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Formulation and characterization of topical microemulsion loaded with naproxen

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***Abstract*---**The aim of this study was to prepare w/o Micro-emulsions of naproxen for topical application & evaluate in vitro permeation of Naproxen. On the basis of ternary phase diagram and drug solubility test Tween-20, Oleic acid and Polyethylene Glycol 400 was selected and these are eminently used as an appropriate transporting system for introducing Naproxen for transdermal drug delivery. The physicochemical properties of microemulsions such as conductivity, droplet size, viscosity and pH were measured. The in vitro permeability of Naproxen compared with commercial and microemulsions. The permeation rates of Naproxen from micro-emulsions were higher (1.2 times) than marketed gel formulation. Finally, according the histological examination of microemulsions did not show irritant effect on treated skin. In conclusion, the results of this study indicated that the microemulsions especially F5 formulation can be considered as potentially useful vehicles for topical application.

***Keywords*---**formulation, characterization, topical microemulsion loaded, naproxen.

Introduction

The most common routes of drug delivery are the oral and parenteral routes with the majority of small molecule drugs conventionally delivered orally [1,2]. The oral

route has the advantage of pre-determined doses, portability and patient self-administration. For these reasons, the oral route remains the most convenient means of delivering medications [3,4]. However, most therapeutic peptides or proteins are not delivered by the oral route, due to rapid degradation in the stomach and size-limited transport across the epithelium [5]. The primary mode of administering macromolecules is therefore via injection [5,6] which is not without limitations, such as the invasive nature of injections eliciting pain and lower acceptance compliance by patients, in addition to the requirement for administration by a trained administrator [7]. Rationally, the conventional routes of medication delivery have many inherent limitations which could potentially be overcome by advanced drug delivery methodologies such as transdermal drug delivery (TDD).

Material and Method

The basic requirement to outline dosage form of the drug is to study pre-formulation on drug and its excipients. The important stage to outline the formula expected with optimal drug dispensation characters and ideal durability etc. The major goal in pre-formulation literature is distinguished the sample based on some physiochemical properties which establish its specification and including the physic-chemical character of the solids, similarity between the formulation excipients and develops analytical techniques [8].

Characterization & Identification of Drug & Excipients

Physical Appearance: white powder
Nature: crystalline, dry granular powder and non-sticky
Odour: none

Spectrophotometry

Measurements of UV spectrum of drug sample was done through UV spectrophotometer (UV-1700, SHIMADZU) after weighing the sample which is measured (10 mg) and put into 100 ml volumetric flask and ethanol is used appropriately for dilution. Then 10 times the stock solution was diluted and scanning of UV spectrum was done in the range of 200-400 nm, resulting a maximum absorption up to 238 nm was shown in the UV spectrum of the obtained sample of Naproxen which is similarly described value in certificate of analysis [9].

Analytical Methodology

The quantity of drug sample exactly weighed on analytical balance and it was diluted in 10 ml of ethanol poured in volumetric flask thereafter covered by black paper. The Mixture of drug was pronounced as primary stock solution which was having concentration (1000 µg/ml) and then in another volumetric flask 1.0 ml of the solution was poured followed by 10.0 ml of ethanol to get conc. of 100 µg/ml solution. Then it is poured in the formerly prepared volumetric flask which is covered by black paper sheet and named as secondary stock solution. After that in dissimilar test tubes 1, 2, 3, 4 & 5 ml, 10 divergent aliquots is taken

and ethanol is used for dilution to obtain concentration of 1, 2, 3, 4 & 5 µg/ml. Then the prepared solution is was measured for its absorbance at maximum 238 nm. For this UV-Vis spectrophotometer is used (instrument) ethanol is kept impassive. The whole procedure is repeatedly done 3 times. Using the software MS- Excel sheets were created by plotting a graph between absorption and concentration value. The final statistical parameters using this software resulting as regression line and correlation coefficient [10]

FTIR Spectroscopy

The KBr method was set on to transform consonantly absorption of the drug. Already dried powder of KBr and very minute quantity of drug sample was grounded in clean mortar pestle to transform the drug in very minute particles because infrared beam shatters the big particles and the inclined baseline of spectrum was affected. Powder is added evenly to the 7 mm collar, together with the die while transferring. Together with the powder the die is put into the fast available KBr press can be a hydraulic press, for short period like 1 minute to form pellet. After taken out the pellet from the die and put into the sample holder of FTIR. Then the software spectrum one is used to record the range between 600-4000 cm^{-1} [11].

