|| ISSN(online): 2589-8698 || ISSN(print): 2589-868X ||
International Journal of Medical and Biomedical Studies
Available Online at www.ijmbs.info
NLM (National Library of Medicine ID: 101738825)
Index Copernicus Value 2019: 79.34
Original Research Article
Volume 5, Issue 7; July: 2021; Page No. 121-127

FORMULATION AND EVALUATION OF CLOPIDOGREL BISULFATE TRANSDERMAL PATCHES

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Article Info: Received 24 May 2021; Accepted 05 July 2021
DOI: https://doi.org/10.32553/ijmbs.v5i7.2037
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Conflict of interest: No conflict of interest.

Abstract
Transdermal drug delivery is an alternative route for systemic drug delivery which minimizes the absorption and increases the bioavailability. The main objective of the present work was to develop a suitable matrix type transdermal drug delivery system of Clopidogrel bisulphate using different polymers HPMC E15, Eudragit L100 and to compare the drug release through physical method and chemical method. Matrix type transdermal patches containing Clopidogrel Bisulfate were prepared by solvent evaporation technique. The prepared transdermal patches were evaluated for Thickness, folding endurance, tensile strength and in vitro studies. The prepared transdermal drug delivery system of Clopidogrel bisulphate using different polymers such as HPMC E15 and Eudragit L 100 had shown good promising results for all the evaluated parameters. Based on the In-vitro drug release, drug content and folding endurance results formulation F4 was concluded as an optimized formulation which shows its higher percentage of drug release.
Keywords: Transdermal drug delivery, Clopidogrel bisulphate, HPMC E15, Eudragit L100

Introduction

At present, the most common form of delivery of drugs is the oral route. While this has the notable advantage of easy administration[1], it also has significant drawbacks namely poor bioavailability due to first pass metabolism and the tendency to produce rapid blood level spikes (both high and low), leading to a need for high and or frequent dosing, which can be inconvenient[2].

Continuous intravenous infusion is recognized as a superior mode of drug administration not only to bypass hepatic "first-pass" metabolism, but also to maintain a constant and prolonged drug level in the body[3]. A closely monitored intravenous infusion can provide the advantages of both direct entry of drug into the systemic circulation and control of circulating drug levels. However, such mode of drug administration entails certain risks and, therefore, necessitates hospitalization of the patients and close medical supervision of administration[4].

To overcome these difficulties there is a need for the development of new drug delivery system; which will improve the therapeutic efficacy and safety of drugs by more precise (i.e., site specific), spatial and temporal placement with in the body there by reducing both the size and number of doses[5,6]. New drug delivery system is also essential for the delivery of novel, genetically engineered pharmaceuticals (i.e., peptides, proteins) to their site of action, without incurring significant immunogenicity or biological inactivation. Apart from these advantages the pharmaceutical companies recognize the possibility of re-patenting successful drugs by applying the concepts and techniques of controlled drug delivery system in bringing new drug to the market[7]. One of the methods most often utilized has been transdermal delivery i.e., transport of therapeutic substances through the skin for systemic effect[8].

The present study was designed to develop a suitable matrix type transdermal drug delivery system of Clopidogrel bisulphate using different polymers HPMC E15, Eudragit L100 and to compare the drug release through physical method and chemical method.

Materials and Methods:

Clopidogrel Bisulfate was gifted from Aurobindo Pharmaceuticals. HPMC E15 and Eudragit L 100 were procured from Qualikem fine chemicals Ltd. Chloroform AR and Methanol AR obtained from Merck Ltd, India. Polyethylene glycol, Calcium chloride, Aluminium chloride, Potassium dihydrogen phosphate and Sodium hydroxide were procured from Finar chemicals limited, India.

Preparation of Clopidogrel Bisulfate Transdermal Films:

Matrix type transdermal patches containing Clopidogrel Bisulfate were prepared by solvent evaporation technique, using different ratios of HPMCE 15 and Eudragit L100. The polymers were weighed in requisite ratios and allowed for swelling for about 6 h. in solvent mixture (1:1 ratio of methanol and chloroform) 15%v/w Polyethylene glycol was in corporate as plasticizer. Then the drug solution was

added to the polymeric solution, casted on to a Petri plate of surface area about 66.44 cm^2. Allowed for airdrying overnight followed by vacuum drying for 8-10 hr. The entire sheet was cut into small patches with an area of 4.9 cm^2 i.e., with a diameter of 2.5 cm. About 13 patches were obtained from each sheet. Formulations F1 to F6 composed of HPMC E15 and Eudragit L100 in different ratios. Formulations F7 to F12 were of same composition as the above but penetration enhancer DMSO was incorporated. All formulations carried 15% v/w polyethylene glycol as plasticizer[9].

