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International Journal of Pharmaceutics 224 (2001) 169–176

international journal of pharmaceutics

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Stabilization of supersaturated solutions of a lipophilic drug for dermal delivery

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Received 5 December 2000; received in revised form 21 May 2001; accepted 4 June 2001

Abstract

The stability of supersaturated solutions of a model lipophilic drug (LAP, a lavendustin derivative) in propylene glycol–water mixtures prepared using the method of mixed cosolvents was investigated. The solutions had a fixed degree of saturation (DS = 4), but contained different ratios of propylene glycol–water. The absolute concentrations of LAP in these solutions varied by approximately a factor of 40, but the solutions at lower concentrations were no more stable than the more concentrated solutions. This shows that stability is primarily a question of the degree of saturation and not of the absolute drug concentration. Solutions of up to 5 degrees of saturation in 7:3 propylene glycol–water mixture were stable when stored for several hours; those at higher degrees of saturation recrystallized immediately. When the solutions were stirred, recrystallization occurred more rapidly. The influence of various polymeric additives on the stability of the supersaturated solutions showed that only sodium carboxymethyl cellulose had a stabilizing effect; however, the solution was very viscous and it is not clear whether the stabilizing effect was due to this high viscosity or to a specific interaction between drug and polymer.

Keywords: Supersaturation; Formulation stability; Polymers; Topical drug delivery; Skin penetration; Percutaneous absorption

1. Introduction

The penetration of drugs into the skin is typically limited by the barrier function of the stratum corneum. Recently, the relatively simple method of supersaturation to increase percutaneous absorption has attracted interest, not the least because of its reduced potential to provoke skin irritation compared, for example, to chemical penetration enhancers. The mechanism of enhancement by supersaturation is based, of course, on increasing the thermodynamic activity of the drug in the formulation. However, supersaturated formulations are inherently thermodynamically unstable and the drug recrystallizes over time.

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0378-5173/01/$ - see front matter
PII: S0378-5173(01)00762-1

Nevertheless, it has been shown that the addition of stabilizing polymers can be used to retard the kinetics of recrystallization.

For example, supersaturated solutions of nifedipine have been stabilized by Eudragit R/S 100L, hydroxypropyl methyl cellulose (HPMC) phthalate, and ethyl cellulose, and improved skin permeation has been observed both in vitro and in vivo as a result (Kondo and Sugimoto, 1987a; Kondo et al., 1987b). Similar results (primarily in vitro) have been reported for supersaturated solutions of hydrocortisone acetate stabilized by HPMC (Davis and Hadgraft, 1991), piroxicam stabilized by HPMC or methyl cellulose (Pellett et al., 1997; Raghavan et al., 2000), ibuprofen by HPMC and cyclodextrin (Iervolino et al., 2000), nonivamide by methyl cellulose and hydroxypropyl cellulose (Fang et al., 1999), estradiol stabilized by polyvinylpyrrolidone (PVP), polyvinyl alcohol, hydroxypropyl cellulose, and HPMC (Megrab et al., 1995), and fluocinonide by PVP (Schwarb et al., 1999).

Equally, PVP has stabilized supersaturated solutions of sulfamethizole and sulfisoxazole (Sekikawa et al., 1978), norethindrone acetate (Ma et al., 1996), estradiol and gestodene (Lipp, 1998), sulfathiazole (Simonelli et al., 1970; Ziller and Rupprecht, 1990), different hydroxybenzoic acid derivatives and phenobarbital (Ziller and Rupprecht, 1990). PVP and HPMC both stabilized supersaturated solutions of paracetamol (Femi-Oyewo and Spring, 1994), while HPMC (and a hydrophobically modified derivative) stabilized supersaturated indomethacin (Ikeda et al., 1994). Finally, carboxymethyl ethyl cellulose has been shown to stabilize nifedipine, spironolactone, and griseofulvin when formulated as supersaturated solutions (Hasegawa et al., 1988).

It is clear, therefore, that various polymers can be used to stabilize a supersaturated drug solution. However, to date, no predictive tool exists for the rational selection of the right polymer for a particular drug. Thus, the objective of this work was to examine, using a model lipophilic drug (LAP, a lavendustin derivative (Fig. 1), log (octanol–water partition coefficient) ≈ 5 (Moser et al., 2001)), whether the rational stabilization of a supersaturated formulation could be achieved.

