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# DEVELOPMENT AND EVALUATION OF MATRIX TYPE TRANSDERMAL PATCHES OF REPAGLINIDE

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## ABSTRACT

Nowadays researchers are working on the existing drugs to improve their efficiency by the means of the different dosage forms. They are working on different novel drug delivery systems for this purpose. Reduced frequency of 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. Repaglinide belong to meglitinide class and lowers the blood sugar level. It stimulate the release of insulin from pancreas. The goal of the study was to develop TDDS of Repaglinide with the use of different polymers in different ratio. Twelve transdermal patches formulations were developed and studied on various parameters like wt uniformity, folding endurance, moisture content, in-vitro release, stability studies. Study concludes successful delivery of Repaglinide by the means of transdermal patches.

**KEYWORDS:** Repaglinide, transdermal patches, *in-vitro* release, stability studies, TDDS.

## INTRODUCTION

Nowadays researchers are working on the existing drugs to improve their efficiency by the means of the different dosage forms. They are working on different novel drug delivery systems for this purpose. The main purpose of such study is related to improvement of patient compliance, reduction in the frequency of administration, and less side effects.[1,2]

As far as Transdermal drug deliv. Formulations are concerned, they administered transdermally possess many benefits as compared with oral dosage form like avoidance of first pass metabolis, and no interaction with the gastric content like food and acid.[1] Formulations can be used in case of unconsciousness, 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.[3] In 20$^{th}$ century, skin is used for longer duration of delivery of different dosage forms. Mostly drugs that are available in market are used to be administered by the oral route, but oral route suffers different limitations like in efficient to maintain required concentration. The first target of any CDDS is safety and efficacy and to provide patient compliance. TDDS is capable to deliver drug at predetermined and controlled rate.[2] TDDS avoids some limitations of parenteral route like avoidance of fluctuation of plasma drug concentration and avoid pain during dose administration through needles.[4,5]

Repaglinide belong to meglitinide class and lowers the blood sugar level. It stimulate the release of insulin from pancreas. One hour is it half life that is very short. Furthermore it has low bioavailability (56%) because of the first pass effect. It is given 3 to 4 times per day in the dose of 0.5-4 mg.[6,7] Matrix type 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 Repaglinide, was used in current study.

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

## MATERIALS AND METHODS

Repaglinide, were obtained from Johnlee Pharmaceuticals Pvt. Ltd. Mumbai. PG (Propylene glycol), Glycerine, PVP K30, Triethanolamine (ml), Sodium lauryl sulfate and Ethanol were obtained from CDH, Delhi. All other ingredients used were of analytical grade.

## PREPARATION

### 1. TPX Membrane technique

Polyester films through backing membrane with concave diameter of 1 cm are used in this method. Drug is dispersed on membrane and is covered by a membrane of TPX. After that it is sealed with an adhesive.[8-12]

**2. Circular Teflon Mould Method**
This method involves preparations of polymer solution in different proportions. After it solution is divided in 2 parts, in one drug is dissolved and in second penetration enhancers are added. Later on plasticizer are added to it and final content is stirred for approx 12 hrs and after it placed in a Teflon mould having circular shape for the evaporation of the solvent for 24hrs.[13-15]

**3. Mercury Substrate technique**
Drug and plasticizer are mixed in a solution of polymer(s). In order to get uniform dispersion it is stirred and is later on poured on the surface of mercury. In order to control evaporation, the whole assembly is covered with an inverted funnel.[16-19]

**4. IPM Membranes technique**
Mixing of drug, polymer(s), and water for approx 12 hrs by the means of a magnetic stirrer. After neutralization of mixturetriethanolamine is added to make it more viscous. The gel thus formed is used with IPM membrane.[20]

Twelve Repaglinide 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 Repaglinide was done by the means of Franz cell for 7 hrs. 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 MTP6 are capable to be stable at $45^0$C as well as at refrigeration temperature. Study concludes successfully delivery of Repaglinide by the means of patches.[21,22]

**Characterization**
**1. Thickness**
Screw gauge was use for the measurement of the patches thickness.[23]

**2. Weight**
Patches (05) having area of 2.009 $cm^2$ were selected and weighed. Average wt was calculated.[9]

**3. Content Uniformity**
Matrix patches having area of 2.009 $cm^2$, dissolved in 10 ml buffer. Later on % drug estimated through UV spectrophotometer at 232 $nm^{44}$ and by using prepared standard curve of the Repaglinide.[24]

