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Research Article

## Development and Evaluation of Matrix Type Transdermal Patches of Torasemide

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### ABSTRACT

TDDS manufacture has numerous benefits over other routes like oral delivery. It avoids limitations linked with g.i.t. absorption, enzyme effect, interaction with drug and food. This route is suitable when patient is suffering from vomiting and diarrhea. Torasemide is a loop diuretic; it comes under category of sulfonamide. It is prescribed in the treatment of edema, CHF, and hypertension. Whenever it is used by oral route, it is associated with many side effects like vomiting, nausea, anorexia, and increased appetite. All transdermal patches were transparent and free from any particle. Release profile of twelve batches of Torasemide was done by the means of Franz cell for 7 hrs. Maximum release was shown by MTP6 (71.28±0.19) and least in formulations of batch code MTP7(24.47±0.04). *In-vitro* release data were plotted in 2 different models i.e. first and Korsmeyer peppas. It was observed that release was governed by the diffusion process. On basis of different properties MTP1 batch was found to be optimum. Study concludes that by the means of patches Torasemide can be administered efficiently.

**Keywords:** Torasemide, transdermal patches, HPMC, *in-vitro* release, stability studies, TDDS.

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### INTRODUCTION

Since previous years there are changes at major level in formulation technology. Innovations in drug delivery systems are not only related with novel pharmaceutical dosage forms but also resulted in development of new formulation for the treatment using existing drugs<sup>1</sup>. These innovations in drug delivery system offer advantages, like improved patient compliance, maintaining steady state concentration levels of drug for prolonged period, reduced dosing frequency, and reduced side effects. TDDS manufacture has numerous benefits over other routes like oral delivery<sup>2</sup>. It avoids limitations linked with g.i.t. absorption, enzyme effect, interaction with drug and food. This route is suitable when patient is suffering from vomiting and diarrhea. Reduced frequency of dose administration, and self medication is possible. Since ancient time, skin is used by humans to apply different types of substances for the intention of therapeutic effect<sup>3</sup>. In 20<sup>th</sup> century, skin is used for longer duration of delivery of different dosage forms. TDDS deliver drugs through skin. Transdermal Patch (TDP) is an adhesive system that is used after placing at skin surface<sup>4</sup>. By the means of patches use of syringe as in parenteral routes can be avoided. That is associated with pain and thus not comfortable for patient specially children. TDP were first developed in the 1970s,

and got approval through FDA in 1979. Initially these were limited for motion sickness having scopolamine. Later on TDP are continuously used for different purposes<sup>5,6</sup>.

Based on the amount of drug, patches are used over the skin for 1 to 7 days. In general drug is kept in large dose inside the patch, to place over the skin for a longer time. By the means of diffusion process, the drug goes directly to the blood via the skin. Drug continuously diffuses to the skin as there is large concentration is present in patch<sup>7</sup>. TDP contain membrane that controls the release of drug<sup>8-11</sup>.

Torasemide is a loop diuretic; it comes under category of sulfonamide. It is prescribed in the treatment of edema that is related with renal disease, CHF, or hepatic disease<sup>12,13</sup>. It is also recommended for the hypertension treatment. Whenever it is used by oral route, it is associated with many side effects like vomiting, nausea, anorexia, and increased appetite. Since this drug is used for the long term duration, so patient compliance is very necessary aspect prior to use of this drug. Furthermore Torasemide is having short half life about 3.5 hr, so that there is need of frequent drug administration to maintain the therapeutic level<sup>14</sup>. Matrix types of TDP are having advantages over others like easy to prepare without use of any sophisticated instrument and difficult procedure. Due to all these issues related with

Toraseamide, it is a suitable candidate to prepare TDP to get controlled release and to avoid side effects and frequent administration.

## MATERIALS AND METHODS

Toraseamide was obtained as gift sample from Schwitz Biotech. Memnagar, Ahmedabad, Gujrat, PG (Propylene glycol), Glycerine, PVP K30 were obtained from CDH, Delhi. Chitosan was obtained from Central Institute of Fisheries, Cochin as gift sample. HPMC K100 (gms) from Cipla, Maharashtra and Ethyl cellulose from Asia private Ltd. Goa were obtained. All other ingredients were of analytical grade.

