# Size Control of Ibuprofen Microspheres with an Acrylic Polymer by Changing the pH in an Aqueous Dispersion Medium and Its Mechanism

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The size of ibuprofen microspheres fabricated by the o/w emulsion solvent diffusion method was controlled by adjusting the pH (1.0—5.0) in an aqueous dispersion phase. As the pH decreased, the diameter of the microspheres decreased, while drug entrapment efficiency and yield of microspheres remained unchanged. In the present system, the size of microspheres increased *via* coalescence and fusion of the oil emulsion droplets before solidification of the droplets occurred. At a lower pH, the solvent (ethanol) diffusion rate from the oil droplets to the squeous phase was accelerated, and the drug and polymer solved in the oil droplets were rapidly deposited, forming a rigid outer-shell on the surface of the droplets to prevent the coalescence and fusion. These accelerations of solvent diffusion and rapid solidification were attributed to that the hydrogen bonding between drug and solvent, and the solubility of drug in the droplets were reduced in the strongly acidic (low pH) aqueous medium.

**Keywords** size control; ibuprofen microsphere; emulsion solvent diffusion method; electric intermolecular interaction; hydrogen bonding; solvent diffusion rate

## Introduction

In the general microencapsulation technique using an o/w emulsion system (*e.g.*, solvent evaporation method), a water-immiscible organic solvent, such as a chlorinated, aromatic or aliphatic hydrocarbon, must be selected to form stable oil microdroplets containing a drug and polymeric wall material.[1—4] As the organic solvent is removed by evaporation, the drug and polymer are precipitated in the droplets, thus forming the microspheres.

The authors reported a newly developed emulsion solvent diffusion method to prepare the ibuprofen microspheres with an acrylic polymer.[5,6] It was a process which included the agglomeration and microencapsulation of a drug during crystallization. An ethanol solution of ibuprofen and polymer, in this process, was dispersed into an aqueous medium under agitation, forming o/w emulsion droplets. The ethanol diffused out of the dispersed emulsion droplets into the aqueous medium. This new process did not require the use of any harmful organic solvent, the elevation of temperature of the system for solvent evaporation, or a long time for processing. However, the mechanism for the formation of ethanolic emulsion droplets in the aqueous dispersion medium has not be clarified.

In the present study, it was found that the size of ibuprofen microspheres fabricated by the emulsion solvent diffusion method could be controlled by adjusting the pH of the aqueous dispersion medium. With decreasing pH, the diameter of microspheres decreased while the drug entrapment efficiency and yield of the microspheres remained unchanged. The purpose of this study was to elucidate this finding by the intermolecular interaction exerted in the drug, polymer and/or solvent to form stable emulsion droplets of ethanol solution even in the aqueous medium.

## Experimental

**Preparation of Ibuprofen Microspheres with Acrylic Polymer** Microspheres were prepared by the emulsion solvent diffusion method.[5,6] Ibuprofen (2500 mg, Taito Koeki Co., Ltd., Japan) and an acrylic polymer (Eudragit RS-PM, 830 mg, Rhom Pharma GmbH, Germany) were dissolved in ethanol (5.00 ml). The ethanolic solution was poured into a pH-adjusted aqueous dispersion medium (400 ml) of sugar ester (DKF-70, 0.050%, Daiichi Kogyou Seiyaku Co., Ltd., Japan) under agitation (150 rpm) at 25 °C, forming transient o/w emulsion droplets. The ethanol diffused out of the dispersed ethanol droplets into the aqueous medium. After the drug and polymer were co-precipitated in the droplets, they were separated by decantation and rinsed twice with 100 ml water. 1/80 M sodium citric acid–hydroclride, and 1/80 M citric acid–sodium hydrogenphosphate buffers were used for preparation of the pH 1 to 2 and pH 3 to 5 aqueous dispersion media, respectively. Eudragit RS-PM is a copolymer (molecular weight = 150000) synthesized from acrylic and methacrylic acid ester with a low content of quaternary ammonium groups. The molar ratio of the ammonium group to the remaining neutral acrylic acid esters is 1:40.