Table 1: Composition of Clopidogrel Bisulfate transdermal patches

rmulationCode	Drug(mg)	HPMC E15 (mg)	ragitL100(mg)	DMSO (ml)
F1	30	60	-	-
F2	30	40	20	-
F3	30	45	15	-
F4	30	50	10	-
F5	30	55	50	-
F6	30	35	25	-
F7	30	60	-	0.03
F8	30	40	20	0.03
F9	30	45	15	0.03
F10	30	50	10	0.03
F11	30	55	5	0.03
F12	30	35	25	0.03

15% v/w polyethylene glycol - plasticizer. 5% v/w DMSO - penetration enhancer

Each patch 4.9 cm^2contains 3.67 mg of Clopidogrel Bisulfate

Characterization of Clopidogrel Bisulfate transdermal films

Physicochemical properties[10]

The films prepared by general procedure were evaluated for the following properties

Weight variation[10]

Six films from each batch of an area of 4.90 cm^2 were weighed individually and the average weight was calculated.

Thickness[11]

The thickness of the film was measured at ten different points on one film using screw gauge. For each formulation three randomly selected films were used and average thickness was recorded.

Folding endurance[12]

Folding endurance of the patch was determined manually by repeatedly folding a small strip of the medicated patch at the same place until broke. The number of times the strip could be folded at the same place without breaking gave the folding endurance number.

Estimation of drug content in polymeric films[13]

The formulated polymeric films were assayed for drug content in each case. Three polymeric films from each formulation were assayed for content of drug.

Procedure

Films from each formulation were taken, cut into small pieces and was allowed to dissolve in a 100 ml solution containing 50 ml of methanol and 50 ml of chloroform. The solution was diluted suitably and the absorbance of the solution was measured using UV-Visiblespectrophotometer at a wavelength of 338 nm against methanol chloroform mixture (1:1) as blank.

Moisture Absorption Studies[14]

The patches were weighed accurately and placed in the desiccator containing 100ml of saturated solution of Aluminium chloride, which maintains 84 % RH. After 3 days, the patches were taken out and weighed. The percentage moisture absorption was calculated using the following formula.

$$\% \textbf{ Moisture absorption} = \frac{\textbf{Final weight} - \textbf{Initial weight}}{\textbf{Initial weight}} \times \textbf{100}$$

Moisture Content Determination[15]

The patches were weighed accurately and placed in a desiccator containing calcium chloride at 40 ^oC for 24 h. Then the final weight was noted when there was no further change in the weight of individual patch. The percentage of moisture loss was calculated as difference between initial and final weight with respect to final weight.

$$\% \textbf{ Moisture absorption} = \frac{\textbf{Final weight} - \textbf{Final weight}}{\textbf{Initial weight}} \times \textbf{100}$$

Mechanical properties[16]

Mechanical properties of the films were evaluated using a microprocessor based advanced force gauze (UltraTest,

Mecmesin, UK) equipped with a 25 kg load cell. Film strip with dimensions 60x10mm and free from air bubbles or physical imperfections were held between two clamps positioned at a distance of 3 cm. During measurement, the top clamp at a rate of 2 mm/s pulled the strips to a distance till the film broke. The force and elongation were measured when the film broke. The mechanical properties were calculated according to the following formulae. Measurements were run in four replicates for each formulation.