Melting Point Determination

The capillary technique used to measure melting point of drug by using melting point apparatus make (Ambassador). One end of the capillary is sealed and dry granules of the drug filled in the tube by outer end and melting point apparatus is used to hold the capillary tube. By the help of thermometer the point of melting the sample of powder is recorded and tally with the certificate of analysis or value of the drug. The melting point of Naproxen recorded to be 265°C, which is exactly like melting point of Naproxen

Excipient selected for the Micro-emulsion formulation

The main observation which is noticed to form nano-emulsion of Naproxen was considered on biological properties of drug, chemical and physical characterization of excipients.

Screening of Oil

The most important requirement of screening in oil phase is the loading capacity of the drug usually the excessive solubility of drug is accepted in oil phase but before, with the help of surfactants and co-surfactants, homogeneous solution was prepared for the formation of nano-emulsion formulation. In an eppendorf tube 45 mg of drug was kept in 1 ml of oil phase, for screening and pursuit drug equilibrium at least for 4 weeks at the same temperature [12].

Screening of Surfactants

During the preparation of Micro-emulsions, the surfactants are the most important content, they are usually non-ionic surfactants because of their outstanding ability

to prepare Micro-emulsion and non-ionic surfactants are easily mixed with other components. They are safer and least toxic, if they are compared with cationic and anionic surfactants [63]. It is considered that tween-20 & tween-80 has topmost ability of solubilisation and easily mixed in oil phase.

Screening of co-surfactants

Co-surfactant because of their qualities of high mixing ability with oil reducing inter- facial tension, are broadly used to form Micro-emulsions and these qualities only, they were being selected [13]. The lipidic excipient were screened and depending on drug disoloubity and mixibility with the other components of excipient to develop Naproxen Micro-emulsion [14].

Drug Solubility Determination

To check the dissolving power of the drug excipients such as surfactants, co-surfactants and oil phase was resolute by mixing the extra amount of drug in an eppendorf tube (1.0ml). If the drug was mixed properly, the procedure was repeated by taking in an eppendorf tube 2.0 ml of excess amount of drug and mixed with the help of vortex mixer and to get the equilibrium, the eppendorf tube was kept on 25 ± 5˚C for 72 hours. Then the sample of drug was centrifuged after 72 hours at 3000 rpm for 10 minutes. An instrument (Model-make) is used for this, after that a membrane of 0.45µm is taken to filter the supernatant and suitably diluted with ethanol, UV spectrophotometer was used to measure the amount of drug which is mixed in various excipients at this respective formula [15].

Aqueous Dispersibility of Pre-concentrate Mix

To produce dilutable Micro-emulsion system, the behaviour of pre-concentrate mixture which contains Smix and oil phase with water is very much essential. For the formulation of Micro- emulsion, the variety of components is required such as surfactants, co- surfactants and oil and how they behave in aqueous media existence. To assess the aqueous dispersity Micro-emulsion is examined visually and slowly the aqueous phase is added in pre-concentrate mix. A transparent system or turbid distribution is produced by the dilution of pre-concentrate mixture along with the aqueous phase shows the formation of Micro-emulsion. The amount of water was decided after visually checked to prepare the pre-concentrate mix to endure in transparent [16].

1. Falcon tube of 15 ml was taken in which 5.0 ml of tween-20 with polyethylene glycol was shifted and slowly mixed for 20 minutes and with equal proportion of surfactant and co-surfactant fraction put together and labelled as Smix.
2. In 2 ml of eppendorf tube 100 µl of oleic acid was poured as oil phase along with 900 µl of Smix and well mixed by vortex shaker.
3. In the mixture of oil phase and Smix a small amount of water was added.
4. In the beginning 100 µl water put additionally and mixed into vortex shaker by shaking well until clear solution is obtained.
5. Continuously 100 µl water was added in vortex shaker and mixed until

clear dispersion is no more.

6. The different combinations of surfactant, co-surfactant and oil was taken and the procedure was done repeatedly and recorded in tables showing various trials.