**Zeta Potential of Drug and Polymer** The zeta potentials (Z-potential) of ibuprofen and acrylic polymer were measured at 25 °C using a streaming potential analyzer (ZP-10B, Shimadzu Seisakusho Co., Ltd., Japan). Values of zeta potential were calculated from the Helmholtz–Smoluchowski equation.[7]

**Fourier Transform Infrared (FT-IR) Spectra** The FT-IR spectra of an intact ibuprofen crystal and ibuprofen–ethanol solution were measured by an FT-IR spectrometer (1720X, Perkin Elmer) using the diffusion reflectance (DR) and thin layer (TL) methods, respectively. The sample for DR was prepared by grinding the drug with KBr. In the TL method, the solution placed on a NaCl plate was analyzed.

**Particle Size, Drug Entrapment Ratio, and Recovery** The microspheres were sieved to determine their average diameter using standard sieves. Drug content in the microspheres was measured by HPLC.[6] The drug entrapment was calculated from the ratio of the amount of drug in the microspheres to that of the loaded drug. The recovery was determined from the ratio of the amount of microspheres (fraction passed through ♯12 mesh with 1410 μm) to that of the loaded drug and polymer.

**Diffusion Rate of Ethanol from Emulsion Droplets into Water Phase** The ethanol diffusion from emulsion droplets into the water phase was monitored by measuring the concentrations of the ethanol in the water phase with gas chromatography.[8] The diffusion profiles observed in this study were analyzed by the first order kinetic model; the plots of the remaining percentage of ethanol in the droplets *versus* time after pouring the ethanol solutions were regressed to a straight line on a semilogarithmic scale.

## Results

**Effect of pH in the Aqueous Dispersion Medium on the Size of Microspheres** Scanning electron microphotographs of the ibuprofen microspheres which were prepared at various acidity of the aqueous dispersion media showed the formation of monodisperse microspheres (Fig. 1). The
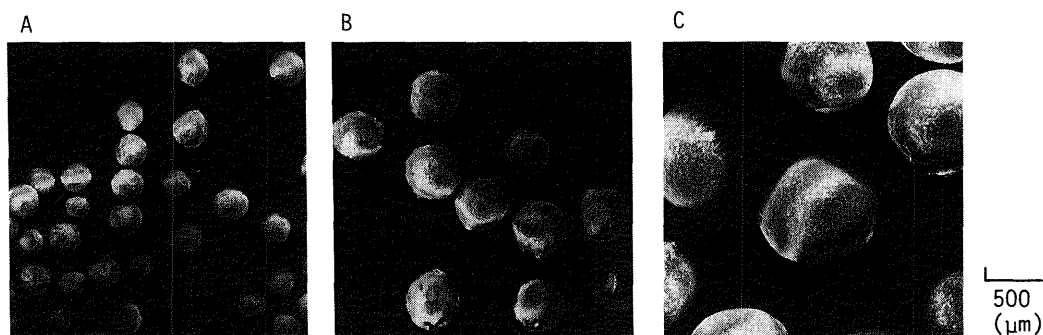
Fig. 1. Scanning Electron Microphotographs of Ibuprofen Microspheres Prepared at Various Acidities of the Aqueous Dispersion Media
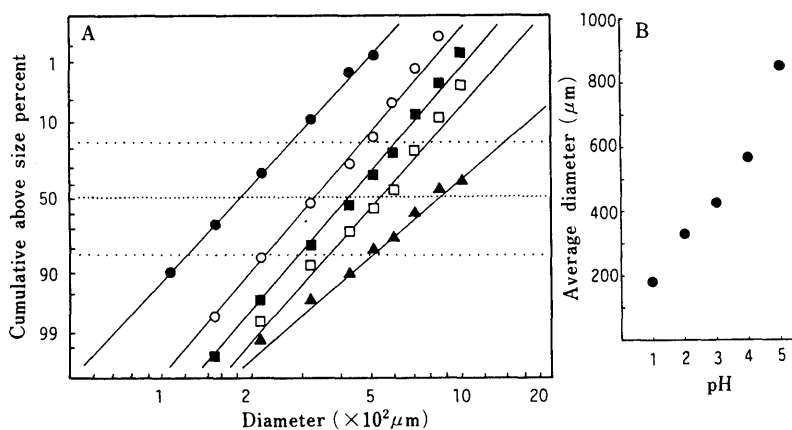A, pH 1.0; B, pH 3.0; C, pH 5.0.