### Formulation development:

Toraseamide was mixed with solvent plasticizer, penetrations enhancer and polymers according the mentioned ratio. The whole mixture was transferred to a petri dish having area of 55 cm<sup>2</sup>. In oven petri dishes, placed for 10 hrs with 40 °C temperature. In order to facilitate evaporation of the solvent, a funnel in inverted form placed over the solution. The prepared film was retrieved by the means of a blade and neutralized by NaOH (2 %). After it patches were stored in a desiccators for further use. Total of 12 formulations of TDP were prepared<sup>15</sup>.

### Evaluation of TDP

#### Physical Properties

##### 1. Thickness

Screw gauge was use for the measurement of the thickness of matrix patches<sup>16</sup>.

##### 2. Weight Uniformity

Five matrix patches having area of 2.009 cm<sup>2</sup> were selected and weighed. Average wt was calculated<sup>17</sup>.

##### 3. Content Uniformity

Matrix patches having area of 2.009 cm<sup>2</sup>, dissolved in 10 ml buffer. Later on % drug estimated through UV spectrophotometer at 232 nm<sup>44</sup> and by using prepared standard curve of the Toraseamide<sup>18</sup>.

##### 4. Folding Endurance

Matrix patches were folded many times at fixed position until their breakage. This test is for the estimation of elasticity of patches<sup>19</sup>.

##### 5. % ML ( % Moisture Loss)

Patches placed in a desiccators, having anhyd. CaCl<sub>2</sub>, with 80-90%RH. Samples were taken from the desiccators after three days and weighed for the estimation of change in wt. Following equation was used to find % ML<sup>20</sup>.

$$\% \text{ ML} = \frac{\text{WI} - \text{WF}}{\text{WI}} \times 100$$

Where, WI=Weight Initial, WF= Weight Final

##### 6. % MC ( Moisture Content)

At room temperature, Patches placed in desiccators, having silica. Patches were taken from desiccators , with 80-90%RH. and weighed continuously until a constant wt is shown by the patches<sup>21</sup>. Following equation was used to find % MC

$$\% \text{ Moisture content} = \frac{\text{WI} - \text{WF}}{\text{WI}} \times 100$$

Where, WI=Weight Initial, WF= Weight Final

##### 7. % MA (Moisture Absorption)

Patches placed in a desiccators, with 100 ml, AlCl<sub>3</sub> (79.50% RH). Samples were taken from the desiccators after three days and weighed for the estimation of change in wt. Following equation was used to find % MA<sup>22</sup>.

$$\% \text{ Moisture absorption} = \frac{\text{WF} - \text{WI}}{\text{WI}} \times 100$$

Where, WI=Weight Initial, WF= Weight Final

##### 8. WVTR (Water vap. transmission rate)

Same size Vials were used as the cells, cleaned, and dried. CaCl<sub>2</sub> (1.0 gm) added to cells, patches having area 2.076 cm<sup>2</sup> were placed at the brim. After weighing cells were placed in a desiccator having KCl with humidity 80-90%. Cells were withdrawn and weighed daily for 7 days. WVTR was calculated using below equation<sup>23</sup>

$$\text{WVTR} = \frac{\text{WF} - \text{WI}}{\text{TXA}} \times 100$$

Where, WI=Weight Initial, WF= Weight Final, T=Time, A= Area

##### 9. Flatness

Matrix patches of length of 1.5cm were cutted from the prepared film. After it, the differences in length due to flatness uniformity was estimated by the below formula-

$$\text{Constriction (\%)} = \frac{\text{LF} - \text{LI}}{\text{LI}} \times 100$$

Where, LF= length final, and LI = length initial

Patches showing 0% constrictions were considered to possess 100% flatness<sup>24</sup>.

##### 10. In-vitro release studies

For this study, locally fabricated Franz cell was used. This cell consists of donor and receptor compartment. A sampling port is attached with the receptor compartment to collect sample for the analysis. Both compartments are attached with rubber bands. Receptor compartment was filled with buffer of Ph 7.4, and rotated with magnetic bead. A patch was incorporated with aluminum foil. One ml sample was withdrawn periodically for 7 hrs and analyzed by UV spectrophotometer at 232nm. After each withdrawal of the sample, a fresh buffer was added to it as a replacement<sup>25</sup>.

