IJBPAS, June, 2021, 10(6): 1841-1849

ISSN: 2277–4998

International Journal of Biology, Pharmacy and Allied Sciences (IJBPAS)

'A Bridge Between Laboratory and Reader'

www.ijbpas.com

# FORMULATION AND EVALUATION OF TRANSDERMAL PATCHES FOR METFORMIN HYDROCHLORIDE

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**Received 10th July 2020; Revised 8th Aug. 2020; Accepted 7th Sept. 2020; Available online 1st June 2021**

https://doi.org/10.31032/IJBPAS/2021/10.6.5505

## ABSTRACT

Diabetes Mellitus is a chronic metabolic disorder characterized by chronic hyperglycemia caused by insulin deficiency, often combined with insulin resistance and it is the most common endrocrine disorder affecting 3 – 4 % of the population and its incidence is rising day by day. In the year 2000, 150 million people worldwide had diabetes and expected to increase year by year. By 2030 the WHO estimates that number of people with diabetes will almost reach to double. For more than two decades, researchers have attempted to find a way to use the skin as a portal of entry for drugs in order to overcome problems associated with conventional modes of drug administration. The principle of transdermal drug delivery systems is to deliver drug across epidermis to achieve systemic effect over a prolonged period of time. Because of these attributes, transdermal drug delivery systems offer many advantages over conventional drug delivery system such as reduced side effects, improved patient compliance, elimination of first-pass metabolism, and sustained drug delivery. Considering all these problems associated with oral administration of anti diabetic drug, attempt has been made to develop TDDS in order to achieve

a better release pattern. Therefore, the present study involves the development of an anti diabetic drug (metformin hydrochloride) in transdermal drug delivery form and their evaluation.

**Keywords: diabetes mellitus, skin, antidiabetic drug, TDDS**

## INTRODUCTION

Skin, being the most extensive organ that receives one-third of the total blood supplied throughout the body, was not known to be a route of drug delivery for systemic drugs until the late 20th century. Over the last decade, the field of transdermal drug delivery has been gaining attention owing to its advantages over conventional oral dosage forms **[3]**. The global transdermal drug delivery market is estimated to grow and reach approximately $95.57 billion by 2025. Overdosing becomes a concern due to fluctuation in peak plasma concentration following oral and parenteral administration, making it a challenge in monitoring effective plasma concentration **[1]**. Transdermal drug delivery systems offer several benefits because drugs administered are able to bypass hepatic first-pass metabolism and factors that alter pharmacokinetics in the gastrointestinal tract. This significantly improves systemic bioavailability with reduced risk of side effects associated with concentration. This generally improves patient compliance as it is easy and convenient to apply with a lesser dosing frequency, as the drug is released at a predetermined rate over a prolonged period. This delivery provides the constant drug release but it also allows the short biological half-life drug continuously and eliminates the pulsed entry into the blood circulation. The Transdermal drug delivery system designed by various methods such as transdermal patches includes matrix, micro reservoir, reservoir, adhesive, and membrane matrix hybrid. Matrix type transdermal patches are most popular as they are easy to construct **[2]**.

Diabetes mellitus is the general term used to describe a group of metabolic diseases characterized by chronic hyperglycemia. The pathophysiology of diabetes is due to defective insulin secretion, impaired insulin action or both. Diabetes can be classified into different types depending on the pathogenesis and clinical manifestations at the time of diagnosis.

Type 1 diabetes mellitus (T1DM) is attributed to the destruction of insulin producing beta cells in the islets of langerhans, leading to absolute deficiency of insulin. Type1A diabetes mellitus, better known as insulin-

dependent diabetes mellitus, is immune mediated diabetes in which the immune system destroys beta cells with varying rates of destruction in different groups of patients. On the other hand, when no autoimmune mechanism of beta-cell destruction and no other known cause of insulin deficiency are identified, it is categorized as Type 1 diabetes mellitus or idiopathic diabetes.