Fig. 2. Size Distribution (A) and Average Diameter (B) of Microspheres Prepared in the Aqueous Dispersion Media
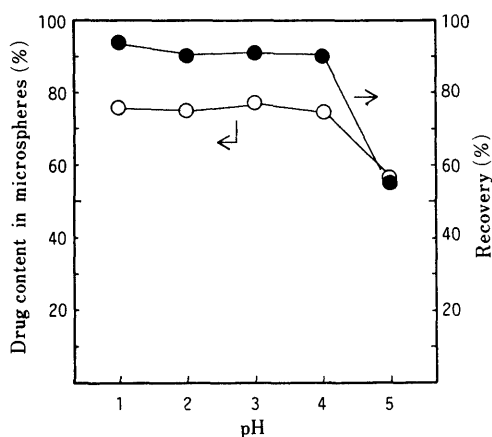pH 1.0 (●), 2.0 (○), 3.0 (■), 4.0 (□) and 5.0 (▲).



Fig. 3. Drug Content and Recovery of Microspheres as a Function of pH in the Aqueous Dispersion Media

particle size distribution of these microspheres plotted on the log–normal scale (Fig. 2A) indicated that the average diameter apparently decreased with a reduction in the pH of dispersion medium: 180 μm at pH 1.0, 330 μm at pH 2.0, 430 μm at pH 3.0, 570 μm at pH 4.0, 870 μm at pH 5.0 (Fig. 2B). The drug content and recovery of microspheres remained constant at <pH 4.0, about 75.0% and 90.0%, respectively (Fig. 3). Seventy-five percent of the drug content was in good agreement with the theoretical values. In the pH range from 1.0 to 4.0, all of the ibuprofen loaded in the system was encapsulated in each microsphere, i.e. the

drug recovery = 100%. On the other hand, the drug content and recovery at pH 5.0 decreased to 53.3% and 55.1%, since some ibuprofen ($pK_a = 5.2$) diffused out in the aqueous medium with pH 5.0 prior to its solidification in the microspheres. Thermal and infrared spectrophotometrical analysis showed the crystalline form of encapsulated ibuprofen in the acrylic polymer was unchanged, compared with an original ibuprofen crystal. The above findings allowed the conclusion that the size of ibuprofen microspheres prepared by the solvent emulsion diffusion method could be controlled by adjusting the pH in an aqueous medium.

## Discussion

**Electrostatic Interaction of Drug and Polymer** Many reports indicated that the electrostatic interaction of polymers and/or drugs was a key factor for microencapsulation, e.g., the formation of coacervated or liberated emulsion droplets and the entrapment of drug in wall materials.[9−11] In such systems, the diameter and the drug content of microcapsules strongly depended on the pH of aqueous dispersion medium.

In the present system, when the ethanol solution of drug and polymer were dispersed in water phase, the drug and polymer were immediately deposited on the surface of ethanol droplets (the interface of ethanol and water). Afterward, as a result of the counter diffusion of ethanol and water in the droplets (effusion of ethanol and influx of dispersion medium), the physicochemical property of the

ethanol droplets rapidly resembled that of the aqueous dispersion medium. Therefore, the electric interaction between polymer and drug in the present system was investigated by measuring the Z-potentials of drug and polymer dispersed in water as a function of pH (Fig. 4). The Z-potential varies depending on the degree of ionization of individual molecules. Ibuprofen had a negative Z-potential which increased over the pH range of 4 to 2 as the carboxyl group became ionized. Below pH 2, the Z-potential of ibuprofen remained constant (0 mV). The positive charge of acrylic polymer increased with decreasing pH. The curve drastically increased at pH < 2.5, compared with the pH range of 5 to 3. At a higher pH, the quaternary ammonium group of polymer became slightly ionized, showing a low Z-potential value. As the pH decreased, the degree of ionization increased so as to cause an increase in Z-potential.

