

Manipulating Solids CSD in a Supercritical Fluid Crystallizer: CO₂-Benzoic Acid

The final properties and end use of many organic solids often depends on their crystal-size distribution (CSD), e.g., bioavailability for pharmaceutical solids. The objective of this study was to develop an alternate technology for crystallizing and manipulating size distribution of organic solids by crystallization from supercritical fluids. Such a technology might be superior to conventional-size manipulation techniques, such as milling and recrystallization from organic solvents, which might contaminate the products and affect their physical-chemical stability. Supercritical carbon dioxide was used as solvent to dissolve and then crystallize benzoic acid. A batch crystallizer was constructed and operated in the supercritical region. Seeded and unseeded crystallization experiments were performed. Different depressurization vs. time profiles for the supercritical fluid were used to produce crystals of various sizes.

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Introduction

The ability of supercritical fluids (SF) to dissolve many solids has been known for a century (Hanney and Hogarth, 1879). Interest in using SF in various fields including distillation and extraction has increased dramatically in recent years. Numerous extraction and separation processes using SF have been reported in the literature (Paulaitis et al., 1983; Irani and Funk, 1977; McHugh and Krukonis, 1986). A potential application of SF technology might be in the area of crystallization. Paulaitis et al. (1983) suggest that solid nucleation from a SF offers the potential to change particle-size distribution without the limitations inherent in grinding and precipitation from solution, such as temperature effects and coprecipitation of impurities. The advantages of crystallization at supercritical conditions over conventional crystallization is especially clear, when nonvolatile, thermally-labile pharmaceutical substances are to be crystallized. As a noncontaminating solvent at close to ambient temperature, a SF such as SF CO₂ might be an attractive alternative to conventional organic solvents. Supercritical fluid crystallization (SFCN) has been suggested as the final step in SF extraction of biomolecules (Larson and King, 1986). The objective of this study is to develop techniques for manipulating particle size in the crystallization of organic compounds (e.g., pharmaceuticals) from SF. To achieve this, conventional crystallization techniques are modified and applied to SF.

There have been numerous studies on solubility of organic solids, volatile and nonvolatile, in SF CO₂ (Mackay and Paulaitis,

1979; Kurnik et al., 1981, 1982; Johnston et al., 1982; Dobbs et al., 1986; Chrastil, 1982; Drukonis and Kurnik, 1985; McHugh and Paulaitis, 1980; Van Leer and Paulaitis, 1980). In most of these studies, SF CO₂ is passed through a packed bed of the solid of interest whereby the fluid dissolves some solid and carries it out of the high-pressure vessel. Upon expansion to atmospheric pressure, the solid is precipitated and collected in a trap (Kurnik et al., 1981). This process is a crude form of crystallization. In the present work, however, we attempted to construct and operate a batch crystallizer and identify parameters which control the product-size distribution. Once these parameters are identified, we can proceed to manipulate the final crystal-size distribution (CSD).

In conventional batch cooling crystallization, a saturated solution is cooled from an initial temperature at which the solution has a high solubility to a final lower operating temperature (with lower solubility) along an optimal cooling curve. This "optimal" cooling is used to maintain a reasonably constant level of supersaturation and, consequently, a constant crystal growth rate. If a large average crystal size is desired, optimum cooling begins with a sharp initial decrease in temperature to induce controlled nucleation of the solid, followed by slow cooling in order to maintain a supersaturation level high enough for the nuclei to grow but not too high to result in further primary nucleation. Further primary or excessive secondary nucleation would cause the formation of small crystals and widen the distribution. As the solid surface area in the solution grows, the cool-

ing rate is increased, therefore maintaining the supersaturation and the crystal growth rate constant. If a small average size is desired, however, the cooling process must be done in such a way as to promote primary nucleation.

When the solute-laden solution is a supercritical fluid, the option exists of inducing supersaturation by varying either temperature or pressure. In this study pressure was chosen as the main variable. Depressurization schemes for crystallization from a SF solution analogous to conventional cooling crystallization were constructed. These schemes promote formation of small-or large-sized particles as desired.

