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Proniosomes: A versatile drug delivery

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Abstract
Proniosomes are the dry formulations of surfactant-coated carrier, which can be measured out as and rehydrated by brief agitation in hot water immediately before use to yield aqueous niosome dispersion similar to those prepared by conventional method. These proniosomes minimize problem of physical stability of niosomes such as aggregation, fusion and leaking and convenience in transportation, distribution, storage and daosing. Proniosomes can be converted into niosomes upon simple hydration of the skin so proniosomes offer a versatile vesicle delivery concept with the potential for delivering drug via the topical/transdermal rout.

Keywords: Proniosomes; Niosomes; sorbitol; maltodextrin; transdermal.

1. Introduction

Drug delivery system like liposomes and niosomes in dispersion can carry hydrophilic drug by encapsulation or hydrophobic drugs by partitioning of drug into hydrophobic domain. Liposomes are unilamellar or multilamellar spheroidal structure composed of lipid molecules, often phospholipids, assembled into bilayer. Liposomes have potential application in pharmaceutics. But in a dispersed aqueous system, liposomes having problems associated with degradation with hydrolysis [1] or oxidation [2]; sedimentation, aggregation, or fusion of liposomes [3] during storage and difficulty in sterilization and large scale production [4].

Payne *et al*. (1986) introduced proliposomes which are an elegant alternative to conventional liposomes formulation. Proliposomes are dry free flowing granular product which could be hydrated immediately before use. He further reported that the proniosomes particle size is not markedly effected by prolong storage at 20 ^{o}C, and potency of Amphotricin B in proliposomes form does not change over 6 months of storage at 20 ^{o}C. But in term of the physical stability of the proliposomes preparation, a vaccume or nitrogen atmosphere is still required during preparation and storage to prevent the oxidation of phospholipids [5-7].

In 1985 Baillie *et al*., [8] produced niosomes from a hydrated mixture of cholesterol and nonionic surfactant such as monoalkyl or dialkyl polyoxyethylene ether, which are more stable then proliposomes and did not need any special atmosphere or low temperature for storage. They may be regarded either as inexpensive alternative, of non-biological origin, to liposomes and behave *in vivo* like liposomes.

However, even though niosomes exhibit good chemical stability during storage, there may be problem of physical instability in niosomes dispersion. Like liposomes, aqueous suspension of niosomes may exhibit aggregation, fusion leaking of entrapped drug, or hydrolysis of encapsulated drug, thus limiting the self-life of the dispersion.

Proniosomes are the dry formulations of surfactant-coated carrier, which can be measured out as and rehydrated by brief agitation in hot water immediately before use to yield aqueous niosome dispersion similar to those prepared by conventional method. These proniosomes minimize problem of physical stability of niosomes such as aggregation, fusion and leaking and convenience in transportation, distribution, storage and dosing. Proniosomes can be converted into niosomes upon simple hydration of the skin so proniosomes offer a versatile vesicle delivery concept with the potential for delivering drug via the topical/transdermal route.

Advantages of Proniosomes are as follows:

(1) Proniosome is dry and free flowing powder.
(2) Proniosomes represent a significant improvement by eliminating physical stability problems such as aggregation, or fusion of vesicles and leaking of entrapped drug during long term storage [9].
(3) Compared to niosomes prepared by conventional methods, proniosomes derived niosomes are superior in their convenience of storage, transport and dosing.
(4) The release data indicates that proniosomes derived niosomes are at least as effective as conventional niosomes in their release characteristics and may therefore offer improved bioavailability of some drugs with poor solubility, controlled release formulation or reduced adverse effects of some drugs.
(5) Because proniosomes are dry powder, further processing is possible. To provide convenient unit dosing, the proniosomes powder may be processed to made beads, tablets or capsules.
(6) Angle of repose measurements indicates that the fluidity of proniosomes dry powder is equal to or better than that of carrier powder so further processing of proniosomes powder should be straightforward.
(7) One of greatest advances offered by proniosomes powder is their ease of use. The hydration of proniosome powder is much easier than the longer shaking process required to hydrate the surfactants in conventional dry film method and can be implemented in a 'point of use' application.
(8) Proniosome derived niosome suspension appears to be as good as or better than conventional niosomes preparation, and may be an appropriate preparation to use as a hydrophobic drug carrier.