Formulation of naproxen Micro-emulsions

The variety of Micro-emulsion formulations were prepared with the help of ternary phase and the data obtained through it, the selected oil, surfactant and co-surfactant were decided proper parts of pre-concentrate mixture were obtained as formula of Naproxen .

Procedure for Preparation of Micro-emulsion

Smix in proportionate ratio is mixed with oil phase and then treatment was done with aqueous phase and then added in the drug and loading was done drop by drop while constant stirring and sonication.

Characterization of Micro-emulsion Formulation

Droplet Size Distribution

Through Malvern, Zeta Sizer (Micro-series) the measurement of various droplet size was measured. The sample was taken around 5 ml and then filtered in nylon membranes followed by sonicated for 10 minutes. After that sample was taken around 1-2 ml and transported to cuvette of the zeta sizer and then scanning was done for 10 minutes followed by data recording. The percentage of droplet potency or volume percentage v/s size of Micro-emulsion system was recorded .

Measurement of Electrical Conductivity

Digital conductivity meter model 611E was used to evaluate the electrical conductivity of the formulation. Primarily the cell constant of the conductmeter model using the solution of KCl at 25˚C temperature, afterwards 1.0ml of formula was withdrawn in 10ml capacity beaker and dipped the platinum electrodes in the beaker, then the conductmeter displayed the conductance value which is recorded till the continuous value was shown by the instrument. Every formulation was then slowly diluted with the aqueous phase into the beaker and properly all the contents were mixed and as the procedure its conductance of dispersion system was recorded**.**

Morphological Evaluation of Formulation

With the help of transmission electron microscope, the structural and morphological assessment of the formulation was done, over a wax coated paper a small drop of sample which is not diluted was placed and copper made circular grid in the form of film with size of 400 mesh was applied externally and then 10ml of 2% w/v uranyl acetate was used for few seconds to stained the sample and dried it. The recording of the morphology of sample surface was recorded on TEM model Morgani 268D operated at 70kV.

Determination of pH

With the help of pH meter Mettler Toledo model seven compact, this parameter is important to keep away the skin irritation. The caliberation of pH meter was done prior to record pH value with standard buffer solution. The measurement of the pH value of formulation was done .

Thermodynamic Stability

To perform 6 heating cooling cycle the refrigerator temperature is set between 4˚ C to 45˚ C and store at each temperature for 48 hours. The Micro-emulsion formulations which are stable at 4˚C and 45˚C were centrifuged at 3500 rpm for 30 minutes and observed for phase separation.

Determination of Viscosity

Brookfield Viscometer using a 61 spindle was used and rheological evaluation of Micro-emulsion formulation was done. Five similar volumes (100 ml) of Micro-emulsion formulation were taken in five different 150 ml capacity of beaker marked as F1, F2, F3, F4 and F5. Instrument was set to run in order to record the rheological parameters at fixed shearing rates (i.e. 10, 20, 40 and 50) and fixed temperature at 25˚C. The readings of each Micro -emulsion formulation were recorded in triplicate to avoid the error.

Result and Discussion

Naproxen has been stipulated in dermatology to reduce inflammation of skin and relieve itching. It has been reported that Naproxen played a beneficiary role in atopic-dermatitis (eczema). The objective of this research is to characterize and formulate the Naproxen Micro-emulsion designed for transdermal delivery. The rationale of present research is to analyze the probability of Naproxen Micro-emulsion to increase its bioavailability and absorption through skin. Literature survey demonstrated that oleic acid as an oil phase has been integrated in numerous Micro-emulsion system. Addition of oleic acid in Micro-emulsion systems demonstrated that it yield clear dispersion and revealed drug penetration modification characteristics. It behave as an eminent vehicle for lipophilic drugs, it also demonstrated an eminent similarity, compatibility, common and mutual miscibility with various Smix excipients.

