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# FORMULATION AND EVALUATION OF MATRIX TYPE TRANSDERMAL DRUG DELIVERY OF PIOGLITAZONE

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## ABSTRACT

Matrix type Pioglitazone Transdermal patches were prepared by solvent casting method using two different polymers i.e., Hydroxyl propyl methyl cellulose (HPMC) E 15 and Guar Gum. Polyethylene glycol is used as plasticizer and Dimethyl sulfoxide (DMSO) is used as penetration enhancer. The prepared formulations were subjected to various physicochemical evaluation tests such as weight variation, thickness, moisture content, moisture uptake, folding endurance, drug content. The in-vitro releases of the drug from the formulation were studied using cellophane membrane. It has been found that 89.09% of pioglitazone was released *Invitro* in the period of 12 hours. These findings suggest that delivery of pioglitazone through TDDS may overcome first pass effect and thus gives better glycaemic control in diabetic patients.

**KEYWORDS:** Pioglitazone, HPMC, Guar Gum, Polyethylene glycol, Dimethyl sulfoxide, Solvent casting method.

## INTRODUCTION

Oral route of administration is the most commonly preferred route of administration for drug delivery. Though oral route has advantages it also have significant disadvantages such as, first pass metabolism, drug degradation in GIT because of enzymes, pH etc. in order to overcome these disadvantages Novel Drug Delivery Systems (NDDS) has raised.[1]

During past few years, interests in the development of the NDDS for already existing drugs have been renewed. By which efficacy of drug, safety and patient compliance has been increased.[2]

Transdermal Drug Delivery systems are the NDDS which are self-containing discrete dosage forms which are also known as "Transdermal Patches".[3]

When these transdermal patches or skin patches are applied on the skin, they deliver the medication through the skin at predetermined rates or at controlled rate into the blood stream through a semi permeable membrane.[4,5]

Transdermal delivery is the most promising method for drug application. It reduces the load that the oral route commonly places on the digestive tract and liver. It enhances patient compliances and minimizes harmful side effects of a drug.[6]

Advantages of transdermal patches are, they increase the bioavailability, steady drug-plasma levels, reducing dosage frequency as they promote longer duration of action, continuous delivery of drug with shorter half-life, reduced side effects, avoiding gastro intestinal compatibility, enhancement of therapeutic efficacy, self administration is possible, therapy can be terminated/stopped at any point of time, increased patient compliance as they are painless and non-invasive, can be administered to unconscious patients and also cost effective.[7,8,9,10]

Components that make transdermal systems are polymer matrix/ drug reservoir, membrane, drug, permeation enhancers, pressure sensitive adhesives, backing laminates, release liners, other excipients like plasticizers and solvents. There are three major types transdermal systems have been classified and they are i) Reservoir system ii) Matrix system a) Matrix-adhesive b) Matrix-dispersion and iii) Micro Reservoir system.[11]

Diabetes mellitus is a metabolic disorder/disease characterized by chronic hyperglycemia (high blood glucose levels) caused by deficiency of insulin or by insulin resistance. Also accompanied by the greater or lesser carbohydrate, protein, lipid metabolism.[12, 13]

Pioglitazone (5-({4-[2-(5-ethylpyridin-2-yl) ethoxy] phenyl} methyl)-1,3-thiazolidine-2,4-dione) is a medicament belongs to thiazolidinedione group of drugs to manage type 2 diabetes mellitus with molecular weight 356.439 Daltons and exerts its pharmacological action primarily by promoting insulin sensitivity and increased uptake of glucose. Mechanism of action: Pioglitazone acts as selective agonist at peroxisome proliferator activated receptor gamma (PPARγ) for the insulin action in target tissues like adipose tissue, skeletal muscle tissue, and liver. Activation of PPAR-gamma receptors increases the transcription of insulin-

responsive genes that are involved in control of the glucose production, transport, and the utilization. In this way, pioglitazone both enhances the tissue sensitivity to insulin and reduces production of glucose via liver (hepatic gluconeogenesis). Thus, insulin resistance associated with type 2 diabetes mellitus is improved without an increase in insulin secretion by pancreatic β cells. M-III and M-IV are the active metabolites of the pioglitazone. The serum half-life of pioglitazone and its metabolites are (M-III and M-IV) ranges from 3-7 hours and 16-24 hours.