##### Drug release kinetic data analysis:

Release data was evaluated through PCP disso software for the kinetic models. Zero, first, Higuchi's and Peppas's model were studied<sup>26</sup>

##### 12: Stability study

Based on different evaluation parameters matrix patches of Toraseamide of two batches MTP1 and MTP5 were found to be optimum formulations. These two formulations were subjected to accelerated study for the three months at different temperatures. The formulations of two batches MTP1 and MTP5 were air tight packed and kept for three months on 40°C (75% RH). Samples evaluated through UV spectrophotometer at 232 nm for the absorbance. By the means of the calibration curve the amount of the Toraseamide was estimated<sup>27</sup>.

## RESULTS

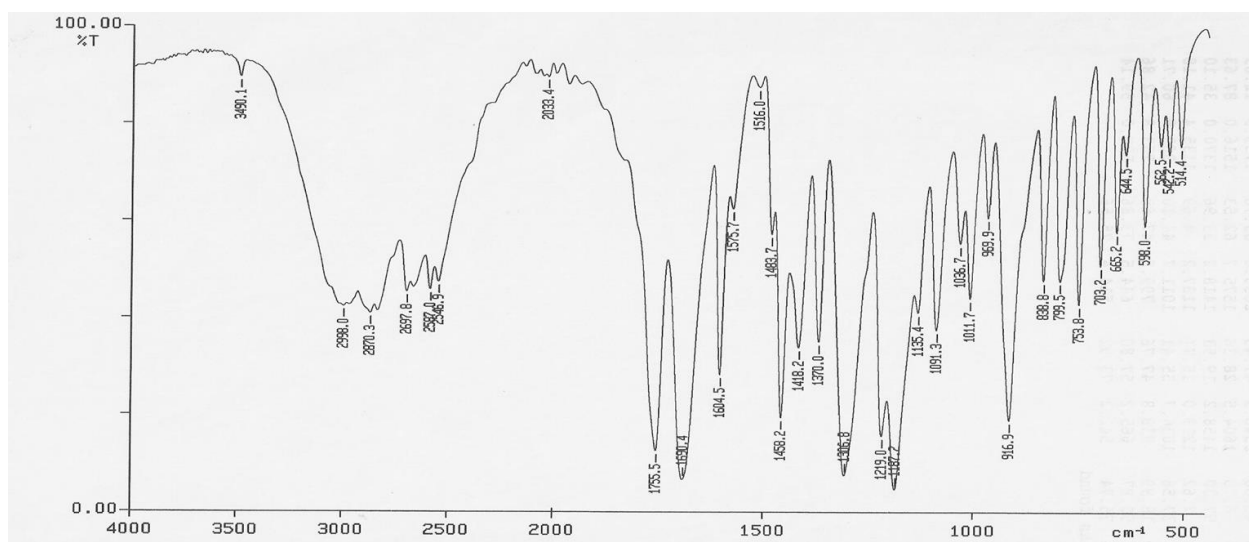


Figure 1: Torasemide FTIR

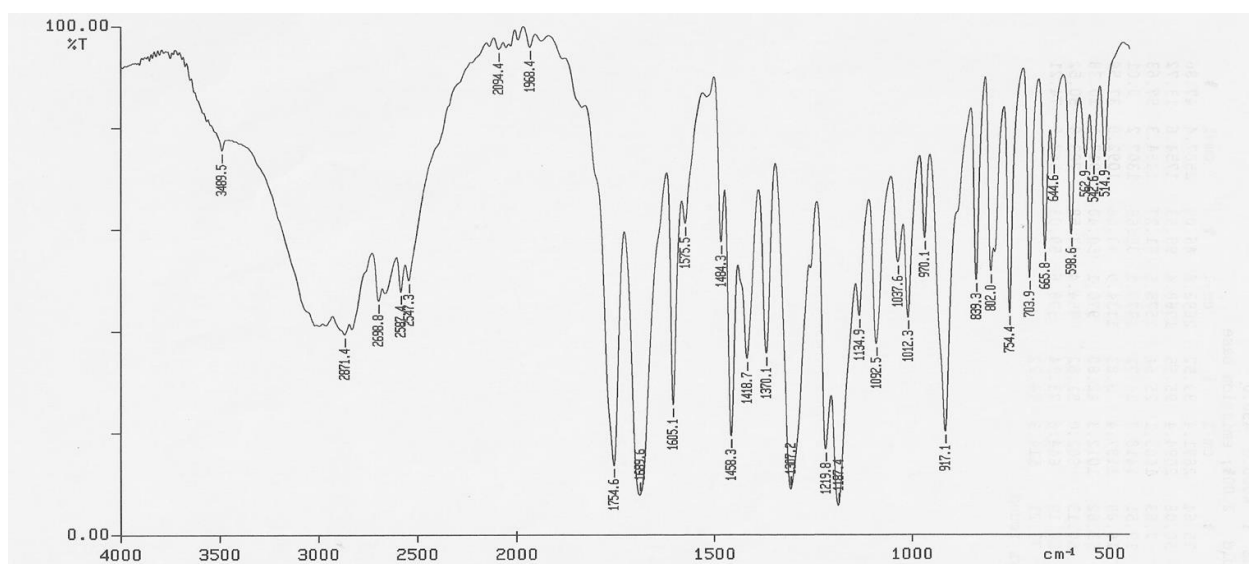


Figure 2: Torasemide +PVP K30+ Chitosan+ Ethyl cellulose+ HPMC FTIR

Table 1: Torasemide Matrix patches formulations composition

