin from the enterochromaffin cells of the small intestine, and that the released serotonin then activates 5-HT<sub>3</sub> receptors located on vagal efferents to initiate the vomiting reflex. Therefore Metoclopramide HCl works by blocking the reception of serotonin at these 5-HT<sub>3</sub> receptors. Metoclopramide HCl has the half-life of 5-6 hours. Its total bioavailability in the body is 60% due to first pass metabolism. The total dose of Metoclopramide HCl is Oral: 0.5 mg/kg every 6 hours on days 2 to 4 hours before chemotherapy and repeat 2 hours after chemotherapy. In this work an attempt was made to formulate and evaluate TDDS for sustained release

Metoclopramide HCl by solvent casting method. Low molecular weight, good permeability and shorter half-life of Metoclopramide HCl made it a suitable drug candidate for the development of transdermal patches. The main objective of formulating the transdermal system was to prolong the drug release time, reduce the frequency of administration and to improve patient compliance. The transdermal patches were prepared using solvent evaporation method using combination of EC and Carbopol 934P in various ratios using Propylene glycol as plasticizers and Span 80 as a permeation enhancer. Thickness, mass, folding endurance and drug content were found to be uniform and reproducible. In case of EC: Carbopol 934P films, flux and drug release rate increased with the increase in the concentrations of hydrophilic polymers i.e., Carbopol 934P. The highest drug release was observed with EC: Carbopol 934P 1:3 ratio (92.86%) in 4 hours and EC:Carbopol 934P 1: 2 ratio (89%) in 24 hours. The formulation NEB3 (EC:Carbopol 934P 1:3 ratio) shows optimum diffusion in concentration independent manner. The above formulation gave a maximum drug diffusion of 92.86% over a period of 4 hours. Higuchi's plot for the formulation NEB6 revealed that the predominant mechanism of drug release is diffusion. From the overall *in vitro* permeation studies it could be concluded that the polymeric matrix-type transdermal films of Metoclopramide hydrochloride prepared with the blends of hydrophobic (EC) and hydrophilic polymers (Carbopol 934P) in different ratios holds potential for transdermal delivery which gives a slow and controlled release of drug up to 24 h. Further the studies revealed that the problems of Metoclopramide hydrochloride on oral administration can be overcome by applying the drug topically in the form of transdermal films. As an extension of this work pharmacokinetic studies, *in-vivo* studies on higher animals and controlled clinical studies on human beings can be carried out in future.

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