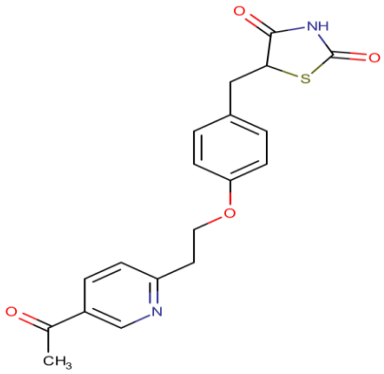


**Figure 1: M-III Metabolite**

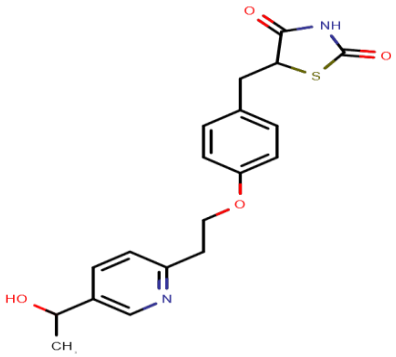


**Figure 2: M-IV Metabolite**

Route of elimination: through oral administration 15%-20% of drug is recovered in urine. Drug is excreted primarily as metabolites and conjugates. It is presumed that oral dose is excreted in the bile either in the form of unchanged or as metabolites in the feces.[14, 15]

## MATERIALS

**Table No 1: Materials used in Formulation of Pioglitazone Transdermal Patches.**

| S. No | MATERIALS | MANUFACTURER / SUPPLIERS |
|---|---|---|
| 1. | PIOGLITAZONE | Gift sample from Hetero Drugs limited |
| 2. | HPMC E15 | Otto chemical-biochemical-reagents |
| 3. | Guar Gum | SD fine chemicals |
| 4. | Methanol AR | SD fine chemicals |
| 5. | Propylene glycol | Finar limited |
| 6. | DMSO AR | SD fine chemicals |

## METHODOLOGY

Preformulation studies such as color, odor was observed, solubility of drug was tested in methanol, pH 7.4 phosphate buffer, acetone and water and melting point was determined by using capillary method. $\lambda_{max}$ was observed spectrophotometrically in phosphate buffer pH 7.4 and calibration curve was prepared by taking aliquots of 2, 4, 6, 8, 10, 12, 14 and 16 µg/ml concentrations respectively. The absorbance of each concentration was recorded at 270 nm.

Drug excipient compatibility studies was performed by Infra-Red (IR) Spectroscopy, one part of the sample and three parts of the potassium bromide are triturated in mortar and small amount of triturated sample was taken in pellet maker and compressed at 10kg/cm$^2$ using hydraulic press. The pellet was kept on the sample holder and scanned from 4000 cm$^{-1}$ to 400 cm$^{-1}$. The resulting IR spectra was compared and checked for any shift in functional peaks and non-involvement of functional groups.

Matrix type transdermal patches were prepared by solvent casting method, using different ratios of HPMC E15 (T1-T4) and Guar Gum (T5-F8) and in combination of both polymers (T9-T10). 30%w/w propylene glycol was incorporated as plasticizer and 12% DMSO (Dimethyl Sulfoxide) is used as penetration enhancer.

**Table No 2: Formulation of Pioglitazone Transdermal Patches.**

| Formulation code | Pioglitazone (mg) | HPMC E15 (g) | Guar gum (g) | Methanol (ml) | Water (ml) | Propylene Glycol (ml) |
|---|---|---|---|---|---|---|
| **T1** | 300 | 0.3 | - | 5 | 15 | 0.2 |
| **T2** | 300 | 0.6 | - | 5 | 15 | 0.2 |
| **T3** | 300 | 0.9 | - | 5 | 15 | 0.2 |
| **T4** | 300 | 1.2 | - | 5 | 15 | 0.2 |
| **T5** | 300 | -- | 0.3 | 5 | 15 | 0.2 |
| **T6** | 300 | -- | 0.6 | 5 | 15 | 0.2 |
| **T7** | 300 | -- | 0.9 | 5 | 15 | 0.2 |
| **T8** | 300 | -- | 1.2 | 5 | 15 | 0.2 |
| **T9** | 300 | 0.3 | 0.3 | 5 | 15 | 0.2 |
| **T10** | 300 | 0.6 | 0.6 | 5 | 15 | 0.2 |

Fabrication technique: accurately weighed quantity of pioglitazone was dissolved in 5ml of Methanol and to this 10ml of water is added. To this accurately weighed polymer HPMC E15 and Guar gum is added slowly by continuous stirring at 80 rpm on magnetic stirrer for 120 min. To this 0.2ml of 30% w/w propylene glycol and 0.2 ml of DMSO is added and mixed and dried at room temperature for 48 hours. The dried films were packed in aluminum foil and as backing laminate aluminum foil is used. Each patch was cut for 2x2 cm$^2$ with dose of 30mg.

## RESULTS

### A) Pre formulation Studies

Organoleptic properties: color- white to grey white, odor- odorless and has faint order of acetic acid, taste- tasteless, and appearance- crystalline powder. Melting point of the drug was

observed at 183$^0$c to 184$^0$c. Drug is soluble in methanol, pH 7.4 and slightly soluble in water and insoluble in acetone.