Proniosomes are mainly composed of non-ionic surfactant (span and tween), phospholipids, alcohol and water with or without cholesterol. Different effect of non-ionic surfactant on levonorgestrel permeation profile showed that the flux value is highest for span 80 and lowest for span 60. However, Fang *et al*. reported different effect of nonionic surfactant in the case of estradiol: span 60 shows the highest flux on estradiol permeation profile. Proniosomes for estradiol and levonorgestrel formulations differ in their content of cholesterol and type and content of alcohol [10].

In 2003, transdermal delivery of ethinylestradiol and levonorgestrel for contraception and hormone replacement therapy is attempted from the proniosomal gel formulation prepared by coacervation phase separation technique. The formulation prepared using span 20 and span 40 (3:1) have shown better in vivo performance [11]. In 2004 permeation of potent nonsteroidal anti-inflammatory ketorolac, across excised rabbit skin from various proniosome gel formulation is investigated using Franz Diffusion cell. Each of prepared proniosomes significantly improved drug permeation and reduce the lag time ($P<0.05$).

In 2005 a proniosomal gel transdermal drug delivery of chloropheniramine maleate (CPM) is developed based on span 40 and extensively characterized *in vitro.* The result showed that lecithin produce more stable and large vesicles with higher loading efficiency but lower dissolution efficiency than cholesterol and dicetyl phosphate (DCP). The type of alcohol had no significant effect on the stability of vesicles (~44um) and entrapped a great amount of drug [12].

Solanki *et al*., (2007) investigated the combined influence of 3 independent variable in the preparation of piroxicam, proniosomes by slurry method and with the help of a 3-factor, 3-level Box-Behnken design. SEM proniosomes images revealed that the surface of carrier particle at the medium level of the surfactant loading appear to be more uniform and thinner then the rough and uneven coating at high surfactant coating [13]. Gupta *et al*., (2007) prepared proniosomal powder of captopril found that surfactant coated carrier method result in 54.16-70.10% of encapsulation and the prepared proniosomal formulation follow zero-order kinetics and release is extended up to 24 h [14]. Gupta *et al*., developed proniosomal gel of captopril for treatment of hypertension [15]. El-laty *et al*., (2008) used sucrose stearates as non-ionic biocompatible surfactant for the nebulisable delivery of cromolyn sodium and used lactose powder as a carrier [16].

1. Formulation of Proniosomes

1.1 Non-ionic surfactant

Sorbitan esters are widely used in cosmetics, food products, and pharmaceutical formulations as lipophilic nonionic surfactant. When used alone, sorbitan esters produce stable water-in-oil and micro emulsion but are frequently used in combination with varying proportion of a polysorbate to produce water-in-oil or oil-in-water emulsions.

Like lipids the non-ionic surfactant also orient in an aqueous medium as planner bilayer lattices wherein polar or hydrophilic heads align facing aqueous media while hydrocarbon segment are so aligned that their interaction with aqueous media is minimized [17]. Mainly two non-ionic surfactant are used,

1.1.1 Sorbitan Esters (Sorbitan Fatty Acid Esters):

Sorbitan monoesters are series of mixtures of partial esters of sorbitol and its mono- and dianhydrides with fatty a acid. Sorbitan diesters are series of mixture of partial ester of sorbitol and its monoanhydride with fatty acid. Sorbitan esters are widely used in cosmetics, food products, and pharmaceutical formulations as lipophilic nonionic surfactant. When used alone, sorbitan esters produce stable water-in-oil and micro emulsion but are frequently used in combination with varying proportion of a polysorbate to produce water-in-oil or oil-in-water emulsions. (Table 1)

Table1: Commonly used sorbitan esters

Name	Synonym
Sorbitan monolaurate	Span 20
Sorbitan monooleate	Span 80
Sorbitan monopalmitate	Span 40
Sorbitan monostearate	Span 60
Sorbitan trioleate	Span 85
Sorbitan tristearate	Span 65