Batch	Torasemide (mg)	Polymer Ratio	Solvent (w/v)	Propylene glycol (Penetration enhancer)	Plasticizer
MTP1	250	Chitosan: PVP K30::20:80	Acetic acid(1%)	10%	Dibutylphthalate (30%)
MTP2	250	Chitosan: PVP K30::40:60	Acetic acid(1%)	-	Dibutylphthalate (30%)
MTP3	250	Chitosan: PVP K30::60:40	Acetic acid(1%)	-	Dibutylphthalate (30%)
MTP4	250	Chitosan: PVP K30::80:20	Acetic acid(1%)	-	Dibutylphthalate (30%)
MTP5	250	Chitosan :EC:: 20:80	Dichloromethane (2%)	10%	Dibutylphthalate (30%)
MTP6	250	Chitosan :EC:: 40:60	Acetic acid(1%)	10%	Dibutylphthalate (30%)
MTP7	250	Chitosan :EC:: 60:40	Acetic acid(1 %)	-	Glycerine (20%)
MTP8	250	Chitosan :EC:: 80:20	Dichloromethane (2%)	-	Castor oil (20%)
MTP9	250	HPMC:PVP K30::20:80	Dichloromethane (2%)	-	Castor oil (20%)
TP10	250	HPMC:PVP K30::40:60	Dichloromethane (2%)	-	Castor oil (20%)
MTP11	250	HPMC:PVP K30::60:40	Acetic acid(1%)	-	Castor oil (20%)
MTP12	250	HPMC:PVP K30::80:20	Acetic acid(1%)	-	Castor oil (20%)

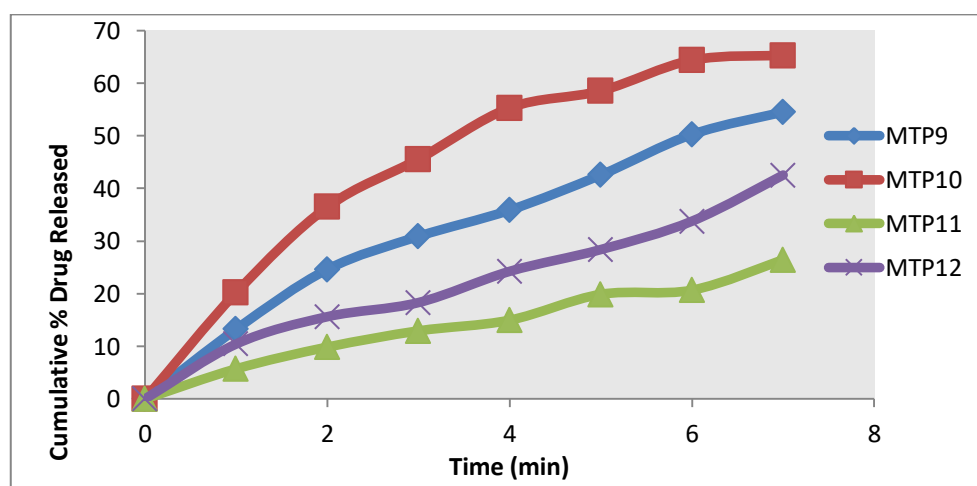
**Table 2: Properties of Torasemide matrix patches**