### B) Determination of $\lambda_{max}$

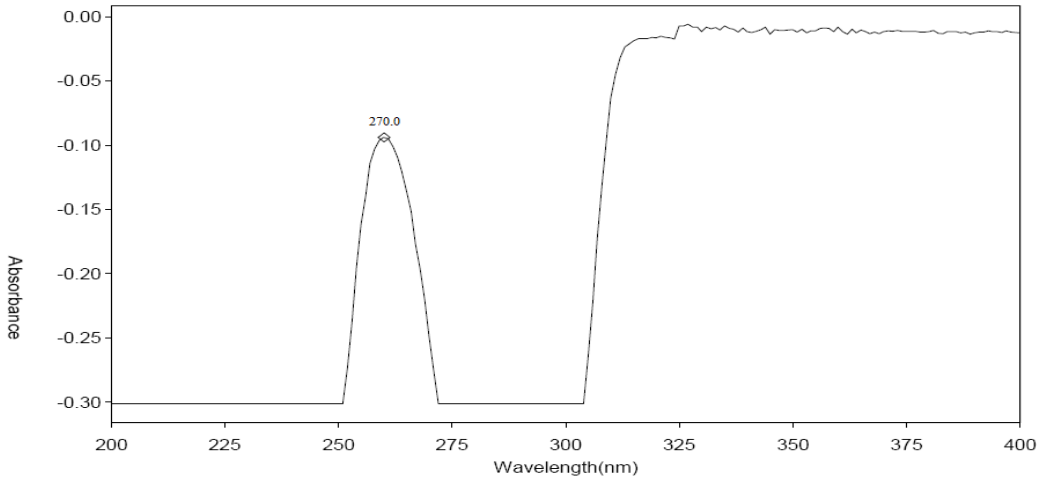


**Figure No 3: $\lambda_{max}$ of pioglitazone in pH 7.4.**

### C) Table No 3: Calibration curve

| Concentration (µg/ml) | Absorbance |
|---|---|
| 0 | 0 |
| 2 | 0.128 |
| 4 | 0.249 |
| 6 | 0.358 |
| 8 | 0.459 |
| 10 | 0.581 |
| 12 | 0.691 |
| 14 | 0.782 |
| 16 | 0.912 |