1.1.2 Polyoxyethylene Sorbitan Fatty Acid Esters (Polysorbate):

Polyoxyethylene sorbitan fatty acid esters (polysorbates) are a series of partial fatty acid esters of sorbitol and its anhydrides copolymerized with approximately 20, 5, or 4 moles of ethylene oxide for each mole of sorbitol and its anhydrides. The resulting product is therefore a mixture of molecules of varying sizes rather than a single uniform compound. Polysorbate containing 20 units of oxyethylene are hydrophilic nonionic surfactant that are used widely as emulsifying agents in the preparation of stable oil-in-water pharmaceutical. (Table 2)

Table 2: Commonly used polysorbates

Name	Synonym
Polysorbate 20	Tween 20
Polysorbate 40	Tween 40
Polysorbate 60	Tween 60
Polysorbate 65	Tween 65
Polysorbate 80	Tween 80
Polysorbate 85	Tween 85

1.2 Cholesterol

It is the major sterol of higher animals and is found in all body tissues, especially in brain and spinal cord [18]. Steroids are important component of cell membrane changes the bilayer fluidity and permeability with their presence in membrane. Due to amphipathic nature of cholesterol it aligns itself in such a way that its OH group orient towards aqueous phase and aliphatic chain align parallel to hydrocarbon chain of surfactant. The presence of rigid steroidal skeleton along side the carbon chain of surfactant could possibly restrict the freedom of movment of the carbon of the hydrocarbon segment thus providing an absolute rigidization [19].

1.3 Lecithin

It is a complex mixture of acetone-insoluble phosphatides that consist chiefly of phosphatidylcholine, phosphatidylethanolamine, phosphatidylserine, phosphatidylino-sitol, combined with various amount of other

substance such as triglycerides, fatty acid, and carbohydrate. It is found that vesicle composed of soya lecithin are of larger size then vesicle composed of egg lecithin possibly due to difference in the intrinsic composition of Soya and lecithin [20].

1.4 Carrier

Sorbitol, Maltodextrin, Mannitol, and Lactose are the carriers which has been used so far in preparation of proniosomes formulations. Sorbitol is D-glucitol. It is hexahydric alcohol related mannose and is isomeric with mannitol. Sorbitol mainly used in the spray-coating method [18]. But the sorbitol carrier in the original proniosomes is soluble in the solvent used to deposit surfactant, so preparation is tedious and the dissolved sorbitol interfered with the encapsulation of one model drug. Maltodextrin used in the slurry method to prepare proniosomes. The time required to prepare proniosomes by this simple method is independent of the ratio of the surfactant solution to carrier material and appear to scalable [21].

1.5 Solvent

Alcohol (Ethanol, Propanol, Butanol, Isopropanol): Alcohol used in proniosomes having great effect on vesicle size and drug permeation rate. Vesicle formed from different alcohol is of different size, they follow the order: Ethanol > Propanol > Butanol > Isopropanol.

Highest size of vesicle in case of ethanol is due to its greater solubility in water and smallest size of isopropanol, may be due to branched chain present in it [20].

2. Preparation of proniosomes

Proniosomes are the dry formulation of surfactant-coated carrier [4]. Drug containing proniosomes can be prepared by two methods:

2.1 Spray-coating method This method is reported by the Hu and Rhodes (1999) in which a round bottom flask containing sorbitol is attached on the rotary evaporator, a surfactant solution is prepared and is introduced into flask by sequential spraying of aliquots onto the surface of sorbitol powder. During spraying period of the rate of application is controlled so that the powder beds of the sorbitol do not become overly wet. The evaporator is then evacuated and the rotating flask is lowered into the water bath at 65-70 ºC. The flask is rotated in the water bath under vacuum for 15-20 min. or until sorbitol appears to be dry, and another aliquot of surfactant solution is introduced. This process is repeated until all the surfactant solution has been applied. After addition of final aliquot, evaporation is continued until the powder is completely dry (about 20-30 min.). The material is further dried in desiccator under vacuum at room temperature overnight. This dry preparation is referred as proniosomal powder [22].

2.2 Slurry method

Proniosomes with the maltodextrin as the carrier are prepared by a slurry method in contrast to the slow spray –coating method. The sorbitol carrier in the original proniosomes is soluble in solvent used to deposit surfactant, so preparation is tedious and the sorbitol interfered with encapsulation of one model drug. The time required to produce proniosomes by this simple method is independent of surfactant solution to carrier material. For the slurry method, of maltodextin powder is added to a round –bottom flask and the entire volume of surfactant solution is added directly to the flask. The flask is attached to a rotary evaporator to evaporate chloroform at 60-70 rpm, a temperature of 43 ºC – 47 ºC, and a reduced pressure of 600mm Hg until the powder appears to be dry and free flowing. The flask is removed from the evaporator and kept under vacuum overnight. Proniosomes powder is stored in sealed containers at 4 ºC [21].