Experimental Procedure

Benzoic acid, an antifungal agent, was chosen as a model compound for crystallization at SF conditions, since it is a compound with appreciable solubility in SF CO₂. Furthermore, sufficient data regarding its solubility in SF CO₂ over a range of temperatures and pressures are available in the literature (Kurnik et al., 1981; Schmitt and Reid, 1986; Dobbs et al., 1986). Because of the lack of data regarding the kinetics of nucleation and growth of benzoic acid in a SF medium, "qualitative" depressurization schemes were devised based on the following logic:

If the objective is to make large crystals, then a high initial supersaturation is used to produce sufficient nuclei which will then be grown to larger size. This was done by equilibrating the benzoic acid-CO₂ mixture in a high-pressure vessel at 55°C and then quickly cooling the crystallizer to 35°C (this would involve considerable pressure loss since a batch crystallizer is a closed system). Once the new equilibrium condition was established, the vessel was depressurized through an expansion valve at a rate (depending on the crystal size of the growing crystals) that might maintain constant supersaturation. This would allow the originally formed nuclei to grow at a constant rate dependent only on the supersaturation, which would be low enough to minimize further nucleation. We refer to the above scheme as *normal depressurization*.

If a small crystal product is desired, then solids formation via primary nucleation throughout the batch crystallization process is desired. A widely used relationship between nucleation rate (primary) and supersaturation (e.g., Mullin, 1972) is usually given as:

$$B^o \propto \exp(-K_1 / \log^2 S)$$

where

B^o = nucleation rate

S = supersaturation as C/C^*

K_1 = constant

Nucleation rate is very sensitive to supersaturation. Therefore, to make small particles the whole crystallization process would involve going from the initial pressure to the final pressure in such a way as to maintain a large supersaturation. (This profile would also minimize the time for particle growth). Sustained nucleation, rather than only an initial burst, is determined by the depressurization (supersaturation) curve. The constant K_1 is a function of fluid/solid interfacial tension. For the purposes of

this study, it was assumed to be constant. We refer to the above scheme as *reverse depressurization*.

The first step in batch crystallization is to make a saturated solution from which crystals can be formed. To do this, a known amount of benzoic acid was placed in a vessel which was then pressurized with CO₂ and heated to the desired operation conditions. The amount of solids needed to produce a saturated solution was known from benzoic acid solubility studies performed elsewhere (Schmitt and Reid, 1986). To insure that no undissolved solid particles remained in the SF solution, the amount of solids placed in the vessel was calculated as just enough to make the solution slightly undersaturated at the starting pressure and temperature of the batch crystallization experiments. The solid-fluid mixture was allowed to equilibrate for about two hours during which time it was assumed that all the solids would dissolve. Once equilibrium was reached, depressurization and hence batch crystallization, was initiated by periodically opening an expansion valve for several seconds, allowing the pressure in the vessel to decrease, and then closing the valve and allowing the system 10 minutes to reach equilibrium at new conditions. Given the low solubility of solids in SF CO₂ (as compared to organic solvents), it was assumed that 10 minutes would be sufficient time for equilibration at the new conditions. [Kurnik et al., (1981) have demonstrated that solid-SF solution equilibrium is rapidly attained.] This procedure was repeated until the system pressure became subcritical. This general depressurization procedure is independent of which optimal curve was used. As the experiment progressed, a pressure vs. time curve was constructed. Given the solubility vs. pressure data for benzoic acid in SF CO₂, variation in the initial concentration level (at the beginning of each 10 minute pulse) with time was calculated. If the actual unmeasured supersaturation decayed to zero in the 10 minute period, then average supersaturation could reasonably be estimated as $(C_t + C_{t+10})/2C_{t+10}$. Such curves are shown for two sample experiments. All supersaturations were calculated, not measured.

In one experiment the objective was to make large particles while in the other the objective was to make small crystals (see Figures 1 and 2). Note that there is a sharp pulse in the value of