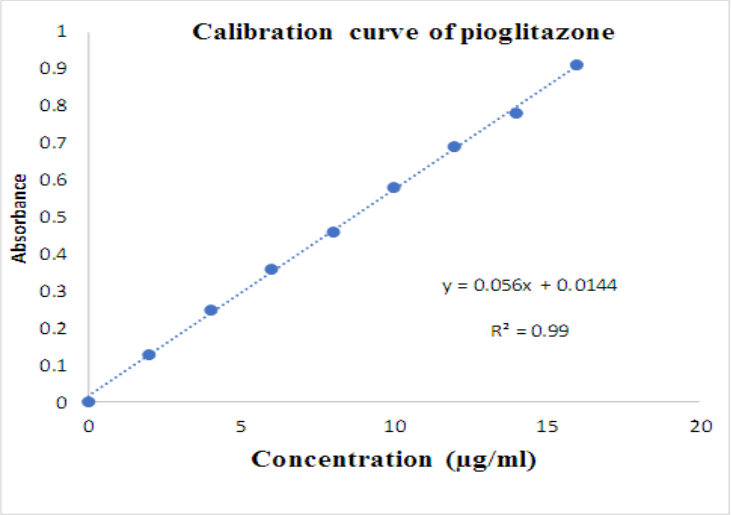


**Figure No 4: Calibration curve of Pioglitazone in phosphate buffer pH 7.4.**

## D) Drug Excipient compatibility studies

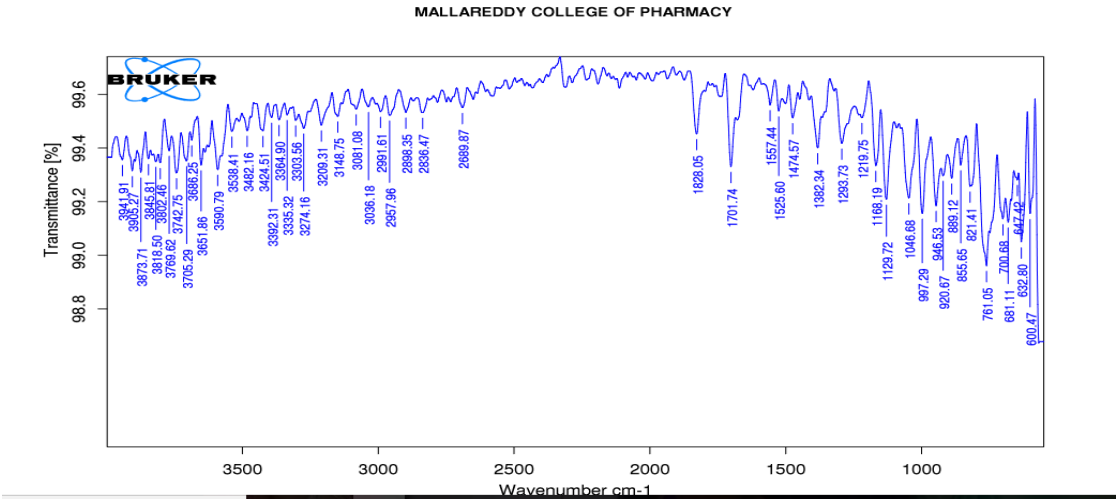


**Figure No 5: FTIR spectra of Pioglitazone.**

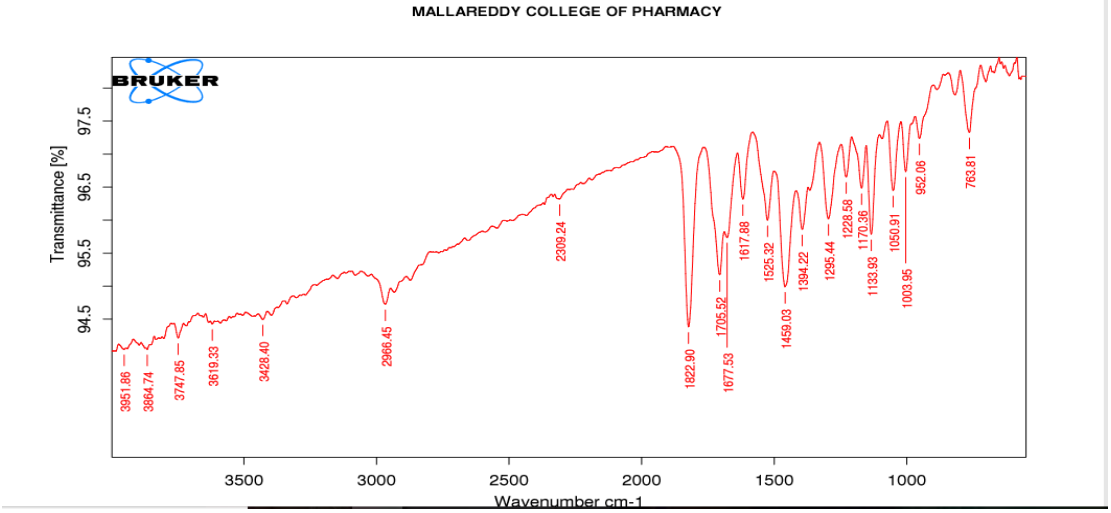


**Figure No 6: FTIR spectra of pioglitazone with HPMC and Guar gum.**

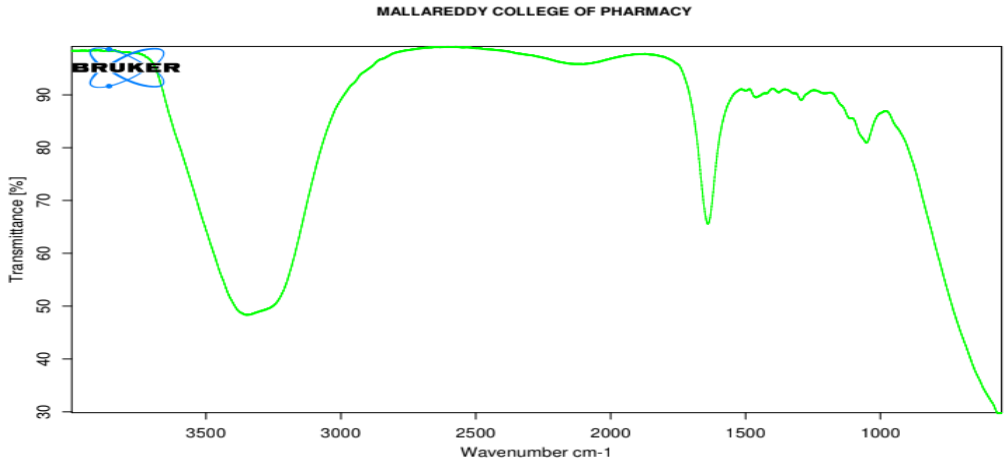


**Figure No 7: FTIR Spectra of Optimized Formulation.**

**E) Table No 4: Physio-chemical evaluation studies.**

| Formulation | Weight variation (mg)±SD | Thickness (mm) ±SD | Folding endurance ±SD | %Moisture absorption ±SD | % Moisture loss ±SD | Drug content (mg)±SD |
|---|---|---|---|---|---|---|
| T1 | 431±3.6 | 0.27±0.008 | 91±5 | 7.89±0.03 | 3.0±0.02 | 69.2±0.04 |
| T2 | 428±2.6 | 0.31±0.027 | 93±4.8 | 7.96±0.04 | 3.7±0.03 | 67.5±0.02 |
| T3 | 435±3.8 | 0.30±0.026 | 89±7.0 | 8.09±0.03 | 3.9±0.02 | 69.8±0.02 |
| T4 | 426±2.6 | 0.30±0.014 | 80±5.0 | 9.12±0.12 | 4.9±0.01 | 70.2±0.04 |
| T5 | 428±4.8 | 0.29±0.017 | 88±7.0 | 12.62±1.54 | 3.8±0.02 | 68.5±0.03 |
| T6 | 433±2.6 | 0.29±0.002 | 86±4.9 | 8.12±0.27 | 4.2±0.05 | 69.8±0.01 |
| T7 | 429±3.9 | 0.31±0.006 | 92±2.5 | 10.73±0.82 | 3.1±0.08 | 70.1±0.12 |
| T8 | 436±2.6 | 0.27±0.011 | 95±7.0 | 9.32±0.01 | 4.2±0.07 | 70.3±0.3 |
| T9 | 435±3.8 | 0.24±0.014 | 102±7.9 | 8.33±0.02 | 5.4±0.08 | 68.4±0.5 |
| T10 | 428±2.8 | 0.21±0.021 | 89±6.9 | 9.23±0.13 | 3.8±0.08 | 79±0.11 |