3. Preparation of Niosomes

Proniosome powder (prepared as described above) is weighed into screw capped vials. Water at 80 ºC is added and the vials capped. The vials are attached to a vortex mixer and agitated at the maximum setting for 2 minutes as shown in figure 1 [21].

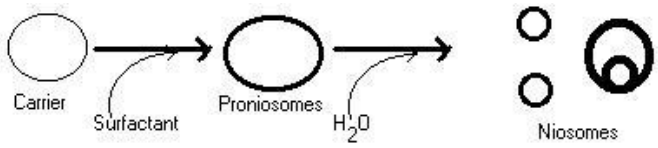

Fig 1: Formation and conversion of proniosomes

4. Characterization of proniosomes

4.1 Morphology of dry Proniosome powder

Proniosomes are sprinkled on double-sided conductive carbon tape on an aluminum stub. Excess sample is blown off with compressed air. The specimen is then coated with Au/Pb (60/40) using a Ladd sputter coater at 2.5 KV and 20 mA for 45 seconds. The coated specimen is observed using a Philips 515 Scanning electron Microscope at 50 KV and recorded on Polaroid PIN 55 film [4].

4.2 Measurement of angle of Repose

The angle of repose of dry proniosomes powder can be measured by a funnel method (Lieberman *et al*., 1990) [23]. The Proniosomes powder is poured into a funnel which is fixed at position so that the 13 mm outlet orifice of the funnel is 10 cm above the surface level. The powder flow down from the funnel to form a cone on surface, and the angle of repose is then calculated by measuring the height of the cone and diameter of its base [4].

4.3 Stability studies

Proniosmal formulations are stored in glass tube covered with aliminium foil under above temperature conditions. After 7, 15, and 30 days they are observed visually and under optical microscope for the change in consistency, liquid crystalline structure and appearance of drug crystals upon storage [24].

5. Characterization of noisome

5.1 Morphology of Noisome

The morphology of hydrated niosomes dispersion prepared from proniosomes is determined using transmission electron microscopy. A drop of niosomes dispersion is diluted 10-fold using deionised water. A drop of diluted niosomes dispersion is applied to a carbon –coated 300 mesh copper wire grid left for 1 min. to allow some of niosomes to adhere to the carbon substrate. The remaining dispersion is removed by absorbing the drop with corner of a piece of filter paper. After twice

rinsing the grid (deionized water for 3-5 s) a drop of 2% aqueous solution of uranyl acetate is applied for 1s. The remaining solution is removed by absorbing liquid with tip of piece of filter paper and sample is air dried. The sample is observed with a JEOL 100 CX transmission electron microscope at 80 KV [4].

5.2 Entrapment efficiency

Entrapment efficiency can be measured by two methods:

(a) Measuring the unentrapped free drug
(b) Measuring the entrapped drug in niosomes.

a) First, the methods that have been used for the removal of unentrapped material include Exhaustive dialysis, Gel filtration, Centrifugation, Ultra centrifugation. The niosomes dispersion is, centrifuged for 15 min. and transparent solution is separated from the precipitate. The precipitate consisted of the vesicular pellet and is washed three times with phosphate buffer solution (pH 6.8). All supernatants are collected and analyzed by UV and HPLC to determine the unentrapped drug.

b) For entrapped drug vesicles are re-suspended in 2.5% v/v Triton X-100, added to solubilize the vesicle. The solution is diluted with phosphate buffer to 10 ml and heated for 30 min at 80 ºC in water bath. The concentration of drug is determined by UV and HPLC. In all cases a drug free proniosomal formulation is used as the blank [25].

5.3 In Vitro Drug Release Studies

5.3.1 In Vitro Drug Release Studies of niosomes from Proniosomal powder formulation:

After the separation of free drug by centrifugation of phosphate buffer, saline is added and vortexed for 10s to prepare the dispersion. This niosomal dispersion is placed in membrane. Aliquots are withdrawn and replaced with the same volume of fresh buffer, at each sampling point. The withdrawn are analyzed for the drug content spectrophotometrically [15].