UV Spectrophotometry

Table Calibration curve of Naproxen in ethanol

S. No.	Concentration (µg/ml)	Absorbance (nm)
1	0	0
2	10	0.1298
3	20	0.2294
4	30	0.3409
5	40	0.4756
6	50	0.5902

7	60	0.6901
8	70	0.8184
9	80	0.9758

FTIR Studies

The details of FTIR spectrum of drug sample, it is calculated in the range of 4000 to 600 cm^{-1} through KBr pellet method. Elucidation of FTIR spectra of sample revealedthe vibration frequency observed as alcohol OH, fluoride F, ketone C=O and aromatic are 1244.51 cm^{-1}, 1376.71 cm^{-1}, 1129.47 cm^{-1} and 819.99 cm^{-1}. In Naproxen formulation, design and development, the major precondition of pre-formulation studies is to explain the compatibility among the drugand excipients. To examine drug-excipient compatibility studies, the drug and excipient kept for one month in the form of pre-concentrate mixture containing different proportions. After a period this mixture were taken out and studied for the change in nature of powder and its coloration. In the table different combinations which contain variety of proportions such as drug and oil, drug and co-surfactant anddrug and surfactant. Physically when it was observed no change in inherent and ultimate result/nature. In all functional groups frequencies of mixture is similarly matched to that of pure drug- excipients which is shown in FTIR scans given in figure2.2, 2.3, 2.4, 2.5, 2.6 and 2.7, the final result has come up that every excipient selected for the formulation development of nano-emulsion was sticky mass, oily with no change in appearance, coloration and nature as compared to sample kept in the beginning.

Drug Solubility Studies

Table Solubility of Naproxen in oils, surfactant and co-surfactant

Oils		Surfactant		Co-surfactant	
Liquid paraffin	5mg/ml	Tween 20	28mg/ml	Polyethylene Glycol 400	45mg/ml
Castor oil	15mg/ml	Tween 80	35mg/ml	Polyethylene Glycol 200	32mg/ml
Oleic acid	40mg/ml				
Olive oil	10mg/ml				

Formulation Trial Studies

Evaluation of aqueous dispersibility of several excipients such as co-surfactant/surfactant mixture (Smix) and oil phase were resulted in development of coarse emulsion and clear Micro-emulsion. By the selection of oil phase, co-surfactantand surfactant upon water dilutions, the outcome of this mixture might be a development of dilutable ternary system. These studies have been established on the hypothesis that upon water dilution of Micro -emulsion gives the clear dispersion system. Therefore, the outcome of the selected pre-concentrate mixture is to produce a clear dispersion and final result is the development of w/o Micro -emulsion with globule size ranging from 50 nm to 200 nm. Evaluation of the phase behavior when drug was loaded into Micro -emulsion to produce clear dispersion was also done.

Several concentrate mixture comprised of co-surfactant, oil phase and surfactant upon dilutions with fixed amount of distilled water were kept for visual examination. The results shown due to solublization of oil phase and Smix the appearance of clear dispersion on water dilutions shown in formation of Micro - emulsion and inspite of Micro-emulsion formulation loss of clarity in the system stipulate the formation of coarse emulsion.

To examine the dilutability of concentrate mixture comprised of Smix and oil phase, characteristic study was executed and various trials were tried. Trial A comprised of Smix (1:1 Tween-20: PEG 400) containing castor oil as an oil phase, the outcome in the development of turbid dispersions if distilled water was added to the mixture. Therefore, A1 to A4 systems resulted in the turbid dispersions if diluted with water as shown in figure 3.8. Trial B here change is in the oil phase from castor oil to olive oil using Smix (1:1 Tween-20: PEG 400). There was no change in the physical behavior of the system, all systems turned to turbid dispersions by the addition of distilled water as shown in the figure 3.9.

Trial C in this trial oleic acid was used as an oil phase but its Smix (1:1 Tween-20: PEG 400) was changed in comparison to trial B. all the systems C1 to C4 were examined clearly transparent and data is represented in table 3.5 and figure 3.10. Trial D in this trial oleic acid was used as an oil phase but its Smix (1.5:1 Tween-20:PEG 400) was changed in comparison to trial C. all the systems D1 to D4 were examined clearly transparent and data is represented in table 3.6 and figure 3.11. Trial E in this trial oleic acid was used as an oil phase but its Smix (1:1.5 Tween-20:PEG 400) was changed in comparison to trial D. all the systems E1 to E4 were examined clearly transparent and data is represented in table 3.7 and figure 3.12. Trial F in this trial oleic acid was used as an oil phase but its Smix (2:1 Tween-20: PEG 400) was changed in comparison to trial E. all the systems F1 to F4 were examined clearly transparent and data is represented in table 3.8 and figure 3.13. The complete summary of different trials conducted at pre-formulation stage to find out the attainable ternary component which were used for Micro emulsion systems are mentioned in the table 2.9. The likely components of C, D, E and F trials would be picked up for the formation of Micro-emulsion system of Naproxen.