$$\text{Tensile strength } (\text{kg.mm}-2) = \frac{\text{Force at break (kg)}}{\text{Initial cross sectional area of the sample (mm2)}}$$

$$\text{Elongation at break } (\%\ \text{mm}-2) = \frac{\text{Increase in length (mm)}}{\text{Original length (mm)}} \times \frac{100}{\textit{Cross sectional area}}$$

$$\text{Elastic Modulus} = \frac{\text{Forceat corresponding strain(kg)}}{\text{Cross}-\text{sectional area(mm}^2\text{)}} \times \frac{1}{\text{Corresponding Strain}}$$

$$\text{Strain} = \frac{\text{Tensile strength}}{\text{Elastic modulus}}$$

The tensile testing gives an indication of the strength and elasticity of the film, reflected by the parameters, tensile strength (TS) and elastic modulus (EM) and elongation at break (E/B). A soft and weak polymeris characterized by a low TS, EM and E/B; a hard and brittle polymeris defined by a moderate TS, high EM and low E/B; a soft and tough polymer is characterized by a moderate TS, low EM and high E/B; where as a hard and tough polymeris characterized by a high TS, EM and E/B. Another parameter strain has been used as an indicator of the overall mechanical quality of the film. A high strain value indicates that the film is strong and elastic. Hence, it is suggested that a suitable trans dermal film should have a relatively[17].

Fourier Transform Infrared (FTIR) spectroscopy[18]

The compatibility between the pure drug and excipients was detected by FTIR spectra obtained on Bruker FTIR.The solid powder sample directly place on yellow crystal which was made up of ZnSe. The spectra were recorded over the wave number of 4000 cm^{-1} to 400 cm^{-1}.

Results & Discussion

Preformulation study:

Preformulation studies are primarily done to investigate the physicochemical properties of drug and to establish its compatibility with other excipients.

FTIR Compatibility Studies:

In the FTIR spectra of pure drug and formulation with other ingredients (different polymers) it is observed that the peaks of major functional groups of Clopidogrel Bisulfate, which are present inspectrum of pure drug are observed. It means there are no interactions between drug and other ingredients in a physical mixture and drug is compatible with other ingredients. The FTIR peaks were showed in Figure 1.