5.3.2 In Vito Release Studies on niosome from Proniosomes Gel:

Proniosomes gel is prepared by a coacervation-phase separation method. In vitro release studies on proniosomal gel are performed using locally manufactured Franz-diffusion cell. The dialysis cellophane membrane is mounted between the donor and receptor compartment. A weighed amount of proniosomal gel is placed on one side of dialysis membrane. The receptor medium is phosphate saline buffer pH 7.4. The receptor compartment is surrounded by a water jacket to maintain the temperature at (36 ºC -38 ºC). Heat is provided using thermostat hot plate with a magnetic stirrer. The receptor fluid is stirrer by a Teflon-coated magnetic bead fitted to magnetic stirrer. **S**amples are withdrawn and are replaced by equal volumes of fresh receptor fluid on each occasion. Samples withdrawn are analyzed spectrophotometrically [20].

5.5 Stability Studies

The ability of vesicles to retain the drug is assessed by keeping the niosomal suspension at three different temperature conditions i.e. Refrigeration temperature (4 ºC -8 ºC), Room temperature (25 ºC ±2 ºC), Oven (45 ºC ±2 ºC)

Niosomes formed from proniosomes are characterized after one month storage for size and size distribution after hydration with agitation, without agitation and for spontaneity of niosomes formation [15, 20].

6. Factor affecting vesicles size, entrapment efficiency and release characteristics

6.1. Drug:

Entrapment of drug in proniosomes increase vesicle size, probably by interaction of solute with surfactant head group, increasing the charge and mutually repulsion of surfactant bilayer, thereby increasing vesicle size as shown in Table 3 [26].

Table 3: Maximum entrapment efficiency of different drugs

Drugs used in proniosomes	Percentage entrapment
Estradiol [28]	98.03±0.23
Ketorolac [40]	99.2±5.1
ChloropheniramineMaleat [12]	16.7±1.01
Captopril(proniosomes powder) [15]	70.10±1.28
Captopril (proniosomal gel) [14]	78.71±1.48
Cromolyn Sodium [16]	49..96±2.36

6.2. Type of surfactant:

Span 40 and span 60 gives the vesicles of larger size with higher entrapment of drug and the drug leaching from the vesicles is low, due to high phase transition temperature and low permeability. High HLB value of span 40 and 60 result in reduction in surface free energy which allow to form vesicle of larger size hence small area exposed to the dissolution medium and skin [20]. Different effect of non-ionic surfactant on levonorgestrel permeation profile show that the flux value is highest for span 80 and lowest for span 60. No significant difference is observed in the skin permeation profile of formulation containing span 60 and span 40 due to their higher phase transition temperature that is responsible for there lower permeability. The encapsulation efficiency of tween is relatively low as compared to span. Because the vesicle can be successfully formed by tween only in the presence of cholesterol in excess of 33.33 mol% (Uchegbu and Florence, 1995) [27]. As the cholesterol content of the formulation decreased, the encapsulation of drug also decreased [28].

6.3 Cholesterol content and charge:

An increase in cholesterol content of bilayers resulted in the decrease in the release rate of encapsulated material and therefore an increase of rigidity of the bilayers obtained. Presence of charge tends to increase the interlamellar distance between successive bilayers in multilamellar vesicle structure and leads to greater overall entrapped volume [26, 28, 29].

6.4 Lecithin type

It is found that vesicle composed of soya lecithin are of larger size then vesicle composed of egg lecithin possibly due to difference in the intrinsic composition of soya and lecithin [20].

6.5 Solvent type

Alcohol used in Proniosomes having great effect on vesicle size and drug permeation rate. Vesicles formed from different

alcohol are of different size, they follow the order [20]: Ethanol > Propanol > Butanol > Isopropanol

Highest size of vesicle in case of ethanol is due to its greater solubility in water and smallest size of Isopropanol, may be due to branched chain present in it [20].