**F) *Invitro* Diffusion Studies**

**Table N0 5: Cumulative % drug release for the batch F1 -F4.**

| Time (hr.) | F1 | F2 | F3 | F4 |
|---|---|---|---|---|
| **0** | 0 | 0 | 0 | 0 |
| **1** | 4.31±0.43 | 1.60±0.45 | 9.08±0.48 | 1.40±0.58 |
| **2** | 11.8±0.24 | 15.8±0.23 | 13.8±0.64 | 16.9±0.16 |
| **3** | 18.9±0.32 | 17.9±0.24 | 15.9±0.32 | 19.8±0.24 |
| **4** | 20.3±0.13 | 23.3±0.56 | 26.3±0.36 | 26.3±0.69 |
| **5** | 28.9±0.24 | 28.9±0.34 | 31.9±0.18 | 29.9±0.28 |
| **6** | 32.8±0.25 | 37.8±0.23 | 36.8±0.69 | 36.7±0.36 |
| **7** | 41.5±0.24 | 39.5±0.67 | 44.5±0.15 | 39.4±0.89 |
| **8** | 48.9±0.12 | 44.9±0.25 | 49.9±0.14 | 49.7±0.15 |
| **9** | 54.8±0.45 | 58.8±0.21 | 54.8±0.32 | 59.8±0.24 |
| **10** | 57.1±0.23 | 60.1±0.25 | 57.1±0.25 | 61.1±0.26 |
| **11** | 62.2±0.22 | 61.2±0.48 | 60.2±0.98 | 66.3±0.24 |
| **12** | 65.5±0.15 | 64.8±0.36 | 66.8±0.35 | 69.8±0.36 |

