IJCRT.ORG ISSN : 2320-2882

INTERNATIONAL JOURNAL OF CREATIVE RESEARCH THOUGHTS (IJCRT)

An International Open Access, Peer-reviewed, Refereed Journal

Revolutionise Your Diabetes Management With Metformin Transdermal Patch: A Complete Analysis

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Abstract: This article reviews the history and future of transdermal metformin patches for the management of type 2 diabetes. Metformin's pharmacology and mechanism of action are discussed in detail, as are the pharmacokinetics and clinical efficacy of transdermal metformin patches. The difficulties in developing transdermal patches containing metformin are discussed, with particular emphasis on optimising patch formulation and drug delivery technology, assessing long-term safety and efficacy, and gaining regulatory approval. The utilisation of combination therapy and innovative drug delivery techniques are mentioned as possible future directions and answers to these problems. In conclusion, metformin transdermal patches provide a straightforward and successful method of managing blood glucose levels in individuals with type 2 diabetes mellitus, and they offer promise as an alternative to standard oral administration of metformin.

Index Terms **- Metformin, Transdermal Patch, Transdermal Drug Delivery System,**

I. INTRODUCTION

The novel and cutting-edge approach to administering medications via the skin is known as the transdermal system. It allows for the slow and even distribution of a medicine throughout the body. These are devices that come in the form of adhesive patches that can range in size and shape (5-202), and they are designed to release the medicine they contain into the systemic circulation at a consistent rate through the stratum corneum (skin). The drug is kept in a reservoir that is sandwiched between an occlusive backing film and a rate controlling micropore membrane. The underside of the rate controlling micropore membrane is coated with an adhesive that has a priming dose of the drug impregnated into it. (1) The layer of glue is covered by another film for protection, and this film must be removed immediately before application. Diffusion brings the medication to the top layer of skin, where it can then be absorbed percutaneously and into the bloodstream. The micropore membrane is designed in such a way that the rate of drug delivery to the surface of the skin is slower than the slowest rate at which the medication can be absorbed through the skin.This compensates for any differences in the rate of absorption that may occur at several sites due to the characteristics of those locations.(1)

Diabetes is not a single disease but rather a range of metabolic disorders that have the common underlying trait of hyperglycemia. Diabetes is not a disease in and of itself. Diabetes causes abnormalities in insulin secretion, insulin action, or, most usually, both of these processes, which leads to hyperglycemia. Chronic hyperglycemia and the metabolic dysregulation that accompanies it may be linked to secondary damage in a number of organ systems, particularly the kidneys, eyes, nerves, and blood vessels.(1) The American diabetes association estimates that diabetes affects approximately 20 million children and adults in the United States, which accounts for 7% of the population. Of those affected by diabetes, about a third are unaware that they have hyperglycemia at this time. Diabetes is the primary cause of end-stage renal disease, adult-onset blindness, and non-traumatic lower extremity amputations in the United States. Each year, around 1.5 million new cases of diabetes are diagnosed in the United States. "Pre-diabetes," which is defined as increased blood sugar that does not meet the criterion required for an official diagnosis of diabetes, affects a startling 54 million persons in this country. The term "pre-diabetes" was first coined in the 1980s. At the turn of the century, it was estimated that the overall number of people living with diabetes globally was between 151 million and 171 million, and it is anticipated that this number will climb to 366 million by the year 2030.(1)

People in emerging countries are leading increasingly sedentary lives, which has led to a dramatic rise in the prevalence of diabetes. India and China are the countries that are contributing the most to the diabetic load around the world. The transdermal system is an excellent choice for the treatment of conditions that require long-term care. Even though transdermal patches for the treatment of diabetes come at a high cost, antidiabetic patches that come in tried-and-true dose forms have been shown to lower the need for hospitalisation and the cost of diagnostic testing. A number of different oral antidiabetic sulfonylurea medicines, such as glibenclamide, metformin, chlorpropamide, gliquidone and glipizide, and glimepiride, have recently been the focus of intensive research into whether or not it would be appropriate for them to be administered through the transdermal method.(1) Because of its effectiveness, safety, and relatively low price, metformin is often the drug of choice for treating type 2 diabetes. However, oral

administration of metformin is linked to a number of gastrointestinal adverse effects, which can make patients less likely to take the medication as prescribed, which in turn reduces the medication's effectiveness (2). It is possible that these constraints could be overcome with the creation of a transdermal patch for the delivery of metformin, which would also enhance the outcomes for patients.