Code	Physical Appearance	Thickness (mm) $\pm$ SD	Mass Uniformity (mg)	% Drug Content	% Moisture Content
MTP1	Smooth tough	0.039 $\pm$ 0.41	44.5 $\pm$ 0.12	95.42 $\pm$ 0.12	2.65 $\pm$ 0.09
MTP2	Smooth tough	0.037 $\pm$ 0.09	43.3 $\pm$ 0.08	96.42 $\pm$ 0.09	2.69 $\pm$ 0.16
MTP3	Smooth flexible but wrinkled	0.040 $\pm$ 0.21	42.7 $\pm$ 0.08	94.42 $\pm$ 0.09	2.59 $\pm$ 0.16
MTP4	Smooth tough	0.038 $\pm$ 0.08	46.2 $\pm$ 0.11	95.41 $\pm$ 0.21	2.45 $\pm$ 0.13
MTP5	Smooth flexible but wrinkled	0.036 $\pm$ 0.19	45.7 $\pm$ 0.14	97.35 $\pm$ 0.32	2.55 $\pm$ 0.15
MTP6	Smooth flexible but wrinkled	0.040 $\pm$ 0.09	47.6 $\pm$ 0.09	97.62 $\pm$ 0.12	3.43 $\pm$ 0.64
MTP7	Smooth tough	0.038 $\pm$ 0.18	44.4 $\pm$ 0.15	96.79 $\pm$ 0.12	3.24 $\pm$ 0.65
MTP8	Smooth flexible but wrinkled	0.041 $\pm$ 0.31	45.1 $\pm$ 0.18	97.65 $\pm$ 0.12	3.45 $\pm$ 0.21
MTP9	Hard and tough	0.051 $\pm$ 0.09	43.2 $\pm$ 0.23	96.31 $\pm$ 0.15	3.35 $\pm$ 0.24
TP10	Smooth tough	0.037 $\pm$ 0.19	45.7 $\pm$ 0.11	97.31 $\pm$ 0.32	2.35 $\pm$ 0.16
MTP11	Smooth flexible but wrinkled	0.038 $\pm$ 0.09	46.6 $\pm$ 0.11	97.22 $\pm$ 0.09	3.43 $\pm$ 0.59
MTP12	Smooth flexible but wrinkled	0.041 $\pm$ 0.11	48.7 $\pm$ 0.09	98.45 $\pm$ 0.09	3.79 $\pm$ 0.08

**Table 3: Characterization of Torasemide matrix patches**

Batch Code	% MA	% ML	WVTR (g/cm <sup>2</sup> /hrs)	Folding Endurance	Flatness
MTP1	6.442 $\pm$ 0.07	2.881 $\pm$ 0.09	2.327X10 <sup>-4</sup> $\pm$ 0.11	> 254	100%
MTP2	5.328 $\pm$ 0.89	3.452 $\pm$ 0.08	2.428 X10 <sup>-4</sup> $\pm$ 0.13	> 235	100%
MTP3	4.355 $\pm$ 0.09	2.824 $\pm$ 0.11	2.631X10 <sup>-4</sup> $\pm$ 0.14	> 264	100%
MTP4	5.482 $\pm$ 0.11	3.232 $\pm$ 0.12	2.747X10 <sup>-4</sup> $\pm$ 0.09	> 278	100%
MTP5	6.784 $\pm$ 0.09	3.431 $\pm$ 0.14	2.832X10 <sup>-4</sup> $\pm$ 0.08	> 265	100%
MTP6	7.108 $\pm$ 0.21	3.759 $\pm$ 0.09	1.458X10 <sup>-4</sup> $\pm$ 0.14	> 267	100%
MTP7	6.231 $\pm$ 0.32	3.545 $\pm$ 0.08	1.871X10 <sup>-4</sup> $\pm$ 0.21	> 282	100%
MTP8	8.132 $\pm$ 0.41	3.639 $\pm$ 0.14	1.562X10 <sup>-4</sup> $\pm$ 0.09	> 257	100%
MTP9	8.108 $\pm$ 0.09	3.559 $\pm$ 0.21	1.358X10 <sup>-4</sup> $\pm$ 0.21	> 260	100%
TP10	7.784 $\pm$ 0.11	3.531 $\pm$ 0.12	1.832X10 <sup>-4</sup> $\pm$ 0.11	> 257	100%
MTP11	5.355 $\pm$ 0.32	3.824 $\pm$ 0.18	2.531X10 <sup>-4</sup> $\pm$ 0.16	> 253	100%
MTP12	6.328 $\pm$ 0.29	3.552 $\pm$ 0.11	1.428 X10 <sup>-4</sup> $\pm$ 0.14	> 247	100%