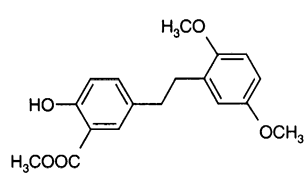

Fig. 1. Chemical structure of LAP.

2. Materials and methods

2.1. Materials

LAP (SDZ LAP 977) was provided by Novartis Pharma AG (Basel, Switzerland). Propylene glycol p.a., was purchased from Fluka (Buchs, Switzerland), acetonitrile and methanol (both gradient grade) from Merck KgaA (Darmstadt, Germany). Purified water was produced with a Milli-Q RG system from Millipore (Bedford, MA). Glass Acrodisc® 25 and Nylon syringe filters (both pore size 0.45 μm) were purchased from Pall Gelman Sciences (Ann Arbor, MI). Aerosil 200 was obtained from Degussa AG (Frankfurt, Germany), Eudragit L100-55 from Röhm GmbH (Darmstadt), HPMC (Pharmacoat 603) from Shin-Etsu (Tokyo, Japan), sodium carboxymethyl cellulose (NaCMC) 7LFD from Aqualon (Wilimgton, DE), Poloxamer 188 and PVP K12 from BASF AG (Ludwigshafen, Germany), PVP K30 from ISP (New Jersey).

2.2. Solubility of LAP in propylene glycol–water mixtures

The solubility of LAP in mixtures of propylene glycol and water at different ratios, with and without additives, was determined by sonicating a suspension of drug substance in the solvent mixture at a frequency of 100 Hz at 25 °C for 24 h. The samples were filtered through a Nylon filter or a glass fiber filter (pore size 0.45 μm), diluted with methanol and analyzed by UV-spectroscopy at 296 nm (Uvikon spectrophotometer 940, Kontron Instruments, Milano, Italy) or by HPLC.

HPLC analysis used a Kontron autosampler 460, Kontron pump 420 and a Jasco UV-975

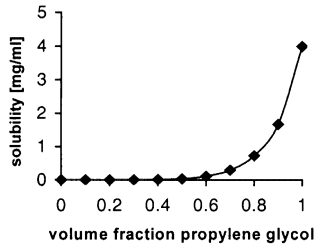

Fig. 2. Solubility curve of LAP in propylene glycol–water mixtures at different ratios.

detector, with a LiChrospher 60-5 Select B 125×4 mm column with a CC 8/4 LiChrospher 100-5 RP-18 precolumn (Machery-Nagel) maintained at a temperature of 50 °C. The mobile phase, consisting of a 40:60 mixture of 10 mM ammonium sulfate (adjusted to pH 6.0 with triethylamine) and acetonitrile, was pumped through the column at 1 ml/minute. The injection sample volume was 20 μl and LAP was quantified by its absorbance at 230 nm. The retention time was ≈ 5 min.

2.3. Preparation and stability evaluation of the supersaturated solutions

Saturated and supersaturated LAP solutions in mixtures of propylene glycol–water (7:3, v/v) were prepared using the method of mixed cosolvents (Davis and Hadgraft, 1991) as described in a previous publication (Moser et al., 2001). The formulations containing polymeric additives (1.5%) were typically prepared by first dissolving the additive in water. However, the additives Aerosil and Eudragit L100-55 were dissolved in propylene glycol, while, for formulations containing PVP above 1.5%, the polymer was added to both solvents before mixing. The supersaturated solutions were maintained in a water bath at 25 °C and sampled periodically over a period of either 24 h or 1 week. The solutions were not stirred (unless otherwise indicated below). The samples were filtered through a Nylon filter or a glass fiber filter (pore size of 0.45 μm), diluted 1:25 (v/v) with methanol, and analyzed spectrophotometrically at 296 nm (Uvikon spectrophotometer 940, Kontron Instruments, Milano, Italy).

The potential adsorption of LAP to filters was examined by assaying the drug in a saturated solution in propylene glycol–water mixture (7:3) before and after filtration. No significant change in drug concentration (ANOVA, $\alpha = 5\%$) (i.e., no adsorption) was observed for either filter used.