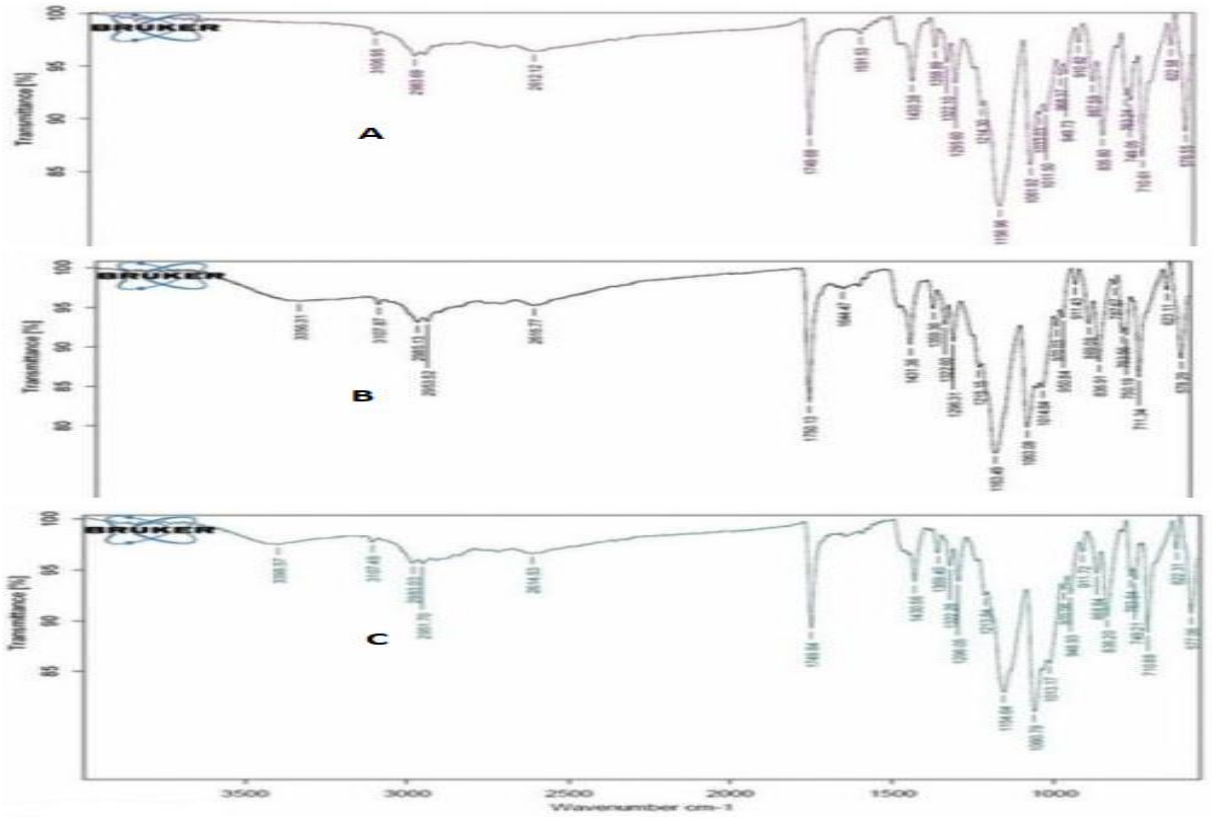

Figure 1: FTIR spectra of A. Clopidogrel Bisulfate B. HPMC E15 and C. Eudragit L 100

Development of Clopidogrel Bisulfate transdermal films:

Films were formulated with HPMC E15 and EudragitL100 (**Table 1**). Many experiments were performed by varying the concentrations of polymer. The experiment was initiated by taking 0.2 g. of polymer and as the polymer concentration increased the patch could accommodate more amount of Clopidogrel Bisulfate. Precipitation of the drug was predominant with 0.2 g of polymer and as the polymer concentration was increased to 0.5 g, the precipitation decreased. No precipitation was observed with 0.6g of the polymer and the films were flexible. Therefore, the polymer amount taken was 0.6 g.

In addition, experiments were conducted to know optimal concentration of plasticizer to be used in all kind of films. Plasticizer at concentration of 5%v/w of film former was insufficient to form films. Plasticizer concentration at 5-10% v/w yielded hard and inflexible films. Further, increasing the concentration of plasticizer above 20%v/w resulted in enormous increase in drying time. Therefore, films were prepared using 15%v/w of plasticizer and the prepared films weresoft and flexible but not brittle. Films were also formulated with penetration enhancer DMSO.

Characterization of Clopidogrel Bisulfate transdermal films

Physicochemical properties: The films prepared by general procedure were evaluated for the following properties:

Weight Variation Test: The results of weight variation test for various transdermal films were shown in Table 2. Results of weight variation test indicated uniformity in weight of patches, as evidenced by SD values, which were less than 2.0 for all formulations. In formulations F1 to F12 the weight of the patchesdecreased with decrease in HPMC E15concentration.

Thickness Variation Test

In thickness variation test, the thickness was found to be uniform. The thickness increased with increase in HPMC E15 concentration. The SD values were less than 2 for all formulations, an indication of more uniform patches. The results of thickness variation test for various transdermal films were shown in Table 2.

Folding endurance number

The folding endurance numbers of HPMC E15 and Eudragit L100 containing patches has in the range of 435 to 566 as shown in Table 2. The folding endurance number gives the mechanical property of the patches, high folding endurance number indicate that has high mechanical property. The folding endurance number was increased with increasing HPMC E15 concentration. These results indicated that the patches would not break and would maintain their integrity with general skin folding when applied.

Estimation of drug content in polymeric films:

Good uniformity in drug content was observed in all transdermal patches as evidenced by low SD values. The drug content is ranged from 2.55 to 3.42 mg per 4.90 cm^2. The results of drug content for various transdermal films were shown in Table 3.

The results of moisture content and moisture absorption studies were shown in Table 3. The moisture content in the patches was ranged from 4.58 to 9.35%. The moisture absorption in the formulations is ranged from 6.42to 11.44%. The results revealed that the moisture absorption and moisture content was found to increase with increasing the concentration of hydrophilic polymer (HPMC E15). The small moisture content in the formulations help them to remain stable and from being a completely dried and brittle film.

The results of mechanical properties (tensile strength, elongation at break, elastic modulus and strain) were shown in Table 4. These observations indicate that the optimized formulations were found to be strong and flexible but not brittle.

The permeation of Clopidogrel Bisulfate from transdermal patches (F1-F12) were depicted in Figure 2. Comparative study of Clopidogrel Bisulfate permeation of F4 & F10 was depicted in Figure 3.