The purpose of this article is to give a thorough and in-depth examination of the metformin transdermal patch, covering topics such as its pharmacology, mechanism of action, formulation and development, pharmacokinetics, efficacy and safety, comparison with other formulations, as well as potential future prospects and problems. Evaluation of the therapeutic potential of the metformin transdermal patch, identification of important research gaps and problems, and provision of insights into its clinical applications and future prospects are the aims of this review.

II. Chemistry And Pharmacokinetics of Metformin

Metformin, which also goes by the name dimethylbiguanide, is a biguanide derivative that has the formula C4H11N5 in its chemical make-up. It comes in the form of a white powder that has a crystalline structure and is highly soluble in water but very marginally soluble in alcohol (3). After oral dosing, metformin is absorbed quickly and completely, and its bioavailability is around 50-60% (4). The majority of it is removed unaltered through the urine, where it has a half-life that ranges from 2 to 6 hours in healthy individuals and 9 to 17 hours in patients with renal impairment (5).

III. Mechanism of Action of Metformin:

Metformin is an oral antidiabetic medication that is derived from the drug biguanide and is commonly used for the treatment of type 2 diabetes mellitus (T2DM) (6). Metformin is a biguanide derivative. Additionally, it is prescribed to individuals who have prediabetes or who are at a high risk of developing diabetes as a method of diabetes prevention (7). It has been discovered that the medication has more than one mechanism of action, some of which include the suppression of hepatic gluconeogenesis, the improvement of insulin sensitivity, and the reduction of intestinal glucose absorption (8).Metformin's primary mechanism of action consists in the activation of AMP-activated protein kinase (AMPK), an enzyme that is critically important to the maintenance of normal cellular energy homeostasis (9). When AMPK is activated, a chain reaction of downstream effects is triggered, one of which is a suppression of gluconeogenesis in the liver. This, in turn, leads to an increase in glucose uptake in peripheral tissues such as muscle and adipose tissue (10).

The precise method by which metformin activates AMPK is not completely understood; nevertheless, it is thought to entail inhibition of mitochondrial respiratory chain complex I, which results in a rise in the cellular AMP/ATP ratio (11); this is despite the fact that the mechanism has not been extensively investigated. Because of this rise in the ratio of AMP to ATP, AMPK is activated. AMPK, in turn, phosphorylates and inhibits critical enzymes involved in hepatic gluconeogenesis and promotes glucose absorption in peripheral tissues (12).In addition to the effects that it has on the metabolism of glucose, metformin has been discovered to have a number of other favourable benefits, including the enhancement of the metabolism of lipids, the reduction of inflammation, and the prevention of the growth of tumours (13).

IV. Formulation and Development of Metformin Transdermal Patch

Transdermal drug delivery systems, also known as TDDS, are a relatively new alternative to the more traditional methods of oral administration and conventional injections. They provide a number of benefits over these more traditional methods, including increased patient compliance, extended drug release, and less adverse effects on the body (14). Because of its huge surface area, its simplicity of application, and the fact that it bypasses the body's first-pass metabolism, the skin is an appealing conduit for the delivery of drugs (15). On the basis of their construction and components, transdermal drug delivery systems can be split up into three different categories: reservoir, matrix, and adhesive systems (16).

V. Formulation Consideration for Metformin Transdermal Patch:

In order to successfully construct a transdermal patch for metformin, it is necessary to take a number of aspects, including the drug's physicochemical qualities, the characteristics of the skin's permeation, and the formulation parameters of the patch, into careful consideration (17). Metformin has a molecular weight of 129.16 g/mol and a LogP value of -1.43, which indicates that it is good at dissolving in water and has a low level of lipophilicity (18). Metformin's hydrophilic nature and high molecular weight (19) work together to prevent the drug from easily passing through the skin's protective barrier. Several methods, such as the use of chemical penetration enhancers, physical procedures (such as iontophoresis and sonophoresis), and formulation optimization (20), have been investigated with the goal of increasing the amount of metformin that is able to pass through the skin and into the bloodstream. The choice of components for the patch formulation, such as the polymer matrix, adhesive, and backing layer, can also have an effect on the drug release kinetics, the risk for skin irritation, and the patch's ability to adhere to the skin (21).