2.4. Differential scanning calorimetry and X-ray diffraction analysis

Samples were prepared by mixing the drug with the additives in a SPEX 6700 Freezer/Mill (SPEX Industries, Inc., Edison, N.I.) for 5 min.

For differential scanning calorimetry (DSC) analysis, 5–10 mg samples were scanned (DSC 7, Perkin–Elmer) under nitrogen at 10 °C/min between -60 and 80 °C.

The powder X-ray diffraction pattern of the samples was recorded with a Scintag XDS 2000 diffractometer using CuK_{α} radiation (45 kV, 40 mA).

3. Results and discussion

3.1. Solubility of LAP in propylene glycol–water mixtures

The solubility of LAP in propylene glycol–water mixtures increased exponentially with increasing volume fraction of propylene glycol (Fig. 2), indicating that the method of mixed cosolvents was suitable for the preparation of supersaturated solutions. To investigate the stability of supersaturated formulations, a vehicle was chosen which (a) allowed the preparation of solutions at several degrees of saturation and (b) showed a relatively high solubility for LAP. Specifically, a propylene glycol–water mixture at a ratio of 7:3 (v/v) was used, which allowed a theoretical maximal degree of saturation of 9 (Moser et al., 2001) with a LAP solubility (0.3 mg/ml) which would be sufficient to sustain dermal delivery for a reasonable period of time post-application to a patient.

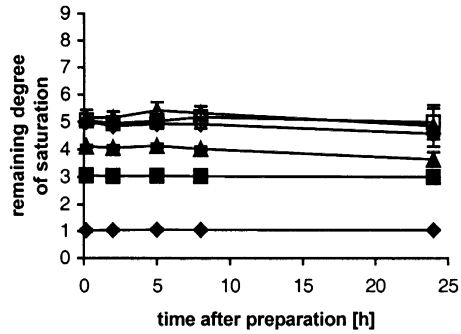

Fig. 3. Stability of solutions of LAP in propylene glycol–water mixtures at: 1 (◆); 3 (■); 4 (▲); 5 (◇); 6 (□); and 9 (△) degrees of saturation. The degree of saturation was determined 0.17, 2, 5, 8, and 24 h after preparation ($n = 3$, mean ± S.D.).

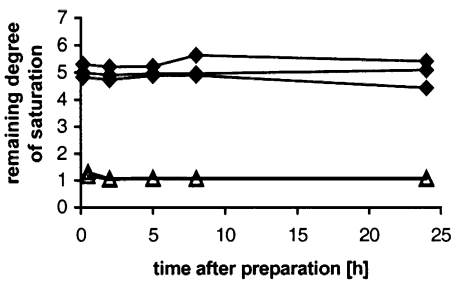

Fig. 4. Stability of solutions of LAP at 6 degrees of saturation in propylene glycol–water (7:3) with (△, $n = 2$) and without stirring (◆, $n = 3$).

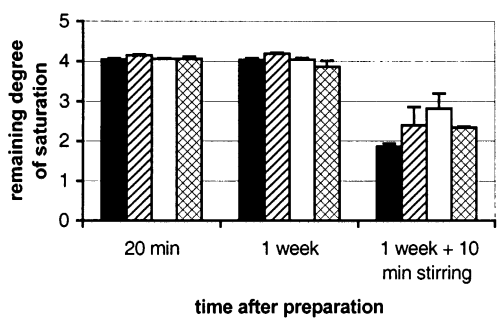

Fig. 5. Stability of LAP at 4 degrees of saturation in propylene glycol–water mixtures at different ratios of the cosolvents (5:5 (filled bars), 6:4 (hatched bars), 7:3 (open bars), 8:2 (cross-hatched bars)). The remaining degree of saturation was determined after 20 min, after 1 week, and after 1 week with subsequent stirring for 10 min ($n = 3$, mean ± S.D.).