When the electrostatic interaction of drug and polymer was a driving force to encapsulate ibuprofen with an acrylic polymer, the maximum drug entrapment ratio and maximum size of microspheres might be obtained at the pH of electrical equivalence point (EEP) of the system,
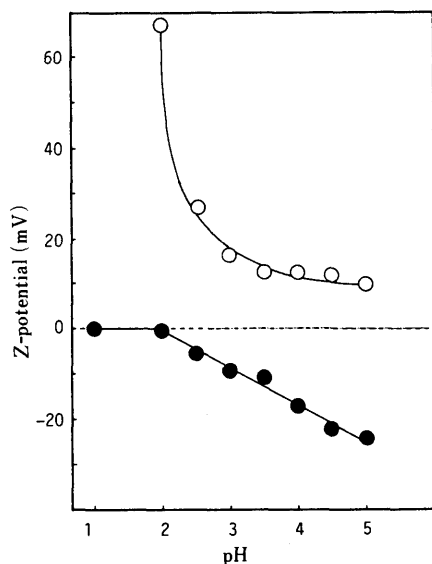
where the drug and polymer carry equal and opposite charges.[12] The EEP in this system was pH 3.5: ibuprofen and polymer had the maximum equal and opposite charge density, 12.1 and −12.0 mV, respectively. As shown in Figs. 2 and 3, the drug entrapment efficiency remained constant from pH 1 to 4, and the size of microspheres decreased proportionally to increasing pH. At pH 1 to 2 where ibuprofen had no electrical charge, microspheres were still formed with constant recovery (90%) and drug entrapment ratio (95%), even compared with the microspheres prepared at EEP (pH 3.0).

The results suggested that microencapsulation by the emulsion solvent diffusion method and size control by adjusting the pH in a water phase could not be explained by the electrostatic interaction of the drug and polymer.

**Hydrogen Bonding between Drug and Solvent. a) The Rate of Ethanol Transfer from the Oil Phase to Water** The microspheres were produced via forming o/w emulsion droplets where the drug and the polymer were entrapped in the oil droplets. The water-miscible organic solvent which constituted the oil droplets was transferred from the droplets into the outer water phase during processing. This transfer of organic solvent might occur by simple diffusion if the solvent was physically trapped in the droplets. However, the solvent (ethanol) in the present system was assumed to associate with the drug and/or polymer through molecular interactions since the ethanol solution composed of ibuprofen and acrylic polymer produced stable emulsion droplets in the water phase.

In order to investigate such interaction, three ethanolic solutions were separately dispersed into the water phase; ibuprofen (50.0 w/v%)–ethanol, polymer (16.6 w/v%)–ethanol, and ibuprofen (50.0 w/v%)–polymer (16.6 w/v%)–ethanol solution. Immediately after pouring the polymer–ethanol solution, a large irregular polymer matrix was fabricated. No o/w emulsion state was observed. For the drug–ethanol and drug–polymer–ethanol solution, the finely discrete emulsion droplets of their solutions were formed in the water phase, resulting in forming spherical ibuprofen agglomerated crystals and spherical microspheres of ibuprofen covered with polymer after 30 min, respectively (Fig. 5).

The ethanol transfers from these three ethanolic solutions into the water phase were also monitored, as shown in Fig.



Fig. 4. Effect of pH on the Z-Potential
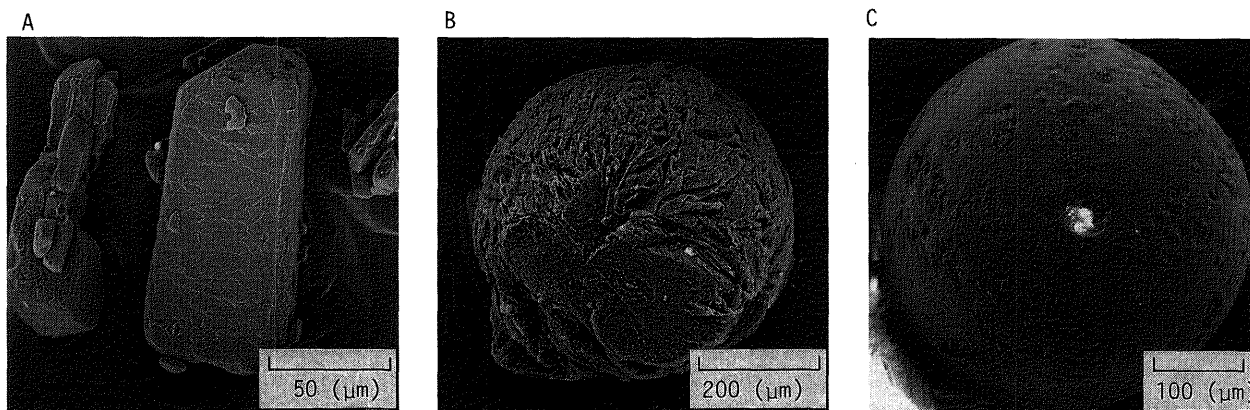
Ibuprofen (●), acrylic polymer (○).