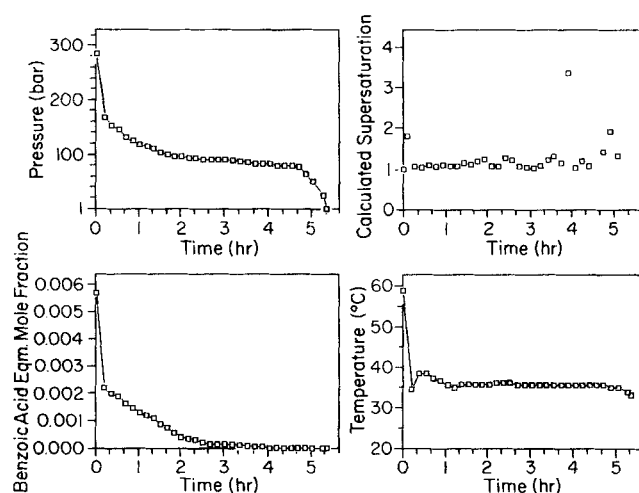


Figure 1. Pressure, equilibrium solute mole fraction, calculated supersaturation, and temperature vs. time in a batch experiment to grow large crystals.

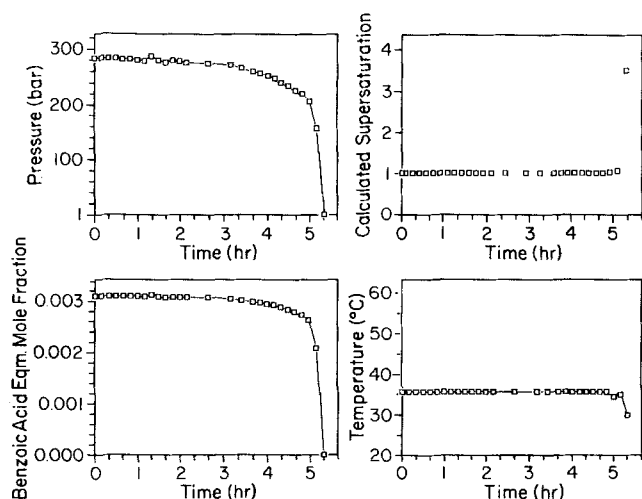


Figure 2. Pressure, equilibrium solute mole fraction, calculated supersaturation, and temperature vs. time in a batch experiment to make small crystals.

calculated supersaturation as the system crosses the critical pressure, since at that point the solids solubility drops suddenly from a moderate level to virtually zero. Supersaturation, which is defined as a ratio of concentrations is hence forced to a high value. The effect on CSD of this high supersaturation value is not great since most of the benzoic acid has been removed from the solution before the system pressure crosses the critical point.

Figure 3 shows the apparatus used in this study. A Milton-Roy Supercritical Extraction System, Model X10, was modified as a batch crystallization system. A Whitey 31RS4 metering valve with 0.16-cm orifice, wrapped with heating tape and regulated by a rheostat, was used for depressurization of the crystallizer. The valve was opened manually every 10 minutes to release pressure based on the depressurization schemes described above. A small temperature change (2–3°C) was involved in this process. However, the crystallizer attained its original temperature in a few seconds. The crystallizer was a 316SS vessel capable of withstanding 414 bar with fully-openable enclosures. The crystallizer internals are shown in Figure 4. Baffles and a magnetic stirrer were put in the high-pressure vessel in order to simulate the internals of a conventional batch crystallizer. Due to low solvent density, however, it is expected

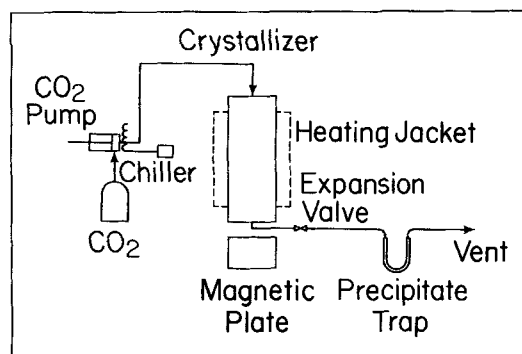


Figure 3. Batch crystallization apparatus.