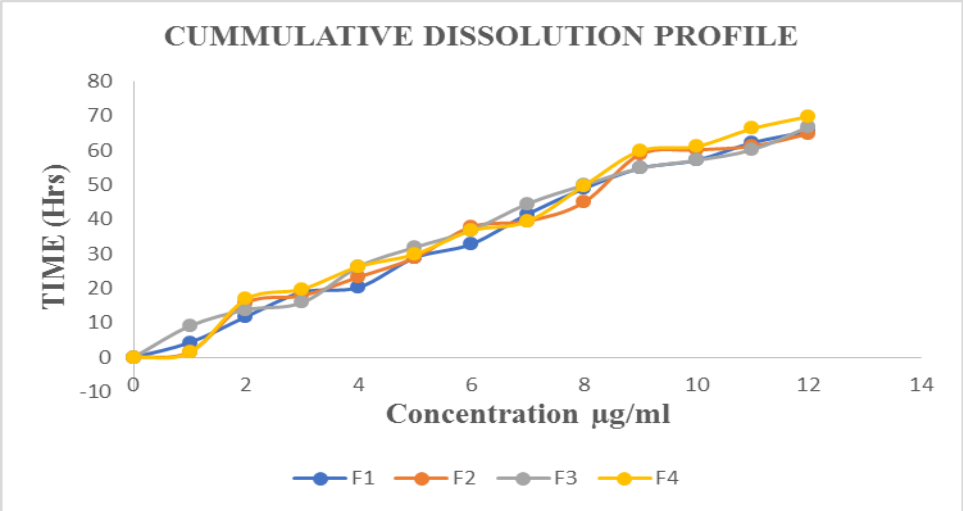


**Figure No 8: cumulative dissolution profile of Formulation 1 to Formulation 4.**

**Table No 6: Cumulative % drug release for the batch F5 – F8.**

| Time (hr.) | F5 | F6 | F7 | F8 |
|---|---|---|---|---|
| **0** | 0 | 0 | 0 | 0 |
| **1** | 2.08±0.45 | 3.43±0.98 | 4.11±0.14 | 2.43±0.98 |
| **2** | 9.08±0.26 | 13.25±0.87 | 10.31±0.47 | 14.25±0.87 |
| **3** | 12.8±0.58 | 24.65±0.74 | 18.8±0.78 | 23.75±0.74 |
| **4** | 15.9±0.14 | 28.81±0.41 | 21.9±0.89 | 29.71±0.410 |
| **5** | 27.3±0.36 | 33.56±0.12 | 27.3±0.96 | 36.86±0.23 |
| **6** | 34.9±0.96 | 45.15±0.23 | 31.9±0.63 | 44.75±0.25 |
| **7** | 36.8±0.85 | 47.16±0.36 | 36.8±0.32 | 49.16±0.58 |
| **8** | 47.5±0.74 | 53.53±0.69 | 44.5±0.21 | 52.13±0.89 |
| **9** | 49.9±0.12 | 57.86±0.98 | 51.9±0.14 | 59.26±0.96 |
| **10** | 54.8±0.36 | 62.43±0.85 | 58.8±0.45 | 67.63±0.63 |
| **11** | 57.1±0.14 | 67.80±0.52 | 67.1±0.56 | 68.40±0.32 |
| **12** | 68.2±0.25 | 69.09±0.23 | 71.2±0.69 | 72.09±0.21 |

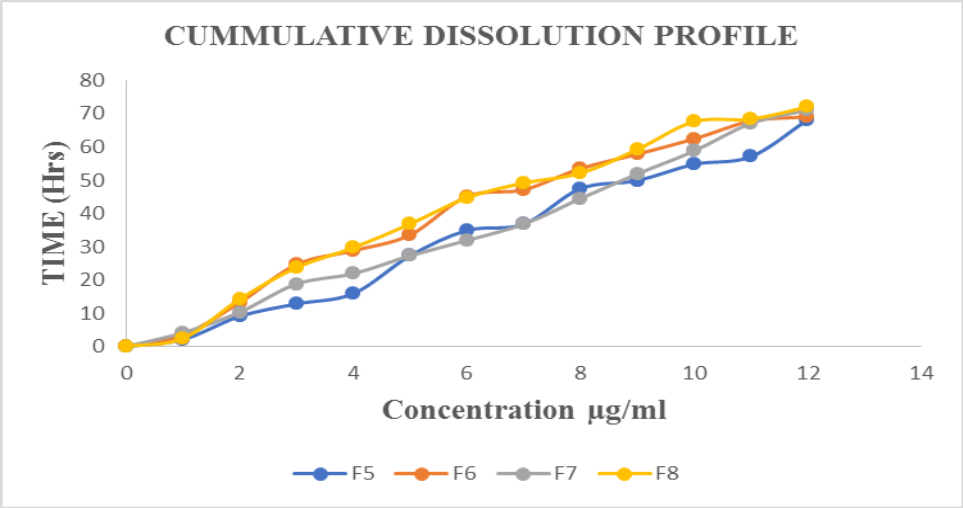


**Figure No 9: cumulative dissolution profile of Formulation 5 to Formulation 8.**

**Table No7: Cumulative % drug release for the batch F9 – F10.**

| Time (hr.) | F9 | F10 |
|---|---|---|
| **0** | 0 | 0 |
| **1** | 1.60±0.14 | 3.43±0.36 |
| **2** | 15.8±0.14 | 11.25±0.36 |
| **3** | 17.9±0.25 | 21.65±0.65 |
| **4** | 23.3±0.36 | 30.81±0.54 |
| **5** | 28.9±0.69 | 42.56±0.41 |
| **6** | 39.8±0.58 | 51.15±0.12 |
| **7** | 47.5±0.47 | 62.16±0.23 |
| **8** | 55.9±0.14 | 70.53±0.25 |
| **9** | 64.8±0.25 | 78.86±0.25 |
| **10** | 66.1±0.360 | 83.43±0.48 |
| **11** | 69.2±0.85 | 87.80±0.59 |
| **12** | 72.8±0.96 | 89.09±0.01 |