N=3

**Figure 3: In vitro study of patches (MTP1 to MTP4)**

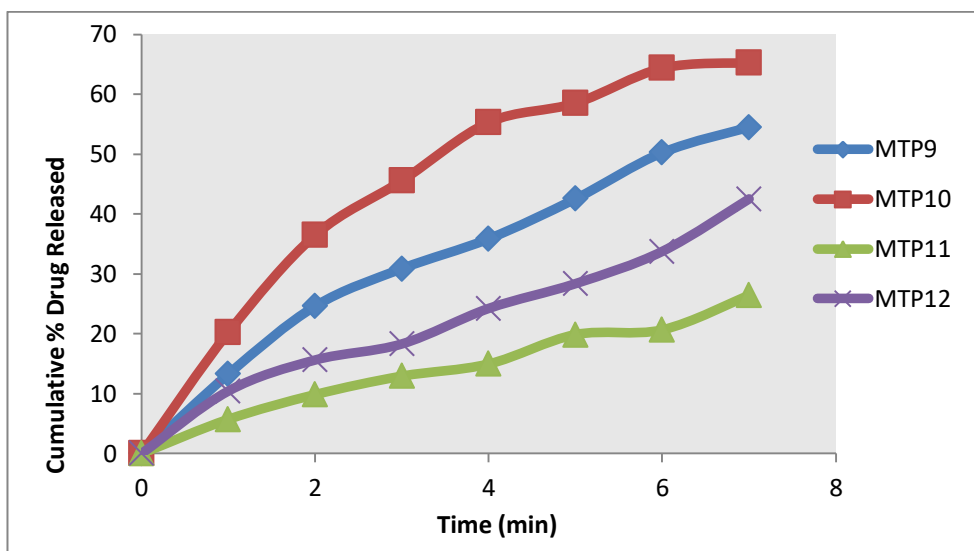


Figure 4: *In vitro* study of patches (MTP5 to MTP8)

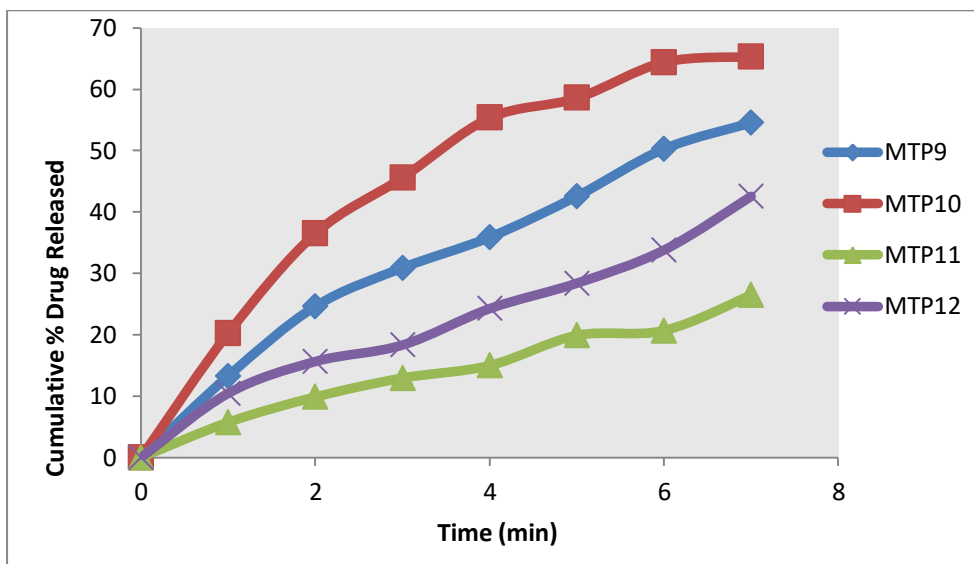


Figure 5: *In vitro* study of patches (MTP9 to MTP12)