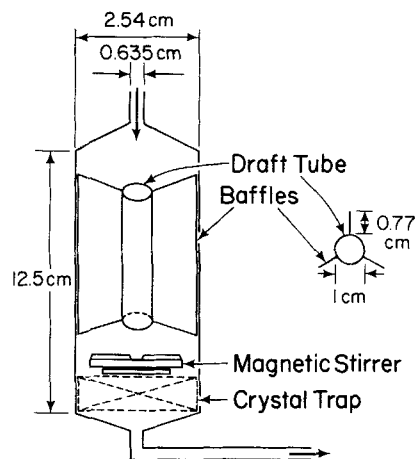


Figure 4. Batch crystallizer internals.

that only the SF, but not crystal magma, was circulated. The crystallizer was sitting on a magnetic plate which turned the magnetic stirrer at a constant RPM. Crystals nucleated and then grew mainly on the baffle walls. A crystal trap, made of two high mesh sieves with glass wool placed between them, was placed under the internal magnetic stirrer to prevent the escape of small crystals through the expansion valve. A heating jacket maintained the vessel temperature at set values. In experiments in which initial cooling was required, the heating jacket was opened and an air jet was used for rapid cooling. Once the new temperature was achieved, the heating jacket was reinstalled and the temperature setting was adjusted to the new value.

At the end of an experiment, once the crystallizer pressure became subcritical, the crystallizer was depressurized to 1 atm, opened, and the solid products were removed. During the experiments some solids would form downstream of the expansion valve and were collected in a U-tube. These solids were products of expansion of SF CO₂-benzoic acid solution and are not considered as products of the crystallization processes. Only the solids collected inside the high-pressure vessel are formed by nucleation and growth processes at supercritical conditions. The experimental conditions are summarized in Table 1.

The benzoic acid crystals had an elongated needle-like habit and were not suitable for sieving. Thus, solids product surface areas were determined and used as a measure of particle size. BET surface adsorption measurements were made using a Quantachrome Quantasorb, model QS-10 adsorption/desorption device. Nitrogen was used as the adsorbing gas with helium as the carrier gas.

Results and Discussion

Table 1 shows the changes in the product solids surface area, which depended on the depressurization scheme used.

Experiments 26 and 33 were done essentially over equal time periods so that particle residence time in the crystallizer would not be a parameter in comparing their final products. Therefore, only the different depressurization schemes (through nucleation and growth mechanisms) affected the product surface areas. As expected nucleation followed by growth resulted in a smaller specific product surface area (larger particles), while continuous depressurization without initial nucleation produced finer particles. These processes can be observed from the stepwise

Table 1. Batch Crystallization Experiments

Experiment	Initial P (bar)	Initial T (°C)	Operation T (°C)	Depressurization Time (min)	Depressurization Curve	Product Surface Area (m ² /g)	Ratio of Surface Area over Raw Material**	Crystallized Compound
22	282.8	55	35	1080	normal*	0.1178	0.56	BA†
26	282.8	35	35	320	reverse*	0.5800	2.78	BA
27	289.7	35	35	3	reverse	1.0877	5.21	BA
31	282.8	35	35	expansion	expansion	0.9875	4.73	BA
33	282.8	55	35	322	normal	0.2399	1.15	BA
47	202.8	50	45	462	normal	—	—	Ph‡
48	200.0	45	45	81	reverse	—	—	Ph
50	282.8	35	35	35	reverse	—	—	BA
51	282.8	35	35	25	reverse	—	—	BA

*"Normal" refers to the depressurization scheme designed to make large particles, whereas "reverse" refers to making small particles.

**Raw material surface area = 0.2087 m²/g, i.e., the starting solid which was dissolved in SF CO₂ to make a saturated solution.

†BA = benzoic acid

‡Ph = phenanthrene

progression of experiments 33 and 26 as drawn on a benzoic acid solubility vs. pressure curve (see Figures 5 and 6). In these figures, each "step" was performed in 10 minutes. In experiment 33, nuclei were initially formed which then had the opportunity to grow at a constant supersaturation level without appreciable subsequent nucleation, while in experiment 26 small particles were formed towards the end of the run at high supersaturation and had no time to grow. The variation of pressure, equilibrium solubility, calculated supersaturation, and temperature of these experiments are shown in detail in Figures 1 and 2.

An atmospheric expansion experiment for the production of small benzoic acid particles was also performed (#32), and the surface area of its product was compared to the results of experiment 27. As seen from Table 1, the surface area of the product of batch crystallization (#27) is larger. Given the accuracy of these data, it can be assumed that the surface areas for these two experiments were the same. Thus, to make significantly smaller particles, and larger surface areas, expansion out of the supercritical region is not necessary. All that is needed is rapid depressurization from a high pressure to a low pressure, all above the critical point, since high supersaturation causes the formation of small particles. Crossing the critical pressure, which is done in atmospheric expansion, is just one way of creating large supersaturations, but high supersaturation levels can easily be created without leaving the SF phase as shown in experiment #27.