7. Applications

7.1 Topical/Transdermal (TT) delivery system:

The skin is a major target for TT drug delivery. The stratum corneum (SC) provides a main barrier against drug transport, and SC intracellular lipid help to regulate penetration [30]. The lipid matrix, composed of ceramides free fatty acids, plays a major role in barrier function [31, 32]. Despite the advantage of TT drug delivery, SC permeability may limit its usefulness. To increase permeability, chemical and physical approach has been examined to lower SC barrier properties. These approach including tap stripping [33], iontophoresis [34], electroporation [18] and vesicular system, such as liposomes and niosomes [35, 36].

Proniosomes can be converted into niosomes upon simple hydration of skin and the vesicles act as penetration enhancer to reduce the barrier properties of the stratum corneum. Many scientists [37-38] observed two types of vesicle-skin interactions:

(1) The vesicle in contact with stratums coneum aggregate, fuse and adhere to the cell surface. It believed this interaction lead to a high thermodynamic activity gradient of the drug at the vesicles-stratum conium interface, which is the driving force for penetration of lipophilic drug across the stratum conium.
(2) The type of interaction involves the ultrastrutral changes of the intercellular lipid regions of the stratum corneum and its deeper layer at maximum depth of about 10 um as revealed by Freeze Fracture Electron Microscopic (FFEM) And Small Angle X-ray Scattering (SAXS).

Proniosomes offer a versatile delivery concept with the potential for delivering drug via the TT route. They are mainly composed of non-ionic surfactants (span and tween), phospholipids, alcohol and water with or without cholesterol. The method of preparation based on the simple idea that a mixture of surfactant/alcohol/aqueous phase can used to form a concentrated proniosomal gel as mentioned in Table 4 [10].

Table 4: Proniosomes as Topical/Transdermal formulations and uses

S. No.	Drug Incorporated	Uses
1.	Levonorgestrel [20]	Contraceptive agent
2.	Estradiol [28]	In hormonal insufficiency
3.	Ethinylestradiol and Levonorgestrel [11]	Contraception and hormonal replacement therapy
4.	Ketorolac [40]	Analgesic and moderate anti-inflammatory activity
5.	Chlorpheniramine Maleate [25]	Skin disorders as sunburns, urticaria, angiodema, pruritus and insect bite
6.	Captopril [15]	Hypertension and congestive heart failure
7.	Furesimide [41]	Antihypertensive and diuretic
8.	Piroxicam [31]	Rheumatoid arthritis or osteoarthritis.

7.2. Oral drug delivery

Captopril is an orally effective angiotensin-1 converting enzyme inhibitor and is used in the treatment of hypertention and CHF. Captopril has a relatively short half-life ranging from 1.6 to 1.9 h. The drug is considered as drug of choice in hypertention therapy due to its effectivness and low toxicity. Captopril which is water soluble, is usually prescribed to patient who are chronically ill and require long-term use for its therapeutic benefits. Development of once daily captopril oral formulation would be a significant advantage for patient compliance, accompanied by minimization of drug side effect as a result of reduction of drug blood concentration fluctuation in long term therapy. Different attempts have been made to design long acting devices in the form of sustained or controlled release preparation to deliver a drug like coated tablet, bead, hydrophobic tablets, a pulsatile delivery system, microcapsule, a bioadhesive system, floating tablets and capsules. Hydrophobic tablets showed that the release patteren of captopril complied with the zero-order kinetics for controlled release formulation, but the release period is comparatively short. This is the same situation with captopril bead formulation. Even in floating tablets in vitro sustained release is up to 8 h, which is short. Morever, gastric Retention of these system depend upon gastric motility, pH and presence of food. The prepared proniosomal formulation follow zero-order kinetics, and release is extended up to 24 h [14].

7.3. Nebuliser drug delivery

H.M. El-laithy *et al*., (2008) prepared controlled release proniosomes –derived niosomes, using sucrose stearates as non-ionic biocompatible surfactant for the nebulisable delivery of cromolyn sodium. Cromolyn sodium is a anti-asthmatic and antiallergic drug. It is known that frequent inhalation of cromolyn sodium solution from nebuliser (4-6) time daily is necessary because it is cleared rapidly with an elimination half-life of ~80min. Many strategies are applied to improve the aerosolisation behavior and the deposition of drug in the lung. Therefore in order to reduce number of dose and to achieve constant drug blood level, controlled drug release niosomal and proniosome- derived niosomal formulation are developed using biodegradable sucrose ester [39].

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