Table 4: Different release models for Torasemide transdermal patches

Batch	Kinetic model	Parameters
MTP1	Peppas and Korsmeyer	R = 0.972, K1 = 7.642, n = 0.732
MTP2	Peppas and Korsmeyer	R = 0.971, K1 = 7.442, n = 0.762
MTP3	First order	R = 0.962, K1 = 5.61, n = 0.760
MTP4	Peppas and Korsmeyer	R = 0.954, K1 = -0.070
MTP5	Peppas and Korsmeyer	R = 0.974, K1 = 5.2154, n = 0.864
MTP6	Peppas and Korsmeyer	R = 0.983, K1 = 6.712, n = 0.782
MTP7	Peppas and Korsmeyer	R = 0.955, K1 = 4.284, n = 0.760
MTP8	Peppas and Korsmeyer	R = 0.963, K1 = 8.243, n = 0.718
MTP9	Peppas and Korsmeyer	R = 0.975, K1 = -0.034
MTP10	First order	R = 0.984, K1 = 3.157, n = 0.864
MTP11	Peppas and Korsmeyer	R = 0.975, K1 = 5.846, n = 0.863
MTP12	Peppas and Korsmeyer	R = 0.969, K1 = 7.451, n = 0.745



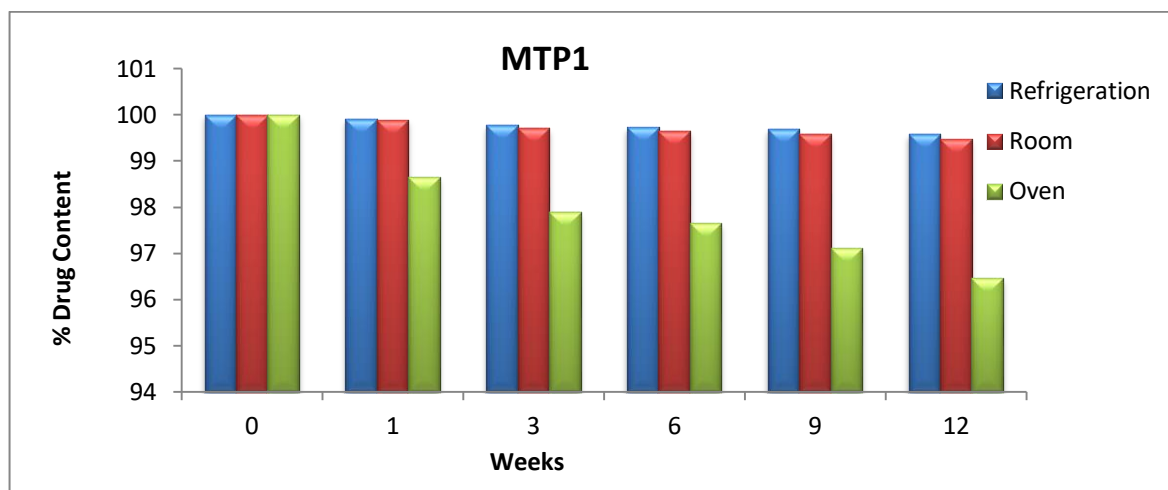


Figure 6: Stability profile of batch MTP1

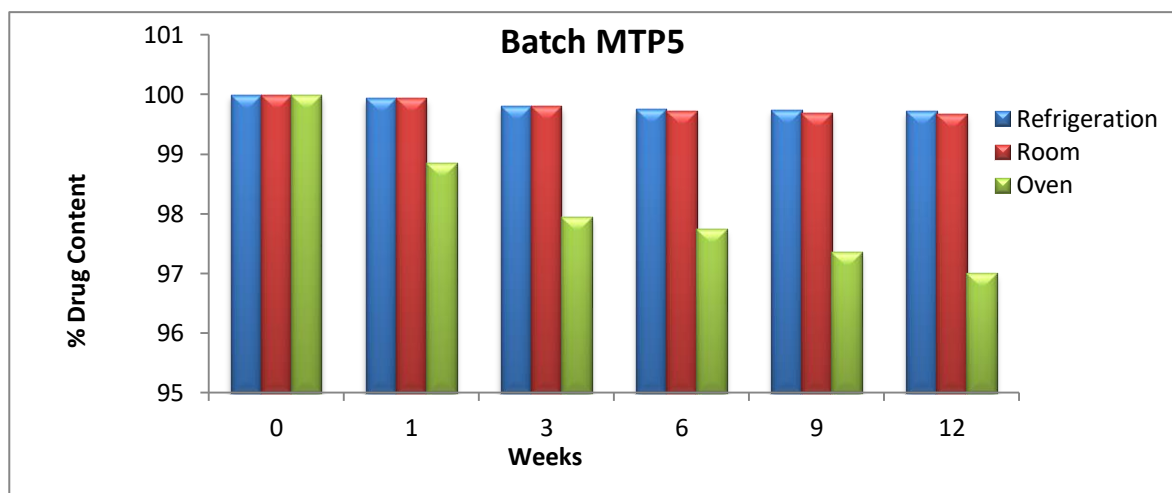


Figure 7: Stability profile of batch MTP6

## DISCUSSION

Torasemide was Schwitz Biotech. Memnagar, Ahmedabad, Gujrat as a Gift sample. The drug was authenticated by different test i.e. solubility, melting point, test according to Indian Pharmacopoeia and analytical methodology was performed on sample to justify the authenticity of sample. The m.p. detected was in the range of 161-165°C, that is matching as mentioned in IP. This justifies the authenticity of given sample of Torasemide. Torasemide sample was soluble in H<sub>2</sub>O, but sparingly in alcohol. This justifies the authenticity of given sample of Torasemide.

**Analytical methodology-** Given Torasemide sample has shown maximum absorption ( $\lambda_{max}$ ) at 232nm. FTIR spectroscopy was used to detect any kind of interaction between Torasemide and used polymers i.e. HPMC, EC, PPV K30. No change in peak was found, that indicate compatibility between them.

### Development and evaluation of formulations-

Twelve Torasemide matrix patches were developed using polymers in different ratio and plasticizer and penetration enhancer.

### Thickness, weight and % content:

Measured thickness of twelve patches was found to be in between  $0.037 \pm 0.19$ - $0.051 \pm 0.09$  mm. Average thicknesses within a batch was uniform, with a little variation. This

difference is because of viscosity difference of polymer solution and also due to absence of temperature control that affect solvent evaporation. Measured weight of twelve patches was found to be in  $42.7 \pm 0.08$  to  $48.7 \pm 0.09$ mg. Measured % drug content found to be  $94.42 \pm 0.09$  to  $98.45 \pm 0.09$ .