**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.[25]

**5. % ML (% Moisture Loss)**
Patches placed in a desiccators, having anhyd. $CaCl_2$, with 80-90%RH. Sampleswere taken from the desiccators after three days and weighed for the estimation of change in wt.[26]

$$\% \text{ ML} = \frac{\text{WI} - \text{WF}}{\text{WI}} \text{X100}$$

Where, WI= Initial Weight, WF= Final Weight

**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.[27]

$$\% \text{ Moisture content} = \frac{\text{WI} - \text{WF}}{\text{WI}} \text{X100}$$

Where, WI=Weight Initial, WF= Weight Final

**7. % MA (Moisture Absorption)**
Patches placed in a desiccators, with 100 ml, $AlCl_3$ (79.50% RH). Sampleswere taken from the desiccators after three days and weighed for the estimation of change in wt.[28]

$$\% \text{ Moisture absorption} = \frac{\text{WF} - \text{WI}}{\text{WI}} \text{X100}$$

Where, WI=Weight Initial, WF= Weight Final

8. WVTR (Water vap. transmission rate)
Cleaned and dried vials of same size were used as the cells. Calcium chloride (1 gm), was added to cells, and patch of area 2.076 $cm^2$ was fitted to brim. Weighed cells were placed in a desiccators. Cells were withdrawn and weighed daily for 7 days.[15]

$$\text{WVTR} = \frac{\text{WF} - \text{WI}}{\text{TXA}} \text{X100}$$

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

**9. Flatness**
Patch of length 1.5 cm were taken for this study. Flatness uniformity was estimated as-

$$\text{Constriction (\%)} = \frac{\text{LF} - \text{LI}}{\text{LI}} \text{X100}$$

Where, LF= length final, and LI = length initial
0% constrictions were considered to possess 100% flatness.[29]

**Table 1: Calibration curve of Repaglinide in phosphate buffer pH 7.4.**

| S.N. | Conc. (µg/ml) | Absorbance |
|---|---|---|
| 1 | 0 | 0 |
| 2 | 1 | 0.085±0.08 |
| 3 | 2 | 0.184±0.08 |
| 4 | 3 | 0.230±0.12 |
| 5 | 4 | 0.332±0.21 |
| 6 | 5 | 0.441±0.09 |
| 7 | 6 | 0.542±0.23 |
| 8 | 7 | 0.624±0.14 |
| 9 | 10 | 0.732±0.15 |

(Mean±S.D), N=3

**Table-2: Evaluation parameters of matrix type transdermal patches of Repaglinide.**

| Batch Code | WVTR ($g/cm^2/hrs$ | % Moisture Content | % Moisture Absorption | % Moisture loss | Flatness |
|---|---|---|---|---|---|
| **MTP1** | $2.327X10^{-4}$± 0.11 | 3.55 ± 0.09 | 6.442 ± 0.07 | 2.881± 0.09 | 100% |
| **MTP2** | 2.428 $X10^{-4}$± 0.13 | 3.89 ± 0.16 | 5.328 ± 0.89 | 3.452 ± 0.08 | 100% |
| **MTP3** | $2.931X10^{-4}$±0.14 | 4.49 ± 0.16 | 4.355 ± 0.09 | 2.824 ± 0.11 | 100% |
| **MTP4** | $2.747X10^{-4}$± 0.09 | 2.28 ± 0.13 | 5.482 ± 0.11 | 3.232 ± 0.12 | 100% |
| **MTP5** | 2.832$X10^{-4}$± 0.08 | 2.55 ± 0.15 | 6.784 ± 0.09 | 3.431 ± 0.14 | 100% |
| **MTP6** | $1.458X10^{-4}$ ± 0.14 | 4.43 ± 0.64 | 7.108 ± 0.21 | 3.759 ± 0.09 | 100% |
| **MTP7** | $1.871X10^{-4}$ ± 0.21 | 3.24 ± 0.65 | 6.231 ± 0.32 | 3.545 ± 0.08 | 100% |
| **MTP8** | $1.562X10^{-4}$ ± 0.09 | 3.45 ± 0.21 | 8.132 ± 0.41 | 3.639 ± 0.14 | 100% |
| **MTP9** | $1.258X10^{-4}$ ± 0.21 | 3.35 ± 0.24 | 7.108 ± 0.09 | 3.559 ± 0.21 | 100% |
| **MTP10** | 1.832$X10^{-4}$± 0.11 | 2.35 ± 0.16 | 7.784 ± 0.11 | 3.531 ± 0.12 | 100% |
| **MTP11** | $2.531X10^{-4}$±0.16 | 3.43 ± 0.59 | 5.355 ± 0.32 | 3.824 ± 0.18 | 100% |
| **MTP12** | 1.428 $X10^{-4}$± 0.14 | 3.79 ± 0.08 | 6.328 ± 0.29 | 3.552 ± 0.11 | 100% |