3.2. Stability of LAP in propylene glycol–water mixtures

The stability of LAP in propylene glycol–water mixtures (7:3) at 1, 3, 4, 5, 6, and 9 degrees of saturation is shown in Fig. 3 (adapted from Moser et al., 2001). Whereas solutions of up to 5 degrees of saturation were clear after preparation and maintained the degree of saturation over 24 h, those at 6 and 9 degrees of saturation were cloudy immediately after preparation (indicating precipitation) and showed a measured degree of saturation of about 5. It appears that the presence of nucleation centers alone is not sufficient in itself to cause further drops in the degree of saturation. In contrast, when a LAP solution at 6 degrees of saturation was stirred, a very fast crystallization occurred and the system rapidly passed through the metastable zone simply leaving a saturated solution (Fig. 4). The former results indicate that the metastable zone of supersaturated LAP solutions in propylene glycol–water mixtures at a ratio of 7:3 is in the range of 1–5 degrees of saturation.

The effect of absolute drug concentration was next examined. The stability of LAP solutions at 4° of saturation in different propylene glycol–water mixtures was compared. The solubility of LAP in these solutions varied from 0.04 to 1.7 mg/ml, i.e., over about a 40-fold range. The degree of saturation remained constant in all solutions, independent of the absolute LAP concentration during 1 week. Stirring, however, caused a significant (although sometimes quite variable) decrease in the degree of saturation (Fig. 5).

3.3. Stabilizing effect of different polymers

When putatively stabilizing polymers are added, LAP solubility can change such that the amount of drug may need to be adjusted to achieve the same degree of saturation. The solubilities of LAP in propylene glycol–water (7:3) mixtures containing different additives were therefore measured (Table 1).

As a starting point for the identification of a good stabilizing polymer for supersaturated solutions of LAP, the drug's solubility parameter was

Table 1
Solubility of LAP in propylene glycol–water mixtures (7:3) in the presence of polymeric additives

Additive	Solubility (mg/ml)
–	0.30
Aerosil 3%	0.28
Eudragit L100-55 1.5%	0.39
HPMC 1.5%	0.35
NaCMC 1.5%	0.33
Poloxamer 188 1.5%	0.39
PVP K12 1.5%	0.35
PVP K12 15%	0.55
PVP K30 6%	0.50

Table 2
Solubility parameters of selected drugs (including LAP) and polymers

Substance	Solubility parameter ($MPa^{0.5}$)
LAP[a]	23.8
Nifedipine[b]	22.9
HPMC[b,c]	26.8/17.2–26.4
PVP[b,c]	25.0/21.2
PVA[b,c]	31.3/19.9–34.4
Pullulan[b]	34.1
Water[c,d]	23.4/47.9
Propylene glycol[c,d]	14.8/25.8–30.3
Hydrocortisone acetate[a,c]	24.7/23.7
Estradiol[a]	24.5

[a] Estimated by the group contribution method of Fedors.
[b] Values from Suzuki and Sunada, 1998.
[c] Values from Hancock et al., 1997.
[d] Values from Shively et al., 1995.

calculated according to Fedors (1974) and compared to that of some polymers used (Table 2). It has been reported that supersaturated formulations of nifedipine (Suzuki and Sunada, 1998) are best stabilized by polymers having similar solubility parameters (whereas those having higher values have a destabilizing effect). LAP, in fact, has a similar solubility parameter to nifedipine, estradiol and hydrocortisone acetate and to PVP and HPMC, two polymers which have been used to stabilize these previously studied drugs (Davis and Hadgraft, 1991; Megrab et al., 1995; Suzuki and Sunada, 1998). However, it was found that 1.5% PVP K12 had no effect on the stability of a LAP solution at 6 degrees of saturation (measured at 24 h), while HPMC had a destabilizing effect. PVP K12 at 15% and PVP K30 at 6% also destabilized the formulation (Fig. 6). Precisely why such results have been obtained with this approach is not clear. It is true that the cosolvent used for LAP differed from that used for nifedipine (Suzuki and Sunada, 1998) and this may be important; on the other hand, the results for hydrocortisone acetate and estradiol were obtained using propylene glycol–water mixtures (Davis and Hadgraft, 1991; Megrab et al., 1995). It should also be noted that estradiol could be stabilized by PVA even though this polymer has a higher (and therefore not ideal) solubility parameter than this drug. We conclude, therefore, that the matching of drug and stabilizing polymer solubility parameters is not yet a reliable method for optimizing supersaturated formulation.