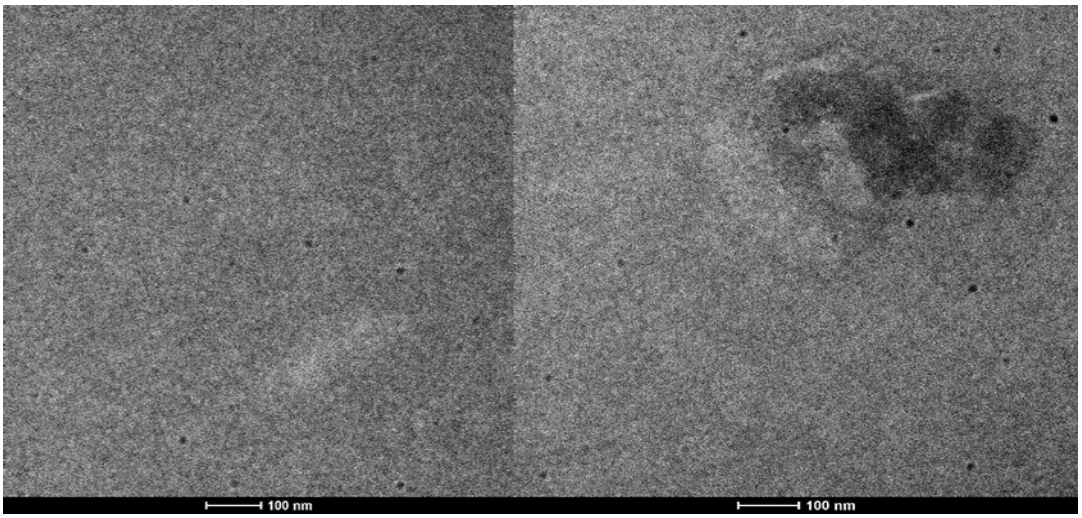
Formulation of Micro-emulsion

In the table the composition of various nano-emulsion formulation which contains oil, drug, aqueous phase and Smix. The formula which was formulated from nano-emulsion area of each phase, the diagram was prepared at Smix level 1:1 and 2:1, oil phase and Smix composition were kept as 19.58% and 79.4% v/v. Another diagram was prepared for two formulations which were portion of oil and Smix phase was keep on varying. The formulation are based on the components of quantity of drug and water phase composition were kept fix 0.01% and 10.3% w/w. All the Micro -emulsion formulations were analysed on the basis of different parameters such as refractive index, droplet size distribution, transmission electron microscopy, electrical conductivity, pH, in-vitro drug release and rheological evaluation.

Droplet Size Distribution

To determine globule size and its poly-dispersity index of nano-emulsion Malvern zeta-sizer Nano series was used. Table 3.16 was prepared after obtaining the results and in figure 3.20, 3.21, 3.22, 3.23 and 3.24 a complete graphical depiction is given. Every formulation was obtained in the globule size range 18.75 nm to 119.9 nm with similar size distribution. Mean globule of formulation is better positioning to the definition of the nano-emulsion (50nm to 200nm) along with best poly-dispersity index which indicates similarity of droplet size.

Morphology Studies



A **B**

Fig: A and B represents morphology of Micro-emulsion formulation

Refractive Index

Refractive index of all the Micro-emulsion formulation at 20˚C was found in the range1.4580 to 1.4606 and at 25˚C was found in the range 1.4562 to 1.4587.