mean ± SD, N=3

**Table-3: Characterization of matrix type transdermal patches of Repaglinide.**

| Batch Code | Physical Appearance | % Drug Content | Thickness (mm) ± SD | Mass Uniformity (mg) | Folding Endurance |
|---|---|---|---|---|---|
| **MTP1** | Smooth tough | 92.42± 0.12 | 0.036 ± 0.41 | 46.5 ± 0.12 | > 264 |
| **MTP2** | Smooth tough | 95.42± 0.09 | 0.032 ± 0.08 | 42.3 ± 0.08 | > 235 |
| **MTP3** | Smooth flexible but wrinkled | 94.42± 0.09 | 0.043 ± 0.21 | 44.7 ± 0.08 | > 264 |
| **MTP4** | Smooth tough | 98.41± 0.21 | 0.037 ± 0.08 | 47.2 ± 0.11 | > 290 |
| **MTP5** | Smooth flexible but wrinkled | 96.35± 0.32 | 0.039 ± 0.19 | 48.7 ± 0.14 | > 265 |
| **MTP6** | Smooth flexible but wrinkled | 97.62± 0.14 | 0.042 ± 0.09 | 48.6 ± 0.09 | > 267 |
| **MTP7** | Smooth tough | 97.79± 0.18 | 0.038 ± 0.18 | 45.4 ± 0.15 | > 272 |
| **MTP8** | Smooth flexible but wrinkled | 97.65± 0.02 | 0.041 ±0.31 | 46.1 ± 0.18 | > 257 |
| **MTP9** | Hard and tough | 96.31± 0.16 | 0.051 ± 0.09 | 44.2 ± 0.23 | > 250 |
| **MTP10** | Smooth tough | 97.31± 0.32 | 0.037 ± 0.19 | 47.7 ± 0.12 | > 257 |
| **MTP11** | Smooth flexible but wrinkled | 97.22± 0.09 | 0.038 ± 0.09 | 46.6 ± 0.11 | > 221 |
| **MTP12** | Smooth flexible but wrinkled | 98.45± 0.09 | 0.041 ± 0.11 | 49.7 ± 0.09 | > 257 |