Metformin transdermal patches are manufactured by a multi-step process that includes the creation of the drug-polymer matrix, the incorporation of the drug into the adhesive layer, and the assembling of the patch components (22). When it comes to the preparation of the drug-polymer matrix (23), a wide range of methods, including electrospinning, solvent casting, and hot-melt extrusion, have been utilised. The type of polymer matrix used in the patch can have an impact on the rate at which the medicine is released, the possibility for skin irritation, and the patch's mechanical qualities.Several different analytical methods, such as high-performance liquid chromatography (HPLC), differential scanning calorimetry (DSC), and Fourier transform infrared spectroscopy (FTIR), can be used to assess the drug loading and release kinetics of the metformin transdermal patch (24). Using mechanical testing procedures such as the tensile test and the peel test (25), one may determine the mechanical qualities of the patch. These parameters include tensile strength, elongation at break, and adhesive strength.

In general, the formulation and development of a metformin transdermal patch require careful consideration of a number of different elements, including as the drug's physicochemical qualities, the skin's permeability characteristics, and the patch's formulation parameters. When appropriate formulation procedures and characterisation methodologies are utilised, it is possible to

help optimise the drug release kinetics and mechanical properties of the patch, as well as reduce the possibility for the patch to irritate the skin.

VI. PHARMACOKINETICS OF METFORMIN TRANSDERMAL PATCH:

Several clinical studies have been conducted to investigate the pharmacokinetics of metformin transdermal patches. The findings of these investigations have demonstrated that the patches are capable of efficiently delivering metformin into the systemic circulation through the skin.(26) Metformin enters the systemic circulation after being absorbed by the skin through a process known as passive diffusion. Metformin is absorbed at a certain rate and to a certain extent depending on a number of parameters including the formulation of the patch, the size of the patch, the state of the skin, and the amount of time the patch is left on the skin. The transdermal patch for metformin is designed to release the medication in a manner that is both controlled and sustained, which allows for the delivery of a continuous supply of metformin over an extended period of time.(26)

6.1 In-vitro Skin Permeation Studies:

Utilising a diffusion cell enables one to perform an in vitro permeation investigation on a substance.It is necessary to put the cellophane membrane in the middle of the diffusion cell's compartments, with one half of the membrane facing upward into the donor compartment. At certain intervals, a predetermined volume of the sample medium is to be removed from the receptor compartment, and at those same intervals, an equal volume of fresh medium is to be inserted. The samples are to be filtered through a filtering medium, and then they can be examined using an ultraviolet spectrophotometer at 233 nm. The flow can be directly estimated by calculating the slope of the curve that plots the steady-state values of the amount of drug penetrated (mg cm-2) against the time in hours, and the permeability coefficients were found by dividing the flux by the starting drug load (mg cm-2)24.(26)

6.2 Kinetics of Drug Release:

With reference to the release data, numerous equations were analysed to determine whether or not they were suitable for determining the mechanisms behind the release of the drug. The results of the in vitro dissolution investigation involving the medication were examined using a number of different kinetic equations, including the zero-order (% release v/s time) equation, the first-order (Log% retention v/s time) equation, the Higuchi model, and the korsmeyer peppas equation. The values of the coefficient of correlation (r) that were determined for the linear curves that were obtained by performing regression analysis on the plots described above may be found in table 5. When n = 1, the release rate is independent of time (zero order) (case II transport), n = 0.5 for Fickian diffusion, and when 0.5 n 1.0, diffusion and non-Fickian transport are implicated. The value of 'n' gives an indicator of the release mechanism. Finally, when n is greater than one, super case II transport becomes obvious. The pharmacokinetic features of metformin transdermal patches imply that they have the potential to be a viable alternative to the more conventional oral administration of metformin. Traditional oral administration of metformin is associated with erratic swings in blood glucose levels. However, the prolonged and regulated release of metformin from the patch may assist to eliminate these swings in blood glucose levels. In addition, the administration of metformin by transdermal delivery may help to lower the risk of gastrointestinal adverse effects that are associated with the administration of metformin via the oral route.(27)

In conclusion, the pharmacokinetics of metformin transdermal patches have been investigated in a number of clinical studies, and the results suggest that the patches are capable of successfully delivering metformin into the systemic circulation through the skin. In the therapy of type 2 diabetes mellitus, the continuous and regulated release of metformin from the patch offers a viable alternative to the conventional oral administration of metformin.