Fig. 5. Scanning Electron Microphotographs of Original Ibuprofen Crystals (A), Spherically Agglomerated Crystal of Ibuprofen without Polymer (B), and Ibuprofen Microspheres with Polymer (C)
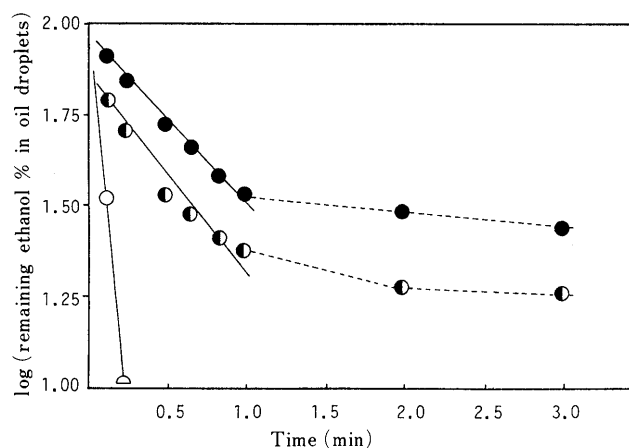
pH of the dispersion media = 3.0.

Fig. 6. Profiles of Ethanol Diffusion to the Dispersion Media after Pouring the Ethanolic Solutions

Acrylic polymer ($\bigcirc$), ibuprofen ($\bullet$) ibuprofen–acrylic polymer (weight ratio $= 3:1$) ($\bullet$).
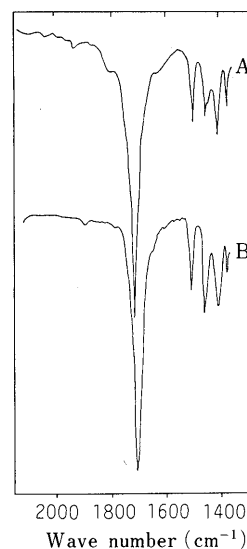


Fig. 7. FT-IR Spectra of Ibuprofen (A) and Its Ethanolic Solution (50.0% w/v) (B)

Table I. Effect of the pH in the Aqueous Dispersion Media on the Ethanol Diffusion Rate from the Emulsion Droplets

| pH | Diffusion rate of ethanol (min$^{-1}$) |
| --- | --- |
| 1.0 | 1.16 |
| 2.0 | 1.08 |
| 3.0 | 0.97 |
| 4.0 | 0.92 |
| 5.0 | 0.71 |

6. When the polymer–ethanol solution was dispersed, the ethanol completely diffused into the water phase within 15 s. On the other hand, the ethanol transfers from ibuprofen–ethanol and ibuprofen–polymer–ethanol systems were significantly retarded, showing biphasic curves which were composed of an initial and a subsequent diffusion phase. The percentage of ethanol removed in the initial phase was approximately 72%. The difference in diffusion behavior from the ethanolic solutions with and without ibuprofen indicated that the intermolecular interaction between ibuprofen and ethanol suppressed the rapid diffusion of ethanol to form the stable emulsion droplets.

Kawashima et al.[13] (1982) reported a spherical agglomeration technique that transferred needle-like or platy drug crystals into a spherical shape during the crystallization step using an o/w emulsion system. In this process, for example, chloroform (water-immiscible solvent) was dispersed in a water phase. It acted as a bridging liquid for the drug crystals suspended in the water phase. The drug crystals were partially solved (wetted) by chloroform, then agglomerated, and finally transformed to a spherical form.[14,15] In the general o/w emulsion system used for microencapsulation, e.g. emulsion evaporation method, dichloromethane or another water-immiscible solvent was employed for producing the oil droplets.[2,16] Drug and polymer were co-precipitated in such oil droplets by evaporation of the solvent. For the two methods (spherical agglomeration and solvent evaporation), the water-immiscible organic phase was indispensable to obtaining the spherical crystals and microcapsules of the drug. These reports and the findings in Figs. 4 and 5 clearly supported that the ethanol was liberated in the water phase and behaved like a water-immiscible solvent as a bridging liquid for the ibuprofen–ethanol system, or as the emulsion droplets for the ibuprofen–polymer–ethanol system.