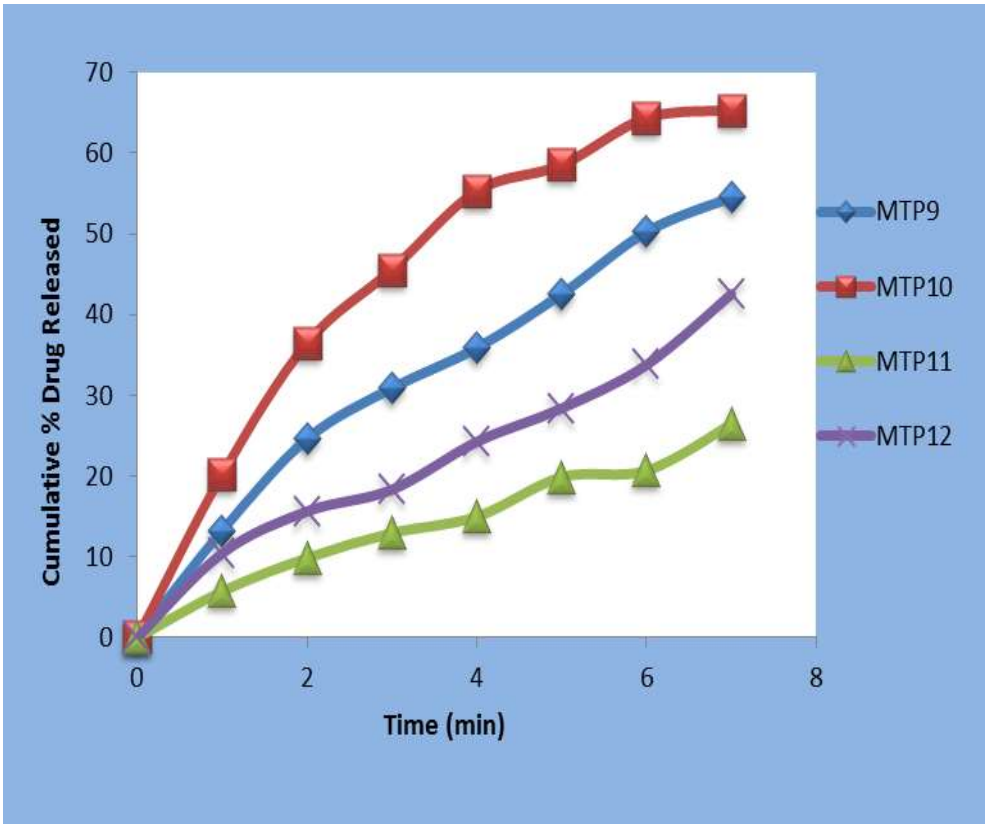


**Figure 1: Percentage of drug released from Repaglinide transdermal patchesofbatch P1to P4.**

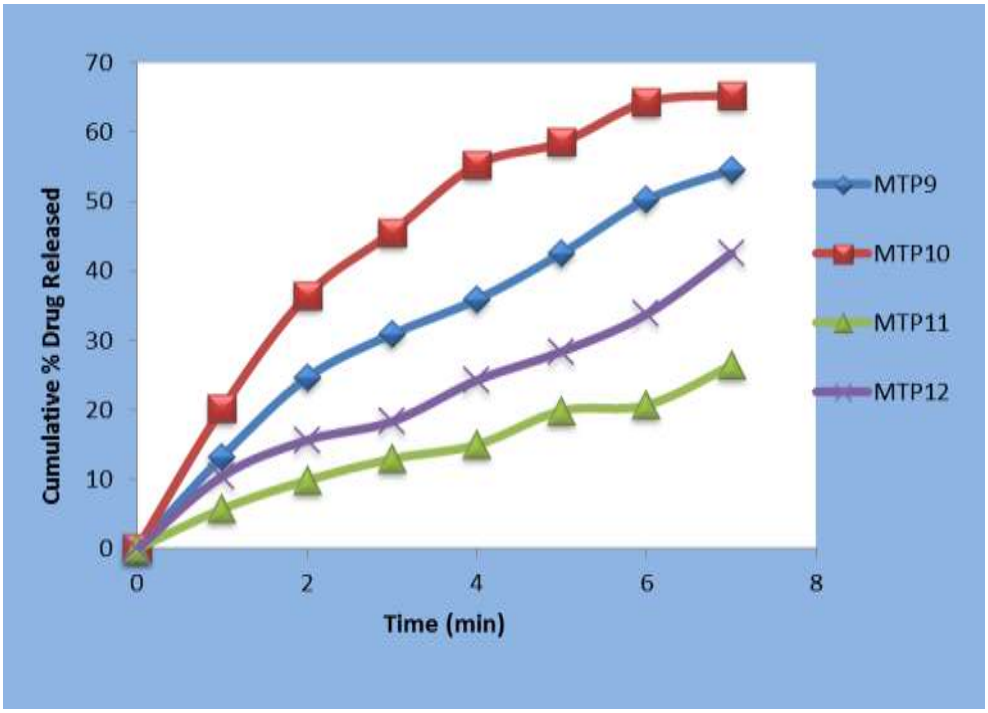


**Figure 2: Percentage of drug released from Repaglinide transdermal patchesof batch MTP5to MTP8.**

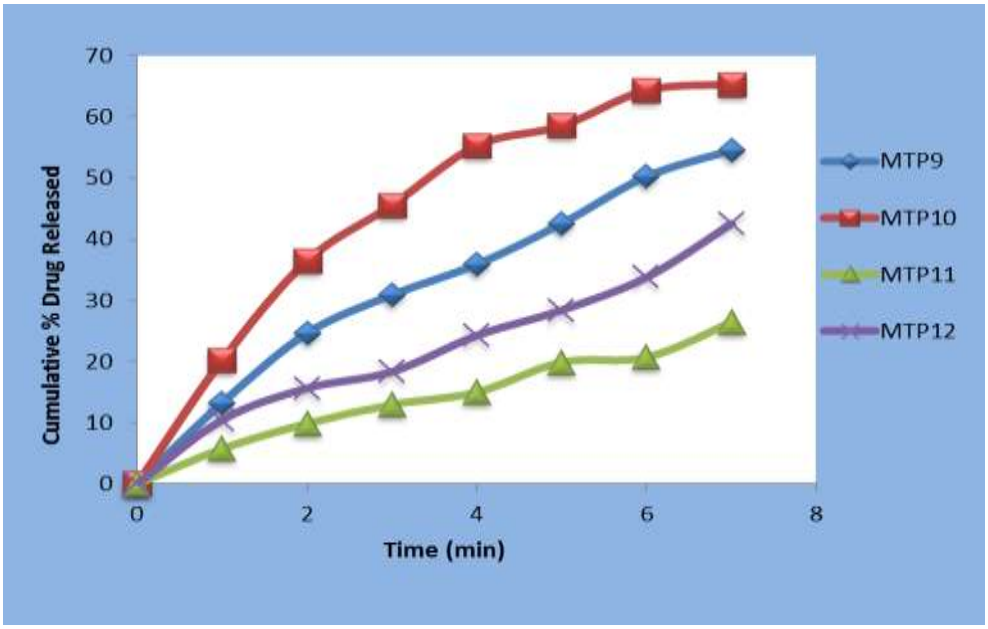


**Figure 3: Percentage of drug released from Repaginate transferral patches of batch MTP9 to MTP12.**

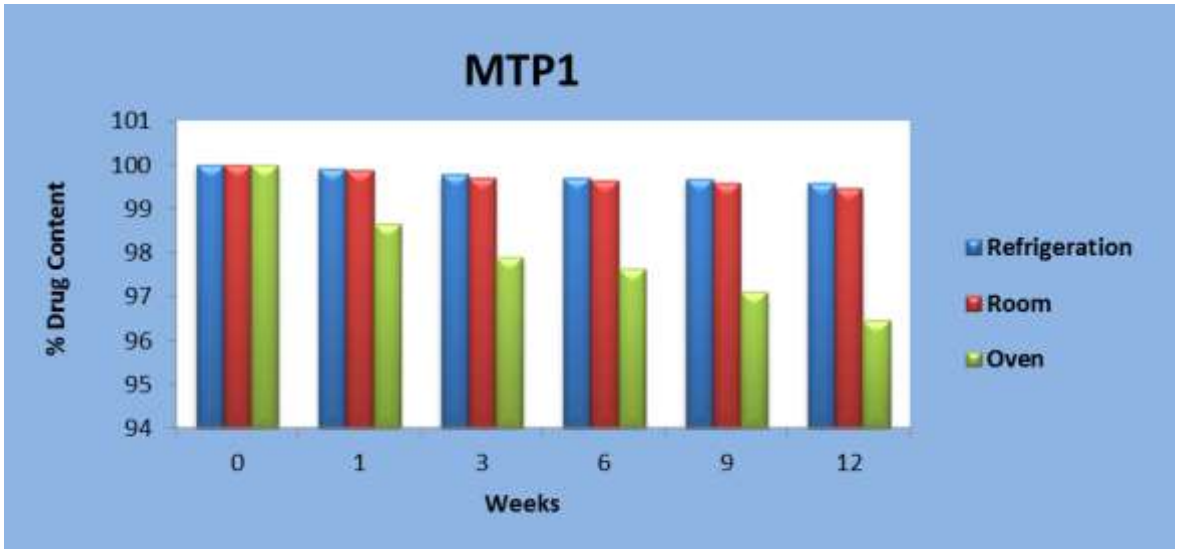


**Figure 4: Stability study of Repaglinide transdermal patches of batch MTP1 at different temperature.**

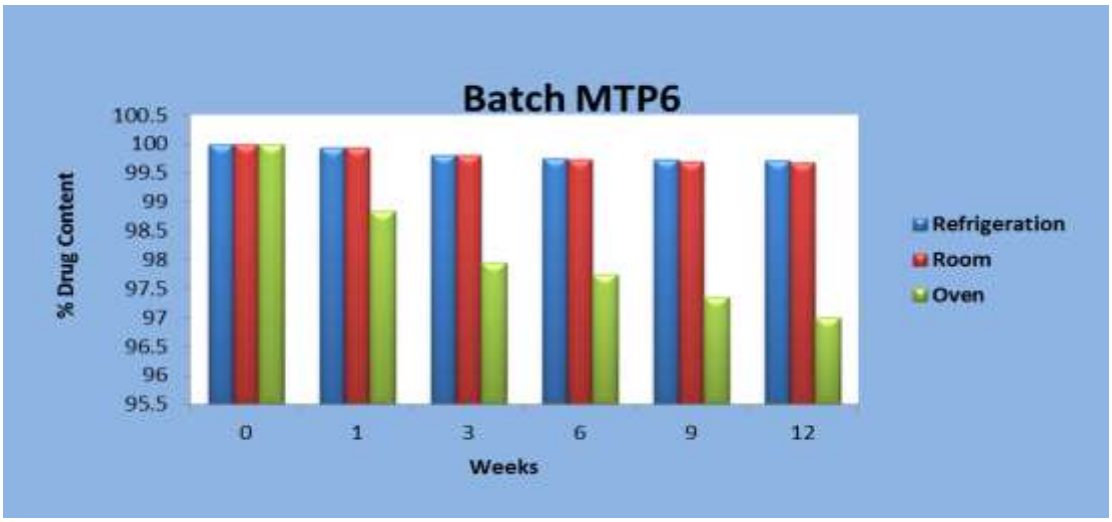


**Figure 5: Stability study of Repaglinide transdermal patches of batch MTP6 at different temperature.**

## RESULTS AND DISCUSSION

### Preformulation studies

Repaglinide was obtained as a gift sample from Johnlee Pharmaceuticals Pvt. Ltd. Mumbai. Solubility and m.p. test was performed in order to check its authenticity. All transdermal patches were transparent and free from any particle. Release profile of twelve batches of Repaglinide was done by the means of Franz cell for 7 hrs. It was observed that release was governed by the diffusion process. On basis of different properties MTP1 batch was found to be optimum. All transdermal patches were transparent and free from any particle.