Type 2 diabetes mellitus (T2DM), previously known as non-insulin dependent diabetes mellitus, is the most common type of diabetes mellitus, accounting for about 90%–95% of diabetic patients. In this type of diabetes, relative insulin deficiency and insulin resistance arising from genetic or environmental factors are observed. Obesity is often associated with T2DM and many patients go undiagnosed for many years.

Gestational diabetes mellitus is characterized by glucose in- tolerance of any degree with onset or first recognition during pregnancy regardless of whether or not such condition continues after pregnancy **[4]**.

The International Diabetes Federation reported that 12% of global health expenditure is on diabetes, corresponding to approximately USD 673 billion in 2015, and it is expected to reach USD 802 billion in 2040 **[7]**. The complications that result in early death and economic burden on healthcare systems create the need to delve into the landscape of drug delivery systems to improve blood glucose monitoring and diabetes treatment to combat this 21st century challenge. T1DM requires a continuous supply of insulin which can be achieved through daily insulin injections, while T2DM is treated with hypoglycemic agents with metformin being the most commonly prescribed medication. Injectable insulin is also used in some T2DM patients **[5]**.

Metformin is antidiabetic drug belongs to the class of biguanides. Metformin works by reducing the amount of glucose (sugar) made by your liver, decreasing the amount of glucose your body absorbs and increasing the effect of insulin on your body. Insulin is a hormone that helps your body remove extra sugar from your blood. This lowers your blood sugar levels. It is comes under two forms tablet and solution. Both forms are taken by oral. Metformin oral tablets comes in two forms, immediate release and extended release **[9]**. Metformin oral tablet can cause mild or serious side effects **[17]**.

The some of the key side effects that may occur while taking metformin as oral are diarrhea, nausea, stomach pain, heartburn etc., In some cases at inappropriate doses, can cause lactic acidosis and or hypoglycemia. Lactic acidosis symptoms can include weakness, unusual muscle pain, trouble breathing, un usual sleepiness, stomach pains, nausea, or vomiting, dizziness or lightheadedness, slow or irregular heart rate. Hypoglycemia (low blood sugar), symptoms can include weakness, confusion, shaking or feeling jittery, drowsiness, dizziness, irritability, sweating, hunger, fast heart rate. When it administered orally required more dose as compared to the transdermal drug delivery. In transdermal patch required fewer doses. It reduces the serious side effects caused by the dose level **[5, 6]**.

## MATERIALS AND METHODS

### Materials

Metformin hydrochloride(ubtained asgift sample from INTERMED pharmaceutics, Chennai.), Sodium benzoate, Propylene glycol, Polyvinyl alcohol, Glycinal, Sodium corboxy methyl cellulose, Glycerine, Polyvinylpyrrolidone K90, Hydroxyl propyl methyl cellulose, Sodium poly acrylate, Titanium dioxide, purified water.

**Table 1: (materials which were used for the formulation)**

| S.no | Materials | F1(mg) | F2(mg) | F3(mg) | F4(mg) | F5(mg) |
|---|---|---|---|---|---|---|
| 1 | Metformin Hcl | 500 | 500 | 500 | 500 | 500 |
| 2 | Sodium benzoate | 10 | 10 | 10 | 10 | 15 |
| 3 | Propylene glycol | 450 | 360 | 360 | 400 | 450 |
| 4 | Polyvinyl alcohol | 30 | 30 | 35 | 40 | 45 |
| 5 | Glycinal | - | 20 | 20 | 20 | 20 |
| 6 | Sodium corboxy methyl cellulose | - | - | 30 | 30 | 60 |
| 7 | Glycerine | 2700 | 2800 | 2700 | 2500 | 2875 |
| 8 | Polyvinyl pyrrolidone K90 | - | 30 | 60 | 60 | 100 |
| 9 | Hydroxyl propyl methyl cellulose K4M | 250 | 240 | 100 | 100 | 100 |
| 10 | Sodium polyacrylate | - | - | 25 | 35 | 50 |
| 11 | Titanium dioxide | 16 | 16 | 16 | 16 | 16 |
| 12 | Purified water | Q.S | Q.S | Q.S | Q.S | Q.S |