It is clear that to make small particles shorter crystallization times are desired. Experiments 22 and 27 can be compared to

show the effect of particle residence time on the final product. In experiment 22, the originally-formed nuclei (by rapid cooling) were allowed to grow for more than 1,000 minutes. As seen from Table 1, the product surface area actually dropped compared to the original benzoic acid solid dissolved in SF CO₂. In contrast, experiment 27 constituted one large depressurization from the equilibrium condition to critical pressure. This resulted in a solid product whose surface area was 5 times the starting material.

To observe the effect of depressurization rate on final product size distribution two short runs were performed (#50 and #51). The population densities for these experiments were measured with the aid of an optical microscope. The results are shown in Figure 7. It appears that faster depressurization shifts the CSD towards the smaller sizes, hence increasing product surface area. This phenomenon can theoretically be modeled using population balance mechanics (Randolph and Larson, 1988). Since there is an apparent correlation between depressurization rate and product CSD, generalized pressure reduction curves could be developed *a priori* for the production of larger- or smaller-sized crystals as desired. Crystal growth and nucleation kinetics in SF would have to be known for such population balance models to be useful.

To further investigate the effect of depressurization schemes on crystal growth, phenanthrene crystals were grown under normal and reverse depressurization schemes (see Figure 8). Under normal depressurization, crystals attain full rounded shape, apparently by conventional growth mechanisms. Crystals grown under reverse depressurization appear skeleton-like, not having

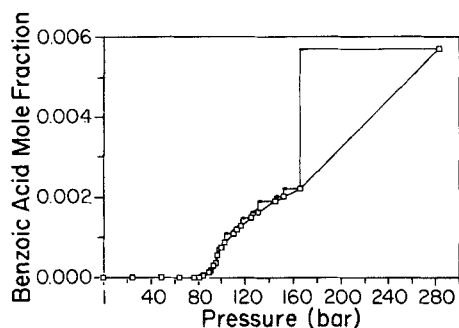


Figure 5. Progression of experiment #33 to make large particles.

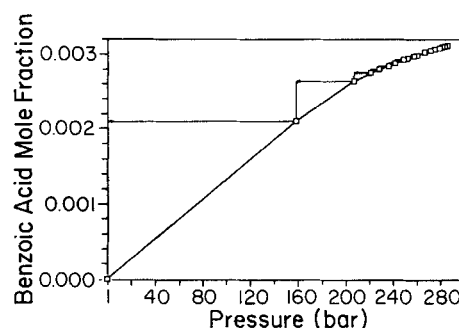


Figure 6. Progression of experiment #26 to make small particles.

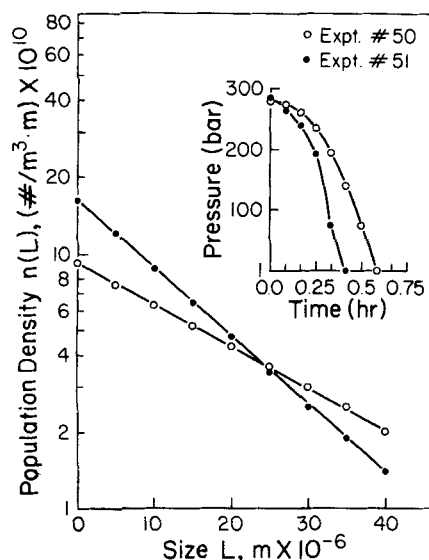


Figure 7. Crystal-size distribution vs. depressurization rate.

had enough time to grow. Such effects are easier to observe on plate-like phenanthrene crystals than on needle-like benzoic acid particles. Note that layer by layer growth can be observed on the phenanthrene particles (Figure 8a, b), suggesting that conventional surface growth mechanisms in liquid solvents also hold for supercritical fluid solvents.