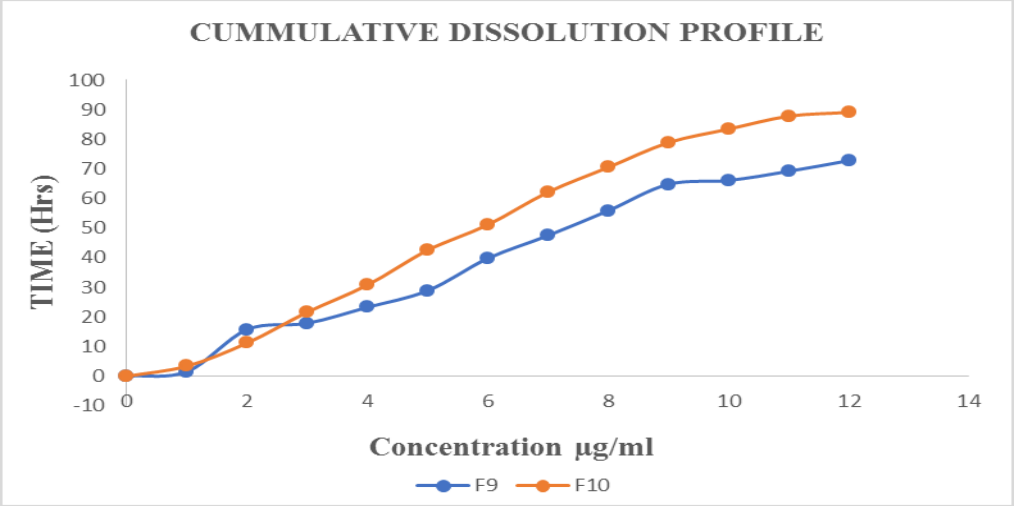


**Figure No 10: cumulative dissolution profile of Formulation 9 and Formulation 10.**

The release rate of pioglitazone transdermal patches was F1<F2<F3<F4<F5<F6<F7<F8<F9<F10 the highest invitro release of pioglitazone transdermal patches from F10 may be due to highest increase in solubility of drug within the mixture due to permeation enhancers that consequently facilitated the drug release from the patch into test media. The total cumulative drug release at the end of 12hrs was below 100% for all dosage forms.

## RELEASE RATE KINETICS

**Table No 8: Release rate kinetics.**

| S.NO | Model | $R^2$ value |
|---|---|---|
| **1** | Higuchi | 0.983 |
| **2** | Peppa's | 0.955 |
| **3** | First | 0.916 |
| **4** | Hixson Crowell | 0.912 |
| **5** | Zero | 0.910 |