Table 2: Weight variation, thickness and folding endurance of Clopidogrel Bisulfatetransdermal patches

Formulations	Weight variation (mg)	Thickness (mm)	Folding endurance
F1	66.9±1.53	0.25±0.79	562.45±0.53
F2	53.76±0.97	0.2±1.27	435.12±1.38
F3	58.26±0.59	0.22±0.95	489.57±0.75
F4	62.41±1.26	0.23±0.83	550.77±0.93
F5	65.75±0.78	0.24±0.56	558.98±0.88
F6	52.37±0.49	0.19±1.54	432.48±0.64
F7	67.55±0.55	0.26±0.67	566.92±1.29
F8	55.45±1.12	0.205±0.98	454.1±1.02
F9	59.62±1.43	0.21±1.38	490.7±0.74
F10	60.78±0.89	0.24±1.26	558.57±0.62
F11	63.51±0.95	0.25±0.58	563.46±1.14
F12	53.25±0.67	0.215±0.63	470.79±1.09

Table 3: Drug content, % Moisture absorbed, %Moisture content of ClopidogrelBisulfate transdermal patches

Formulation	Drug content(mg)	%Moisture absorbed	%Moisture Content
F1	3.35±0.96	10.87±1.58	9.34±0.96
F2	2.83±1.29	7.92±1.82	4.62±0.85
F3	3.05±0.84	9.67±0.95	5.97±1.17
F4	3.26±1.18	8.39±1.46	8.35 ±1.32
F5	3.29±1.04	10.45±0.93	8.45±1.95
F6	2.73±0.55	6.42±1.25	4.58±0.77
F7	3.42±1.37	11.44±1.03	9.35±0.94
F8	2.99±0.92	8.35±0.89	5.21±0.55
F9	3.16±0.75	8.86±0.64	6.32±0.79
F10	3.32±1.55	9.34±0.59	7.56±0.82
F11	3.38±1.27	10.48±1.19	9.12±0.93
F12	2.76±0.86	6.54±1.53	5.89±1.87

Table 4: Mechanical properties of optimized formulations

Formulationcode	Tensile strength (kg/m^2)	Elongation at break (%mm^{-2})
F4	1.38±0.58	24.92±1.42
F9	0.76±0.34	43.18±1.03
F10	1.46±0.78	22.53±0.98

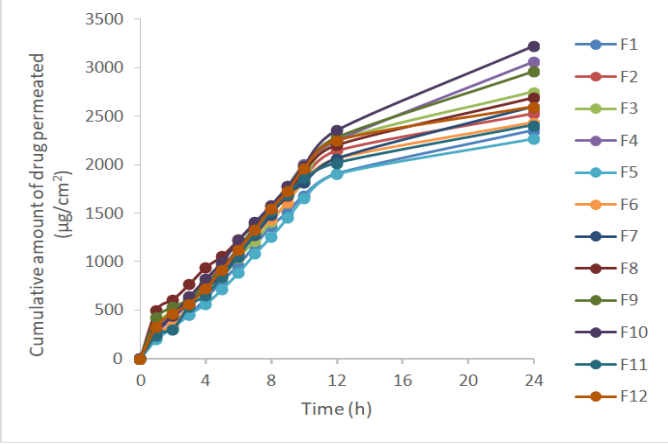

Figure 2: Permeation of Clopidogrel Bisulfate from transdermal patches (F1-F12)

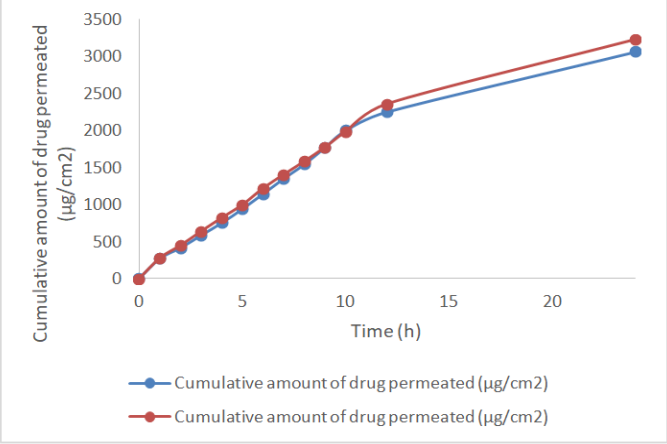

Figure 3: Comparative study of Clopidogrel Bisulfate permeation of F4 & F10

Conventional systems of medication that require multi dose therapy are having many problems. The controlled drug delivery is a newer approach to deliver drug into systemic circulation at a predetermined rate. Our system should duplicate continuous intravenous infusion, which not only by passes hepatic first pass elimination but also maintains a constant, prolonged and therapeutically effective drug level in the body. This is made possible by using intact skin as a port of drug administration to provide continuous delivery of drug into systemic circulation. The drug molecules are then transported to the target site, which could be relatively remote from the site of administration, to produce therapeutic action.