b) IR Spectroscopy The intermolecular interaction between ibuprofen and ethanol was studied by IR spectroscopy (Fig. 7). Intact ibuprofen showed a characteristic C=O stretching vibration of the carboxyl group at 1720 cm$^{-1}$. The absorption of C=O at 1720 cm$^{-1}$ indicated that ibuprofen would be dimerized in a solid state.[17] In the ethanol solution, the C=O absorption was apparently shifted to a lower wave number, 1700 cm$^{-1}$. No significant shifts of other groups were observed, compared with the intact ibuprofen. As reported by Sharma et al.[18] (1988), the shift of proton-accepting group toward a lower wave number would reflect an increase in hydrogen bonding energy, meaning the generation of hydrogen bonding with a proton-donating group. The hydrogen bonding of ibuprofen (C=O group) with ethanol (OH group) was considered to increase hydrophobicity of ethanol. Therefore, ethanol was liberated from the aqueous medium and formed the stable o/w emulsion droplets. There wasn't any IR spectral alteration between the intact polymer and its ethanol solution.

Correlation of the Ethanol Diffusion Rate and the Size of Microspheres The ethanol diffusions from emulsion droplets into the water phase at pH 1 to 5 were measured. All diffusion profiles were biphasic curves on a semi-logarithmic plot, like the curves of ibuprofen or ibuprofen–polymer system in Fig. 6. The first order kinetic model was used to analyze the diffusion process.[19] Regression coefficients $>0.99$ on the first phase were obtained, until the fraction of ethanol removed reached about 70 to 74%, from the least-squares regression line of the amount of ethanol diffused against time. In this study, the slopes of linear portion of the profiles were employed as an index representing the diffusion rate of ethanol. The diffusion rates calculated are listed in Table I. The diffusion rates increased significantly depending on the acidity (pH) of the water phase. Figure 8 shows the average diameter of microspheres plotted versus the diffusion rate. The diameter
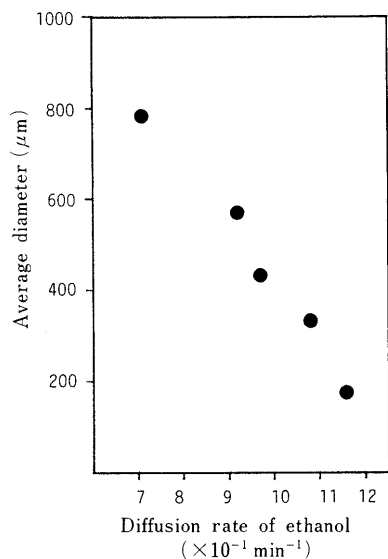
Fig. 8. Correlation of the Ethanol Diffusion Rates and the Size of Microspheres

decreased as the diffusion rate increased. It indicated that the size of ibuprofen microspheres prepared by the present method clearly depended on the rate of ethanol diffusion.

In the emulsion solvent diffusion method, the diffusion of ethanol induced the influx of water from the outer phase into the droplets.[5] The infused water reduced the solubility of drug and polymer in the droplets, resulting in the formation of a film-like membrane on the surface of droplets.[8] Until the solidification of film, the droplets were coalesced by their mutual collisions. With decreasing the pH of aqueous medium, the concentration of hydrogen ions increased in the droplets, which easily disrupted the hydrogen bonding between ibuprofen and ethanol. This phenomenon promoted the counter diffusion of ethanol and water. With the influx of acidic water, the precipitation rate of ibuprofen (weak acidic drug, $pK_a = 5.2$) in the droplets would be also enhanced because of the lower solubility in a stronger acidic aqueous medium. The polymer solved in the ethanol droplets began to precipitate due to the decrease in the solubility caused by an infusion of water. The rapid solidification of droplets by precipitation of the drug and polymer prevented the coalescence and fusion of droplets, forming smaller microspheres. Therefore, decreasing the pH in the water phase increased the diffusion rate of ethanol from the emulsion droplets and reduced the size of microspheres.

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