The m.p. detected was in the range of 126-128°C, and was same as mentioned in IP. Repaglinide sample was poorly soluble in $H_2O$. This justifies the authenticity of given sample of Repaglinide.

### Thickness, weight and % content

Measured thickness of twelve patches was found to be in between 0.032 ± 0.08-0.051 ± 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 ± 0.08 to 48.7 ± 0.09mg. Measured % drug content found to be 42.3 ± 0.08-49.7 ± 0.09.

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

% MA was found to be in the range of 4.355 ± 0.09-8.132 ± 0.41, maximum was observed in MTP8 and minimum in MTP3. % MC was found to be in the range of 2.28 ± 0.13-4.49 ± 0.16. % ML was found to be in the range of 2.881± 0.09-3.759 ± 0.09 maximum was observed in MTP1 and and minimum in MTP6. WVTR was found is maximum in batch code MTP3 i.e. $2.931X10^{-4}$±0.14and minimum in formulations of batch code MTP9 i.e. $1.258X10^{-4}$ ± 0.21.

### Folding endurance

It was found maximum in formulation MTP4 (>290) and least in MTP211(>221). This indicate that due to use of plasticizer, all twelve patches were having sufficient elasticity.

### *In-vitro* release

Release profile of twelve batches of Repaglinide was done by the means of Franz cell for 7 hrs. Largest in batch code MTP1 (72.32±0.17) and least in formulations of batch code MTP7(21.47±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 were 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 Korsemeyer peppas. It was observed that release was governed by the diffusion process.

### Stability study

12 weeks study indicates that patch formulation of MTP1 and MTP6 are capable to be stable at $45^0$C as well as at refrigeration temperature. Therefore, the formulations may be kept at room temperature without affecting the properties.

## CONCLUSION

The main purpose of such study is related to improvement of patient compliance, reduction in the frequency of administration, and less side effects. 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. In current study concludes successful delivery of Repaglinide by the means of transdermal patches.

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