The aim of study is to prepare matrix type of Clopidogrel Bisulfate transdermal patch by using polymers HPMC E15 and Eudragit L 100 and to determine the drug release from these patches through iontophoresis. Polymers HPMC are good thickness as well as matrix forming agents. Eudragit is also good film forming agents and best for the preparation of sustained release dosage forms.

Matrix type transdermal patches containing Clopidogrel Bisulfate were prepared by solvent evaporation technique, using different ratios of combination of HPMC E15 and Eudragit L100 (F1 to F6), and using DMSO as penetration enhancer (F7 to F12) in the above formulations, 15% polyethylene glycol was incorporated as plasticizer.

Preformulation studies such as FTIR are performed for drug and excipient mixtures. In the FTIR spectra of pure drug and formulation with other ingredients (different polymers) it is observed that the peaks of major functional groups of Clopidogrel Bisulfate, which are present in spectrumof pure drug, are observed. It means that there are no interactions between drug and other ingredients in a physical mixture and drug is compatible with other ingredients.

The films prepared by general procedure were evaluated for the following properties such as weight variation, thickness, folding endurance, estimation of drug content, moisture absorption, moisture content determination, measurement of mechanical properties, *ex vivo* permeation studies, Results of weight variation test indicated uniformity in weight of patches, as evidenced by SD values, which were less than 2.0 for all formulations. The weight of the patches ranged from 33.25±0.67 mg for formulation F12(HPMC E15 and Eudragit L100) to 46.9±1.53 for F1(HPMC E15). The weight increased with increase in the hydrophilic polymerconcentration.

In thickness variation test, the thickness was found to be uniform. the thickness increased with increase in polymer concentration. The SD values were less than 2 for all formulations, an indication of more uniform patches. The thickness range was 0.19±1.54 mm for F6 to 0.26±0.67 mm for F7.

The folding endurance numbers of HPMC E15 containing patches has in the range of 562 to 566 and combination of HPMC E15 and Eudragit L100 containing patches has in the range of 435 to 563. The folding endurance number gives the mechanical property of the patches, high folding endurance number indicate that has mechanical property. The folding endurance number was increased with increasing polymer content. These results indicated that the patches would not break and would maintain their integrity with general skin folding when applied.

Good uniformity in drug content was observed in all transdermal patches as evidenced by low SD values. The drug content is ranged from 2.73±0.55mg in formulation F6(HPMC E15 &Eudragit L100) to 3.42±1.55 mg in formulation F7(HPMC E15). The drug content was maximum in the formulation containing more amount of hydrophilic polymer.

The moisture content in the patches was ranged from 4.58±0.77% for F6(HPMC E15&Eudragit L100) to 9.35±0.94% for formulation F7 with HPMC E15). The moisture absorption in the formulations is ranged from 6.42±1.25% for F6 (HPMC E15 &Eudragit L100) to 11.44±1.03 % for F7 (HPMC E15). The results revealed that the moisture absorption and moisture content was found to increase with increasing the concentration of hydrophilic polymer (HPMC E15). The small moisture content in the formulations help them to remain stable and from being a completely dried and brittle film.

Conclusion:

In the present study, an attempt was made to formulate an anti-hypertensive drug Clopidogrel Bisulfate in the form of transdermal patches using different ratios of HPMC E15 and Eudragit L100. From the results obtained, DMSO enhanced the drug release from the Clopidogrel Bisulfate transdermal patches compared with the normal films. The transdermal patches of Clopidogrel Bisulfate with required flux could be prepared with suitable mechanical properties, further studies are recommended to find their therapeutic utility in humans by pharmacokinetic and pharmacodynamic studies.

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