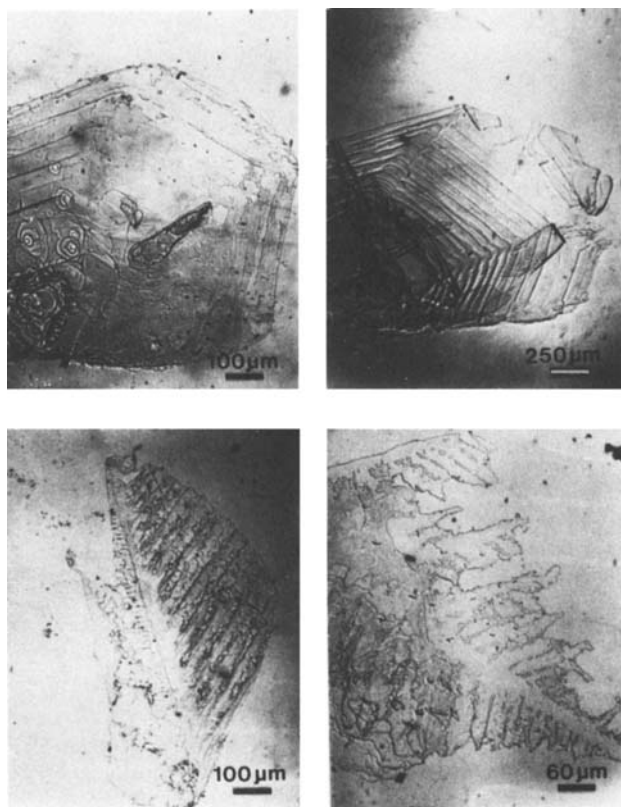


Figure 8. Phenanthrene particles nucleated and grown in SF CO₂: (a, b) normal depressurization, run #47; (c, d) reverse depressurization, run #48.

A rough estimate of benzoic acid crystal growth rate at SF conditions was made by dividing the size of the largest crystal produced in an experiment by the total run time of that experiment. By assuming that this particle was the fastest growing crystal in the batch, this simple calculation gives an estimate of the maximum growth rate that was attained in the SF crystallizer. For all experiments, except for #27, maximum growth rates were estimated at $0.5\text{--}4.1 \times 10^{-6}$ m/min depending on the depressurization rate (i.e., supersaturation level). Note that these growth rates are the same order of magnitude of crystal growth in aqueous media. Furthermore, as with conventional crystallization, growth rate appears to be an increasing function of supersaturation. This calculation gave a large growth rate of 26×10^{-6} m/min for run 27. This run had the fastest depressurization rate and hence the greatest supersaturation level.

Conclusions

In this study nucleation and growth of crystals from a SF medium is clearly established. It has also been established that different depressurization schemes affect the product-size distribution. Another important observation can be made by comparing the results of experiments 27 and 32 (rapid expansion). It appears that a continuous crystallization process remaining in the supercritical region, even for production of small particles, should be superior to atmospheric expansion. Solid products could be removed on-line and the main solvent and possibly any cosolvents could be recycled. What is required is that sufficiently high supersaturation levels be created to promote primary nucleation. The products should be quickly removed from the crystallizer to prevent further growth. Supercritical fluids have liquid-like densities. By operating continuously in the SF region, energy could be saved in repressurization of the main solvent.

For most solids, the solubility in SF solvents is poor. As a result, it might not be possible to devise a cost-effective SF crystallization process. A further step in developing crystallization technology at SF conditions would be to first increase solids solubility in SF phase by addition of small amounts of cosolvents, e.g., Dobbs et al. (1986). Introduction of cosolvents, however, creates the problem of contamination of the solids by an organic liquid. This might be remedied by the introduction of a "wash column" at the end of the crystallization step. This would involve washing the crystals with SF CO₂ in order to remove organic cosolvents. Given the low solubility of many organic compounds in SF CO₂, excessive redissolution of solid product in the wash column is not expected. The crystals would be captured by a fines trap (possibly made of high mesh steel sieves and glass wool) and continuously flushed by pure SF CO₂. In this way, the product crystals could be removed on-line, washed and collected for an extended period, after which the wash column would be isolated and depressurized, and the products removed.

Acknowledgment

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Notation

- $B^{\circ}(C)$ = nucleation rate, volume \cdot time⁻¹
- C = concentration of solute, mass/volume
- C_t = concentration of solute at time t , mass/volume
- C^* = saturation concentration of solute, mass/volume

K_1 = constant in nucleation equation
 S = supersaturation, C/C^*
 t = time, min

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