### Methods

### Preparation of the transdermal patches:-

- **Binder solution:** Weighed quantities of Polyvinyl alcohol is soaked in purified water until clear solution is obtained.
- **Active drug solubilising:** Sodium benzoate is dissolved in Propylene glycol then metformin hydrochloride was added and made it as clear solution.
- **Adhesive solution:** In glycerine hydroxyl propyle methyl cellulose,

Titanium dioxide, sodium carboxy methyl cellulose, polyvinyl-pyrrolidone K90, sodium polyacrylate were added and stirred for 15 minutes then glycinal has added to the mixture and stirred for another 5 minutes.

- **Mixing:** All the above contents were mixed together and made as homogeneous it has resulting with gel like texture.
- **Coating:** Formulated hydrogel mixture are spread over the non oven fabric and packed with release liner then cut into 3 piece by hydrogel coating and cutting line machine. The size of non woven fabric and release liner was adjusted as per the desired patche size(10×14)cm
- **Drying:** The coated patches were allowed to curing for 3 to 4 hours.
- **Packing:** Dried patches are packed with alluminium foil by four side sealing and packing machine

**Evaluation parameters:-**

**Physical appearance**

The patches were visually inspected for colour, presence of dust particles, gel clotting, and proper coating of gel on fabric.

**Weight uniformity**

The patches were subjected to weight variation by individually weighing of randomly selected patches. patches from each batch were weighed individually and the average weight was calculated **[8,11,12]**.

**Thickness uniformity**

The thickness of the patch has assessed at different points of the patch, from each formulation three randomly selected patches and the average was calculated. The standard Deviations of thickness were computed from the mean value **[10-12]**.

**Adhesiveness**

To check the adhesiveness of the prepared patches initial adhesiveness tester are used, transdermal patche was fixed on the initial adhesive tester by affixing cellotape on both side then a steel ball rolled on the sticky surface of the inclinate plate, according to the position of the strength of the cohesive surface can stick to one of the biggest steel ball size, (Ball size 18) not less than 5 seconds **[15]**.

**pH**

one formulated transdermal patch are transferred in a 250 ml stoppered conical flask and 70m of water has added, then placed in a sonicator for 60 minutes with temperature at 40ºC, after it turns to cool shake well and make it as homogenous

and finally the pH of the mixture checked with calibrated pH meter **[15, 16]**.

***In vitro* drug release study**

The paddle over disc method (USP apparatus V) is employed for assessment of the release of the drugs from the prepared patches. One transdermal patch was fixed over a glass plate with an adhesive. Then the glass plate is placed in a 500-ml of dissolution medium or the phosphate buffer (pH 7.4),and the apparatus is equilibrated to 32+ 0.5 ºC the paddle is then set at a distance of 2.5 cm from the glass plate and operated a speed of 50 rpm. Samples (5 ml aliquots) can be withdrawn at a appropriate time intervals up to 12 hours and analyzed by UV spectrophotometer **[12, 17, 15]**.

## RESULTS

**Table 2: Results obtained in physical examination, weight and thickness uniformity**

| Formulation Code | Physical appearance | Weight uniformity(gm) | Thickness uniformity (mm) |
|---|---|---|---|
| 1 | Pass | 8.96±1.2 | 0.90±0.02 |
| 2 | Pass | 9.53±0.8 | 0.92±0.01 |
| 3 | Pass | 9.86±0.5 | 0.91±0.02 |
| 4 | Pass | 10.30±0.2 | 0.94±0.01 |
| 5 | Pass | 10.45±0.5 | 0.96±0.01 |

**3: Results obtained in adhesiveness and pH testing**

| Formulation code | Adhesiveness | pH |
|---|---|---|
| 1 | 2 seconds /Fail | 6.8 |
| 2 | 2 seconds /Fail | 5.9 |
| 3 | 4 seconds/ Fail | 7.2 |
| 4 | > 5 seconds /Pass | 7.0 |
| 5 | > 5 seconds/ Pass | 6.9 |