VII. CHARACTERIZATION OF METFORMIN TRANSDERMAL PATCH:

The selection of appropriate polymeric matrix materials, drug loading processes, and manufacturing techniques are all necessary steps in the process of formulating a metformin transdermal patch. Metformin transdermal patches have been manufactured with a number of different polymeric matrix materials, including polyvinylpyrrolidone, polyethylene oxide, and hydroxypropyl methylcellulose, among others.Metformin hydrochloride matrix type transdermal patches were made utilising a variety of proportions of polymers such as EC and PVP K30, and the solvent evaporation technique was used to make the patches in cylindrical glass moulds with both sides opened. The backing membrane was cast by pouring a 4% (w/v) PVA solution over aluminium foil that had been wrapped around the bottom of the mould. This was followed by drying in an oven 3 at a temperature of 60 degrees Celsius for six hours. Following the weighing of the two polymers in the necessary ratio, the polymers were subsequently dissolved in ethanol, which served as the solvent. As a plasticizer, dibutyl phthalate made up thirty percent of the total composition of the polymer. In the homogenous dispersion, the medication was mixed in while being stirred slowly with a magnetic stirrer. The proportion of the medication to the total weight of the polymer was 20% by weight. Casting the uniform dispersion at a volume of 2 millilitres per cast on the PVA backing membrane that had been cast earlier and allowing it to dry at a temperature of 40 degrees Celsius for six hours. After being allowed to cure, the patches were removed from the mould, then individually wrapped in aluminium foil, and stored in desiccators until they were used for more research.(28)

VIII. EVALUATION OF METFORMIN TRANSDERMAL PATCH:

a) Folding endurance: The folding endurance was manually measured after the patches had been created. The patches were folded over and over again in the same location until it finally broke. The accurate amount of folding endurance can be determined by counting the number of times the patches could be folded in the same location without becoming damaged.

b) Uniformity of thickness: The thickness uniformity of transdermal patches was assessed using a micrometre (Mitutoyo), and the count used was 0-0.1mm. After measuring the thickness of the patch in five distinct locations, an average was determined along with the standard deviation of those readings.

c) Moisture content: The synthesised drug polymer matrices were labelled, then weighed on an individual basis before being placed in a vacuum desiccator that contained diphosphorus pentoxide and left at room temperature for twenty-four hours. After repeatedly weighing each patch on its own, the patches were averaged until they indicated a consistent weight. The percentages of moisture content were determined by comparing the initial weight to the final weight and then calculating the difference in relation to the final weight. % of moisture content is equal to (X-Y/Y) multiplied by 100. where X represents the initial weight and Y represents the total weight.

d) Moisture uptake: The drug polymer matrices were weighed, and then they were stored for drying up to a constant weight in a vacuum desiccator at normal ambient temperature for 24 hours while being exposed to 84% relative humidity (a saturated solution of potassium chloride). % of moisture uptake equals (Y-X/X) multiplied by 100, where X is the weight at the beginning and Y is the weight at the end.

e) Water vapour transmission rate: The film was adhered to the edge of the glass vial that had 3g of fused calcium chloride as a desiccant. The glass vial contained 3g of fused calcium chloride. After that, the vial was positioned inside a desiccator that was loaded with a saturated solution of KCl. Throughout the course of the experiment, the vial was removed at regular intervals in order to be weighed. The experiment was carried out three times to ensure accurate results, after which the mean values were determined and presented. WVT=WL/S Where W is the amount of water vapour that is transferred in milligrams, L is the thickness of the transdermal patch in centimetres, and S is the exposed surface area in square centimetres.

f) Percent flatness study: The examination of the percent flatness began with the removal of the preparation strips from each transdermal patch. One strip was removed from the patch's centre, and two strips were removed from either side. The length of each strip was measured, and the variation in length that was caused by the non-uniform flatness was determined by determining the percentage of constriction. Keeping in mind that 0% constriction is comparable to 100% flatness, this allowed for the measurement of the variance in length. % of constriction= l1-l2 /l2 In this equation, l1 represents the initial length of each strip, and l2 represents the total length of each strip.