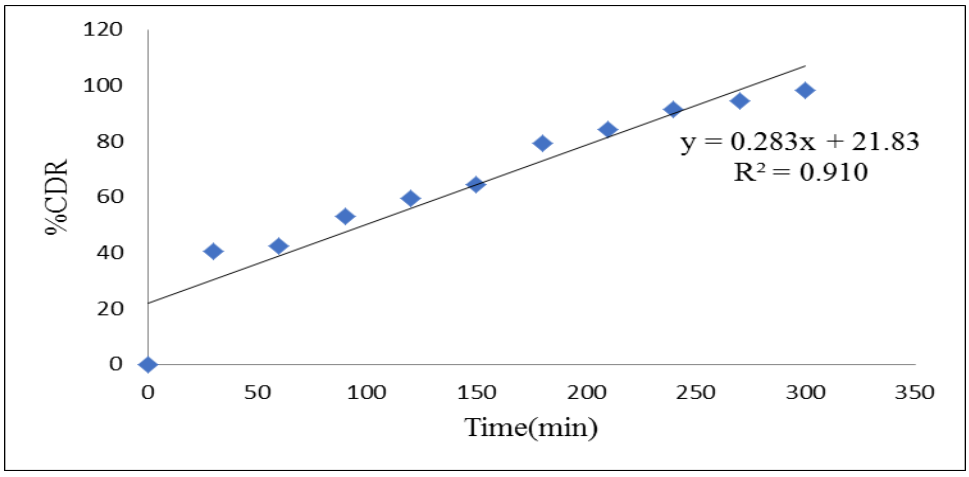


**Figure No 11: Zero order kinetic data of the optimized formula F10.**

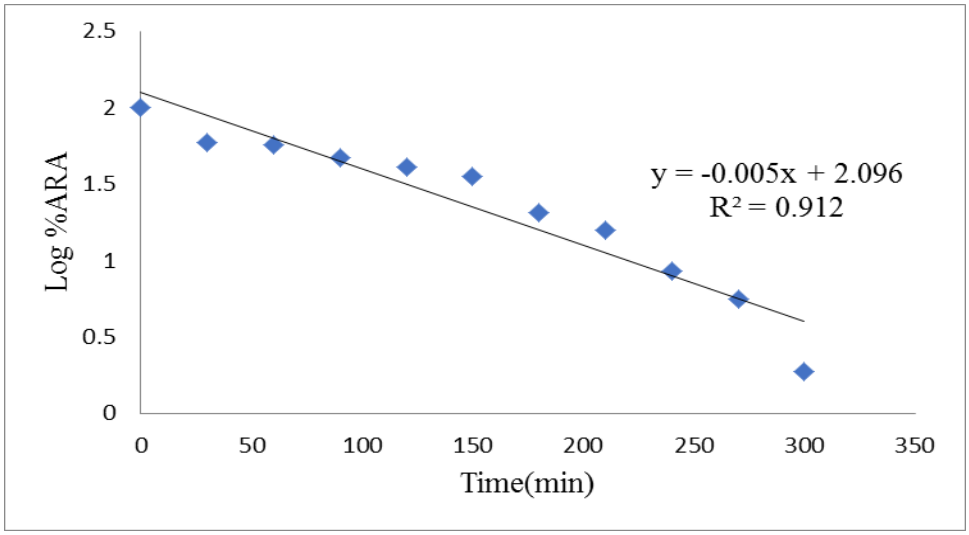


**Figure No 12: First Order kinetic data of the optimized formulation F10.**

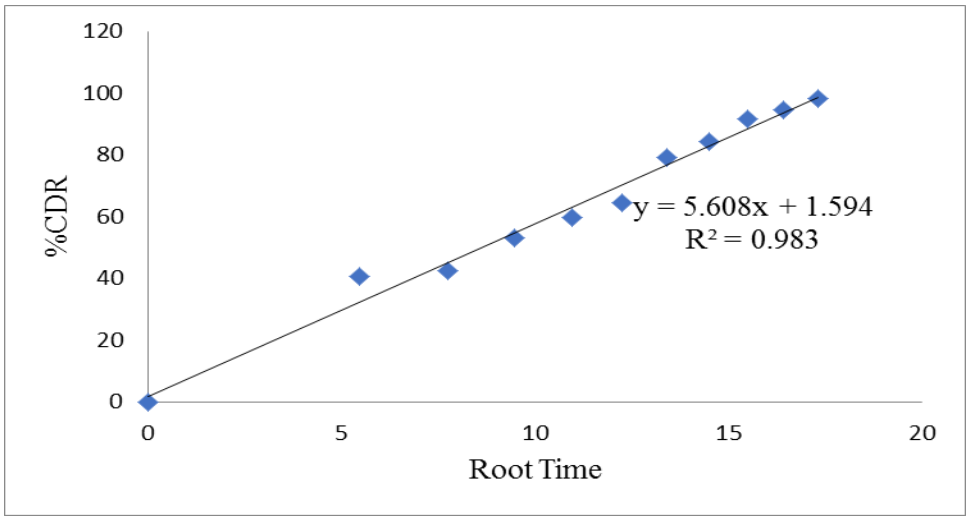


**Figure No 13: Higuchi release kinetics for the optimized formula F10.**

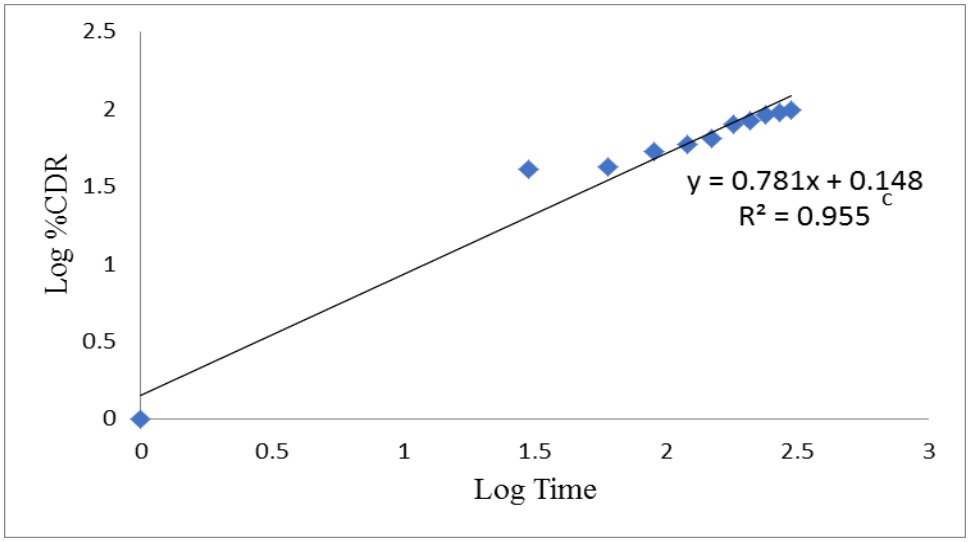


**Figure No 14: Peppa's Release kinetics for the optimized formulation F10.**

## CONCLUSION

The present investigation is concern with the development of the transdermal films and to increase the bioavailability of the drug and its half-life.

The following conclusions were drawn from results obtained;

1) A suitable method of analysis of Pioglitazone by UV Spectroscopy was developed. Pioglitazone showed maximum absorption at wavelength 0270nm. The value of regression coefficient of standard curve was found to be 0.999 which showed linear relationship between concentration and absorbance. Preformulation studies for drug-polymer compatibility by FTIR gave confirmation about their purity and showed no interaction between the drug and selected polymers.
2) Various formulations were developed by using release rate controlling polymers like HPMC E 15 in combination with Guar gum by solvent casting method to this formulation following evaluation are conducted required physicochemical properties such as drug content uniformity, folding endurance, weight uniformity, thickness uniformity, moisture content & moisture uptake.
3) From the results of the drug content determination, it shows that drug was proper distribution of drug in films and deviations are within the level. Optimized Formulation F10 was found to be best among all batches of its consistent release rate for 12 hrs. And the extent of drug release 89%.

It is concluded from the present studies that the transdermal patches of Pioglitazone can exhibit controlled release with the stability and the formulation F10 has fulfilled the objectives of the present study like reduction in the frequency of administration, improved patient compliance.

Studies have shown promising results, and there is a scope for further pharmacodynamic and pharmacokinetic evaluation.

## ACKNOWLEDGEMENT

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