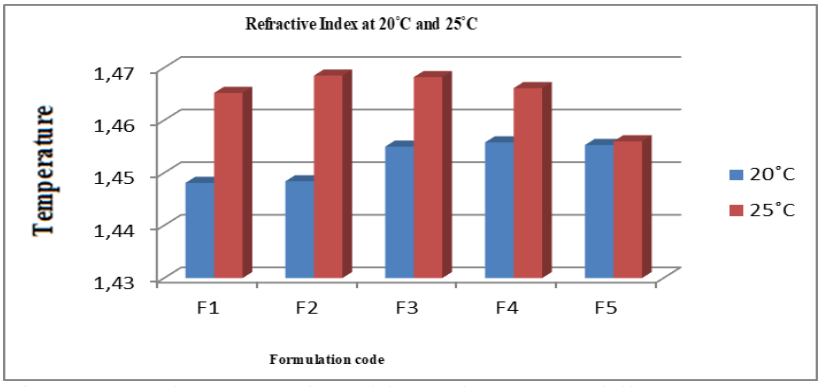


Fig Change in refractive index of formulations at different temperature

pH Studies

From the table it was concluded that the pH of the Micro-emulsion formulation wasfound to be in the range 5.41 to 5.63, and data represented graphically in the figure

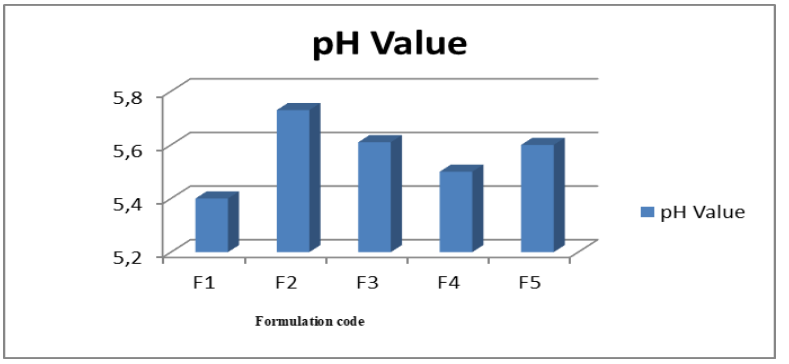


Figure: Representation of the pH value of F1, F2, F3, F4 and F5

In-vitro drug Release Studies

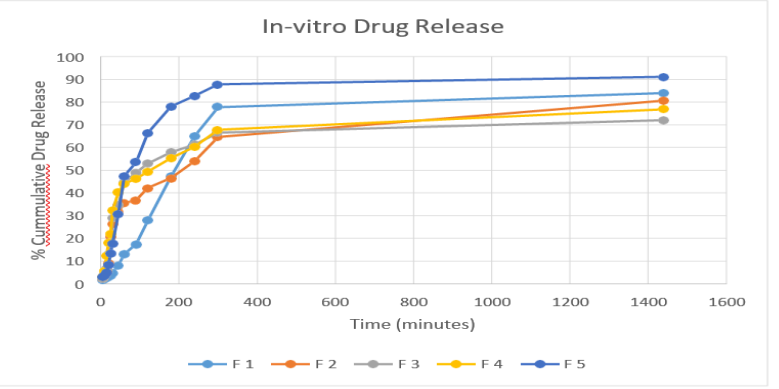


Figure In-vitro drug release of Micro-emulsion formulation

Conclusion

The present research concluded that Naproxen is incorporated into Micro-emulsion formulation by ultra-sonication technique for the improvement of solubility and absorption. Nano-emulsion is more desirable for the transdermal drug administration because it enhanced absorption rate through skin. Micro-emulsions have characteristics that make them more effective transport system than macro- emulsions as they do not show the problem of agglomeration and sedimentation which are generally associated with macro-emulsions. On the basis of ternary phase diagram and drug solubility test Tween-20, Oleic acid and Polyethylene Glycol 400 was selected and these are eminently used as an appropriate transporting system for introducing Naproxen for transdermal drug delivery. Five formulations were formulated as per the composition of nano-

emulsion. The developed nanoemulsion formulation coded as F1, F2, F3, F4 and F5. Several evaluation parameters such as droplet size distribution is 18.75nm, TEM, thermodynamic stability test, pH is 5.63, viscosity, electrical conductivity and refractive index is 1.4587 indicates that F5 is more appropriate as compared to F1 to F4. With the result of Accelerated Stability studies it has been found that all the formulations are stable over the period of time. On the basis of in-vitro skin permeation study F5 formulation shows more drug release i.e. 91.15% as compared to F1 to F4. From above studies it was concluded and examined that Naproxen Micro-emulsion is efficacious for transdermal application in the treatment for Inflammatory action although in-vivo studies are further needs to be conducted to authenticate the results in a more specific way.

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