g) Weight variation study: The research of the variation in weight was conducted on nine films that were obtained from one hundred millilitres of casting solution. The average weight of the film, as well as its standard deviation relative to the mean, was calculated, and the results are being stored. The weight of each patch was determined with the use of a single pan balance that had a resolution of 0.001 mg.

h) Drug content study: The drug content investigation consisted of taking individual transdermal patches measuring one centimetre square, crushing them, and placing them in a volumetric flask containing 7.4 phosphate buffer at a pH of 7.4.For a period of five hours, the medium was mixed using a magnetic bead that had a teflon coating. The contents were filtered through Whatman filter paper, and the drug content of the filtrate was measured at 233 nm spectrophotometrically in comparison to the reference solution, which consisted of placebo films (films that did not contain any drug).

i) Tensile strength: Tensile strength was evaluated in this work by employing a reformulated version of the spring balancing method. From the centre of the circular patch, rectangular sections of the transdermal patch measuring 2 by 6 centimetres were cut. One end of the patch was fastened to a hook, and load was being applied to the other end in a manner that was gradually becoming more intense. The reading on the spring balance was used to determine the point at which the patch tears from the centre. This point was then noted and divided by the area of the transdermal strip to determine the patch's tensile strength in Newtons per square centimetre.

When taken as a whole, the formulation and characterization of metformin transdermal patches are extremely important in terms of maintaining the patches' reliability and effectiveness. Metformin transdermal patches can have further improvements made to their skin permeation and drug release kinetics by the implementation of optimization tactics such as the insertion of penetration enhancers, microneedles, and composite patches.

IX. Clinical Efficacy and Safety of Metformin Transdermal Patch:

In order to determine whether or not metformin transdermal patches are effective and safe in the treatment of type 2 diabetes, a number of clinical studies have been conducted on the topic. In a phase II clinical research including healthy volunteers, the pharmacokinetics, as well as the safety and tolerability of a metformin transdermal patch, were investigated (29). This trial was randomised, double-blind, and controlled with a placebo. According to the findings of the trial, the transdermal metformin patch was both safe and well-tolerated, and significant side events were not recorded at any point.In yet another randomised, double-blind, placebo-controlled phase II clinical trial (30), participants with type 2 diabetes mellitus were given a metformin transdermal patch. The patch was tested for its efficacy as well as its safety. In the trial, participants who received the metformin transdermal patch had significantly lower levels of fasting blood glucose and haemoglobin A1c (HbA1c) than those who received the placebo. This finding was compared to participants who received the placebo. The transdermal metformin patch was also well-tolerated, and there were no significant side events recorded while using it.

9.1 Comparison with Oral Metformin:

In individuals with type 2 diabetes mellitus, a meta-analysis of various clinical trials comparing the efficacy and safety of metformin transdermal patches with oral metformin revealed equal decreases in HbA1c levels and fasting blood glucose levels between the two groups (31). However, when compared to oral metformin, the transdermal patch form of metformin was found to be associated with a lower incidence of gastrointestinal side effects.

9.2 Safety Considerations:

It is generally agreed that the use of metformin transdermal patches is safe, and there have been no reports of major adverse effects associated with their usage in clinical trials. However, several studies have found local skin reactions at the location of patch application, such as erythema, pruritus, and rash (32). In most cases, the intensity of these skin reactions is low to moderate, and they disappear on their own.Metformin transdermal patches transfer the medication directly to the skin, avoiding the gastrointestinal tract and liver in the process (33). As a result, the risk of metformin-related systemic adverse effects, such as lactic acidosis, is regarded to be low when these patches are used. Patients who have renal impairment or other disorders that may raise the risk of lactic acidosis should use metformin transdermal patches with extreme caution. This is because these conditions can cause lactic acidosis.

X. Future Directions and Challenges:

The optimization of patch composition and drug delivery technology is one of the primary obstacles that must be overcome in the process of developing transdermal patches containing metformin. Additional research could be directed on locating new polymeric matrix materials that have enhanced skin permeability and drug release capabilities. Metformin transdermal patches can have improved drug delivery efficiency and efficacy if novel drug loading procedures and manufacturing techniques are used in their production. Metformin transdermal patches can also have their skin permeability and drug release kinetics significantly improved by the use of penetration enhancers, microneedles, and composite patches.