**Table 4: Percentage of drug release in *in vitro* drug release testing**

| Time (hours) | Cumulative percentage of drug release | | | | |
|---|---|---|---|---|---|
| | F1 | F2 | F3 | F4 | F5 |
| 1 | 19.07±0.71 | 20.5±0.65 | 25.1±0.65 | 32.7±0.54 | 28.3±0.66 |
| 2 | 32.3±0.68 | 34.2±0.58 | 48.5±0.55 | 57.28±0.44 | 48.7±0.44 |
| 4 | 56.2±0.57 | 58.4±0.56 | 61.1±0.51 | 63.42±0.58 | 61.1±0.41 |
| 6 | 65.5±0.55 | 68.4±0.58 | 70.1±0.45 | 70.09±0.54 | 71.5±0.42 |
| 8 | 70.68±0.51 | 71.7±0.55 | 80.5±0.69 | 78.56±0.56 | 84.2±0.54 |
| 10 | 72.65±0.50 | 72.4±0.52 | 89.4±0.65 | 91.05±0.45 | 94.1±0.42 |
| 12 | 75.17±0.49 | 82.6±0.50 | 95.7±0.57 | 98.68±0.58 | 99.1±0.52 |

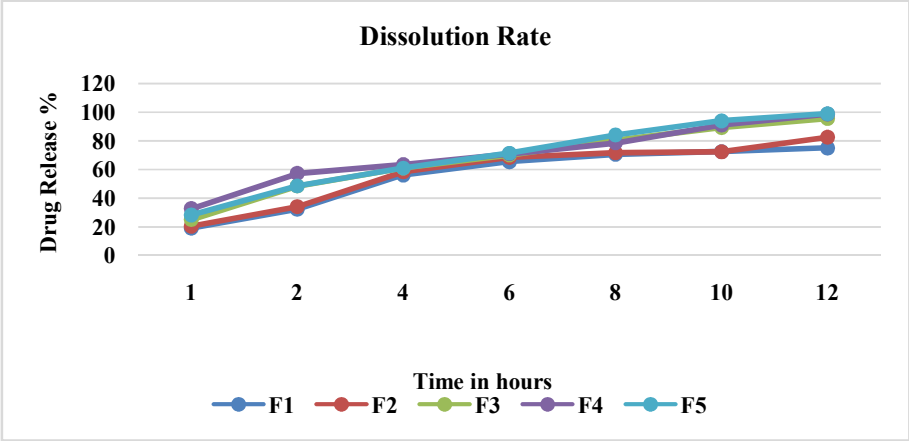


**Figure 1: Plot of time / amount of drug release**

## DISCUSSIONS

In this study matrix type patches were prepared by varying polymer combination and polymer ratios and finished formulations are subjected to various evaluation parameters like weight uniformity, thickness uniformity, physical appearance and percentage drug release.

In the physical examination there is no any defective patches all the patches passes the physical evaluation. Both by weight and thickness uniformity all the formulation has average values. Formulation 1,2,3,4 and 5 passes in physical examination, weight uniformity, thickness uniformity, pH and % drug release testing. Formulation 4 and 5 passes in adhesiveness test but 1,2 and 3 has failed.

## CONCLUSION

In the present study, an attempt was made to formulate and evaluate transdermal drug delivery system for an antidiabetic drug Metformin hydrochloride, transdermal patches of drug in adhesive type were prepared.

All the formulations showed a good quality results in evaluation parameters such as physical appearance, weight uniformity, thickness uniformity, adhesiveness, and pH.

Based above results and discussion we can conclude that F4 and F5 has found to be suitable ratio for formulating drug in adhesive transdermal patches.

Metformin hydrochloride is anti-diabetic drug helps to maintain the sugar level when it administered orally required more dose compared to the transdermal dug delivery. In transdermal required fewer doses. It is very better for topical route, it may improve compliance of patient those unable to take drug orally.

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