### % ML, % MC, % MA, and WVTR

% MA was found to be in the range of  $4.355 \pm 0.09$  to  $8.132 \pm 0.41$ , maximum was observed in MTP8 and minimum in MTP3. % MC was found to be in the range of  $2.35 \pm 0.16$  to  $3.79 \pm 0.08$ , maximum was observed in MTP12 and minimum in MTP9. % ML was found to be in the range of  $2.881 \pm 0.09$  to  $3.824 \pm 0.18$  maximum was observed in MTP11 and minimum in MTP1. WVTR was found is maximum in batch code MTP5 i.e.  $2.832 \times 10^{-4} \pm 0.08$  and minimum in formulations of batch code MTP9 i.e.  $1.358 \times 10^{-4} \pm 0.21$ .

### Folding endurance-

It was found maximum in formulation MTP7 (>282) and least in MTP2 (>235). This indicates that due to use of plasticizer, all twelve patches were having sufficient elasticity.

### In-vitro release

Release profile of twelve batches of Torasemide was done by the means of Franz cell for 7 hrs. Largest in batch code MTP6

(71.28±0.19) and least in formulations of batch code MTP7(24.47±0.04). In the initial stage, a rapid release of drug was observed but later on there was a slow and constant release. It was detected that release was inversely proportional to the polymer ratio. Hydrophobic polymer like Chitosan was having poor release as their slow dissolution affect the release of the drug.

### Kinetic modeling for transdermal patches -

Models for the release kinetic profile are shown in Table 10. PCP disso Version 2 software was used in this study. *In-vitro* release data were plotted in 2 different models i.e. first, and Korsmeyer peppas. It was observed that release was governed by the diffusion process.

### Stability study:

12 weeks study indicates that patch formulation of MTP1 and MTP5 are capable to be stable at 45°C as well as at refrigeration temperature. Therefore, the formulations may be kept at room temperature without affecting the properties.

### CONCLUSION

Twelve Torasemide matrix patches were developed using different polymers in different ratio and plasticizer and penetration enhancer. All transdermal patches were transparent and free from any particle. Release profile of twelve batches of Torasemide was done by the means of Franz cell for 7 hrs. Maximum release was shown by MTP6 (71.28±0.19) and least in formulations of batch code MTP7 (24.47±0.04). *In-vitro* release data were plotted in 2 different models i.e. first, and Korsmeyer peppas. It was observed that release was governed by the diffusion process. On basis of different properties MTP1 batch was found to be optimum.

12 weeks study indicates that patch formulation of MTP1 and MTP5 are capable to be stable at 45°C as well as at refrigeration temperature. Study concludes that by the means of patches Torasemide can be administered efficiently.

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