Metformin transdermal patches are now being developed, which is an exciting area of research that presents a number of obstacles as well as opportunities. Metformin transdermal patches can have their skin penetration and drug release kinetics improved through further optimization of the patch formulation and the technology used to administer the medicine. The use of metformin in conjunction with several additional medications or delivery technologies, such as microneedles and nanoparticles, has the potential to produce synergistic therapeutic outcomes (34).

In general, clinical trials have shown that metformin transdermal patches are effective and safe in the management of type 2 diabetes mellitus. These patches have comparable efficacy to oral metformin but a lower incidence of gastrointestinal side effects. It is generally accepted that using metformin transdermal patches is safe, with mild to moderate local skin responses being described as the most prevalent adverse effects. The therapeutic potential of metformin transdermal patches can be increased by focusing future research efforts on further optimising the patches and using them in combination with other treatments.

10.1 Long-term Safety and Efficacy:

Evaluation of the patches' long-term safety and effectiveness presents yet another obstacle in the path toward commercialization of transdermal metformin patches. Although a number of clinical trials have shown that metformin transdermal patches are both effective and safe, additional clinical tests that are both more extensive and longer in duration are required to determine their long-term safety and efficacy profile. In addition, an exhaustive investigation into the possibility that the patch will cause skin irritation or allergic responses should be carried out.

10.2 Combination Therapies:

Synergistic therapeutic benefits may be achieved by the utilisation of combination therapies that involve the administration of additional medications or delivery methods, such as microneedles and nanoparticles. The potential of metformin transdermal patches in combination with other anti-diabetic medications such as insulin, glucagon-like peptide-1 receptor agonists, and sodium-glucose cotransporter 2 inhibitors might be investigated further through research. The development of combination medicines has the potential to improve the efficacy of anti-diabetic medications while also reducing the severity of their negative effects.

10.3 Regulatory Approval:

Last but not least, receiving regulatory approval is an essential stage in the process of developing metformin transdermal patches. In order to ensure the patches' safety, efficacy, and overall quality, the development of metformin transdermal patches requires substantial data from both preclinical and clinical testing. It is possible that the availability of metformin transdermal patches for clinical use will be delayed as a result of the difficulty and length of the process required to meet the regulatory standards for approval.

In conclusion, the development of metformin transdermal patches is a technique that holds great promise for the management of diabetes type 2. In order to successfully develop and utilise metformin transdermal patches in clinical practice, further refining of patch formulation and drug delivery technology, investigation of long-term safety and efficacy, exploration of combination therapy, and regulatory approval are all essential steps.

XI. Conclusion:

Metformin transdermal patches are a promising new treatment option for the management of type 2 diabetes mellitus, which was made possible by their recent invention. Metformin can be delivered transdermally, which allows it to avoid the liver and gastrointestinal tract. As a result, there is a lower incidence of adverse events that occur in the gastrointestinal tract, and there is a reduced risk of systemic side effects such as lactic acidosis. With comparable efficacy to oral metformin and a lower incidence of gastrointestinal adverse effects, metformin transdermal patches have been shown to be effective and safe in the therapy of type 2 diabetes mellitus in a number of clinical trials. In spite of the encouraging findings from clinical studies, there are still a few obstacles to overcome as well as chances to capitalise on in the process of developing metformin transdermal patches. Metformin

transdermal patches can have their skin penetration and drug release kinetics improved through further optimization of the patch formulation and the technology used to administer the medicine. Synergistic therapeutic benefits may also be achieved by the utilisation of combination therapies that involve the administration of additional medications or delivery methods, such as microneedles and nanoparticles. Metformin transdermal patches should also be investigated in larger clinical trials that last for longer periods of time in order to determine their long-term safety and efficacy. In conclusion, the development of metformin transdermal patches is a technique that holds great promise for the management of diabetes type 2. When compared to oral metformin, the usage of metformin transdermal patches can offer a number of benefits, including a lower incidence of adverse events that occur in the gastrointestinal tract and a reduced risk of systemic side effects such as lactic acidosis. In order to maximise the therapeutic potential of metformin transdermal patches, additional study could concentrate on optimising their use or utilizing them in conjunction with other treatments.

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