DSC has been reported to be useful for the selection of stabilizing additives for supersaturated transdermal drug delivery systems (Lipp, 1998). The heat of fusion and melting point of the

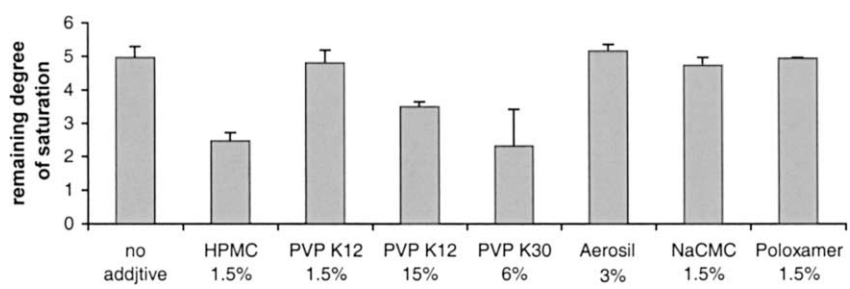

Fig. 6. Stability of LAP solutions at 6 degrees of saturation in the presence of different polymers. The remaining degree of saturation after 24 h is shown. ($n = 6$ for the control solutions (no additive), $n = 3$ for the solutions with polymer, mean $\pm$ S.D.).

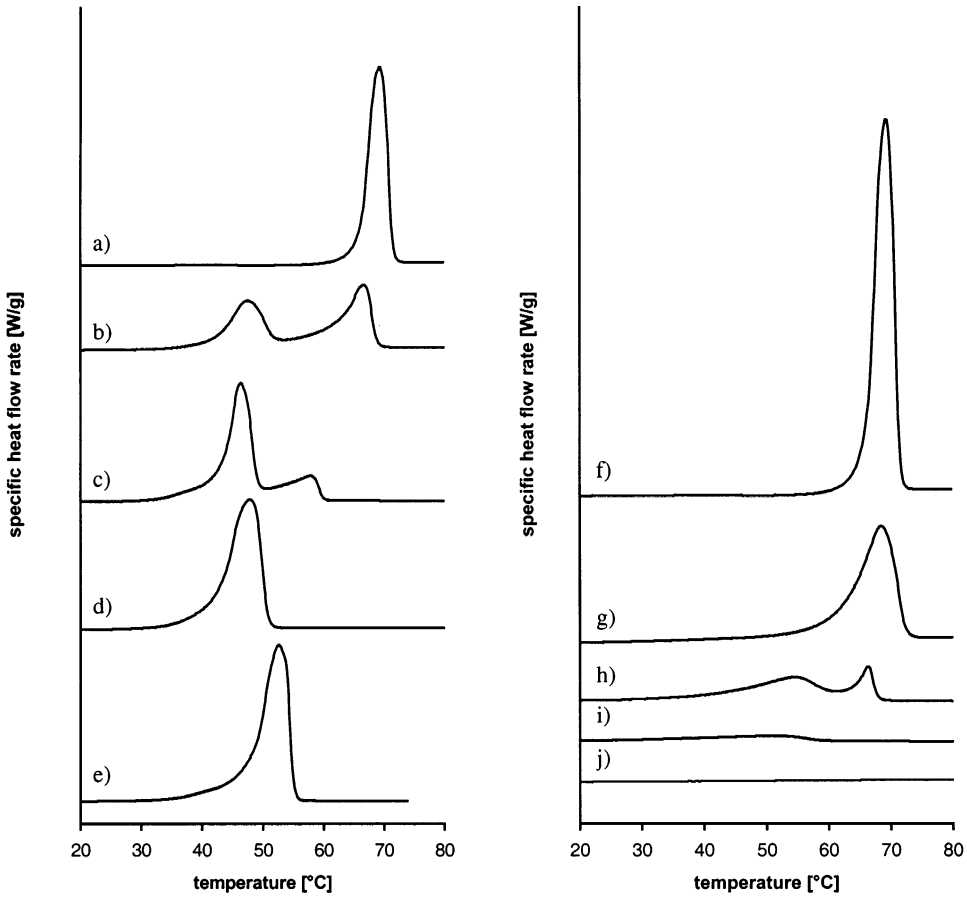

Fig. 7. DSC profiles of (a) pure LAP, (b) LAP:Poloxamer 75:25, (c) LAP:Poloxamer 50:50, (d) LAP:Poloxamer 25:75, (e) pure Poloxamer, (f) pure LAP, (g) LAP:Aerosil 75:25, (h) LAP:Aerosil 50:50, (i) LAP:Aerosil 25:75, (j) pure Aerosil.

pure drug were, therefore, compared to those of a physical mixture of the drug with various polymers. A decrease in the heat of fusion indicated interaction between the drug and the polymer, and correlated with a stabilizing effect. Mixtures of LAP with PVP K30, PVP K12, Poloxamer 188, HPMC, NaCMC, and Aerosil 200 were investigated. While NaCMC, PVP and HPMC showed only minor influence on melting point and heat of fusion, Aerosil and Poloxamer led to important changes (Fig. 7). With Poloxamer, the melting point and the heat of fusion of LAP, decreased significantly. The relative proportion of LAP to Poloxamer in the physical mixture was important, and DSC further indicated the formation of a eutectic mixture at 25:75 drug:polymer. On the other hand, at 50:50, the X-ray diffraction pattern revealed peaks corresponding to crystalline LAP and Poloxamer, and that mixing had not led to any crystal modifications of either substance (data not shown). With Aerosil, DSC again suggested interaction but the nature of this phenomenon was difficult to discern. At a drug:polymer ratio of 75:25, only the melting transition of LAP was apparent; at 50:50, a second, broader and lower-temperature transition appeared that would seem to be unconnected with the polymer, which showed no thermal behavior in the temperature range studied. X-ray diffraction ruled out another polymorph of LAP, the only scattering pattern being observed coming from LAP in its normal crystalline form (data not shown).

As shown in Fig. 6, Aerosil, and Poloxamer did not improve on the 24-h stability of a LAP solution initially prepared at 6 degrees of saturation when compared to the polymer-free control. In other words, the results from the DSC experiments were not predictive of a stabilizing effect.

Finally, the 24-h stability study, again with LAP solutions at 6 degrees of saturation in the presence of various polymers, was repeated but, this time, the solutions were stirred for 10 min at the end of the experiment. The remaining degree of drug saturation was then determined (Fig. 8). Only NaCMC at 1.5% permitted a significantly better stabilization of the formulation over the control. It should be said, however, that these solutions were highly viscous and that this, of course, might explain at least in part their better stability. It remains to be seen whether such improvement in longer-term physical stability translates into sustained and improved drug delivery.

In conclusion, while the literature, and to a very limited extent the results of this study, demonstrate that polymeric additives can stabilize supersaturated drug solutions up to a point, their effects may have limited duration once the formulation is agitated in any way. Attempts, using LAP as a model drug, to identify rational approaches to the selection of an optimal polymeric stabilizer were unsuccessful and point to the need for a better understanding of the physical chemistry of these systems and their ultimate stabilization. Although we did not find any correlation between gross measures of physicochemical properties such as DSC and solubility parameters and the degree of stabilization, it might also be worthwhile to investigate the potential for interactions at the molecular level between a given drug and a 'stabilizing' polymer; for example, is there a correlation between the degree of stabilization achieved and certain physicochemical properties, e.g., the capacity for hydrogen bond formation.

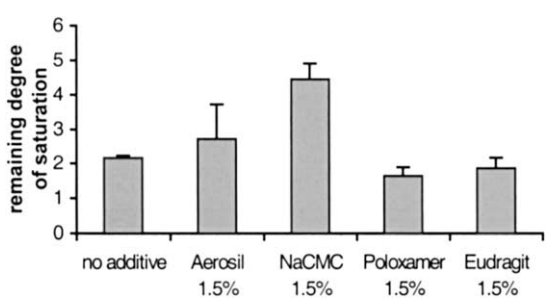

Fig. 8. Stability of LAP solutions at 6 degrees of saturation in the presence of polymers after 24 h followed by stirring for 10 min ($n = 3$–4, mean $\pm$ S.D.).

Acknowledgements

We wish to thank the laboratories of Drs K. Fiebich and S. Pfeffer (Novartis Pharma AG, Technical R&D, PHAD and CHAD, respectively) for the DSC- and X-ray diffraction measurements, and their interpretation. The support of Novartis Pharma AG is gratefully acknowledged.

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