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p-아미노 살리실산과 키틴, 키토산 혼합물의 용해성에 관한 영향

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Effect of Dissolution Properties of *p*-Aminosalicylic Acid with Chitin and Chitosan Mixtures

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요 약 : 수용성 약물의 방출 지연성에 대하여 키틴과 키토산의 적용성을 검토하였다. 본 연구에서는 수용성 약물인 *p*-aminosalicylic acid (PAS)와 키틴, 키토산의 용해거동에 대하여 연구하였다. X-ray 회절에서 본 PAS 결정의 회절세기는 ground mixture 가 physical mixture 보다 적었다. 결정 크기가 작기 때문에 용출 속도는 ground mixture가 physical mixture나 순수한 PAS 분말보다는 훨씬 느렸으며, 특히 chitosan 에 ground mixture한 것이 가장 느렸다. 실제로 약물에 부형제를 적게 넣는점을 고려한다면, PAS-chitosan (1 : 2) ground 혼합물이 실제적으로 약물에 사용할 수 있음을 지적해 준다.

Abstract : The applicability of chitin and chitosan for prolonged-release preparations of a water soluble drug was examined. In this study, the dissolution behavior of physical and ground mixtures of *p*-aminosalicylic acid(PAS), a water soluble drug, with chitin and chitosan was investigated. The intensity of powder X-ray diffraction pattern in a ground mixture (GM) was smaller than that of a physical mixture (PM), suggesting a relative decrease in the size of the crystals of PAS in the ground mixture. The dissolution rate of PAS from the ground mixtures was significantly slower than that from the physical mixtures or from pure PAS powder. Particularly, the ground mixture with chitosan showed the slowest dissolution. These results indicated that the 1 : 2 ground mixing ratio of PAS-chitosan mixture might be suitable and the results obtained at this ratio could be practically useful, because of the amount of excipient should be small for formulation.

INTRODUCTION

The applicability of natural polysaccharides such as agar,[1] Konjac[2], pectin[3] in the design of dosage forms for sustained release has been examined. Chitin,[4] a polysaccharide consisting of β-2-acetoamino-2-deoxy-D-glucose units is one of the principal ingredients of bone of the Cuttlefish and shell of the Crustacea such as crabs, lobsters, prawn and shrimps, and chitosan (β-2-amino-2-deoxy-D-glucan) is easily prepared from chitin by N-deacetylation with alkali. Chitin and chitosan have been reported to have some useful medical applications.[5,6] For example, chitin has been used as a wound-healing accelator,[7] a blood anticoagulant,[8,9] a biodegradable pharmaceutical carrier,[10-12] chitosan membranes have been also proposed as an artificial kidney membrane.[13] Despite these applications, chitin and chitosan are still little utilized in the pharmaceutical field. Since chitin and chitosan don't present any biological hazard, and inexpensive, these natural polymers might be suitable for use in the preparation of dosage forms of commercial drugs.

The aim of the present study was to prepare a prolonged release preparation of a water soluble drug as a part of a series of studies on pharmaceutical applications of chitin and chitosan, and *p*-aminosalicylic acid was selected as a model substance for the evaluation of prolonged-release of water-soluble drugs from the powders containing chitin and chitosan.

EXPERIMENTAL

Materials and Instruments

Chitin and chitosan from Sigma Chemical Co. (U.S.A) was ground in a ball mill and used after passing a 200 mesh sieve. *p*-Aminosalicylic acid (PAS) was obtained from Tokyo Kasei Ind. Co. All other chemicals were used reagent grade without further purification. Powder X-ray diffractometry was carried out using a Philips Model PW-1700 diffractometer with Ni-filtered Cu-Kα radiation. A Dupont Model 99 differential scanning calorimeter (DSC) was used. Each sample, containing 3 mg of PAS was subjected to DSC in the sample pan for solid samples at a scanning speed of 10℃ / min.

Preparation of Ground Mixtures

Nine gram samples of ground mixtures of PAS with chitin or chitosan in 1 : 2, 1 : 4, and 1 : 8 weight ratios were prepared by grinding in a ceramic ball mill for 24 hr.

Preparation of Physical Mixtures

Physical mixtures of PAS with chitin or chitosan in 1 : 2, 1 : 4 and 1 : 8 weight ratios were prepared by simple blending in a ceramic mortar.

Dissolution Rate Study

Dissolution rate of PAS from the different test preparations were measured in 500ml of pharmacopeial disintegration medium of pH 1.2 at 37 ±0.1℃ and 200 rpm in dissolution tester (Cecil Instrument ABMTM Project 2329). The amount of PAS was used 1.25g-equivalent, because of the saturated concentration of PAS in pH 1.2 at 37℃ was measured to be 2.5g / l. Each test preparation was transfered directly into the dissolution medium and stirred with a two-bladed stainless steel paddle. At appropriate time intervals, 5.0 ml of test solution was withdrawn and filtered through a membrane filter (pore diameter 0.45 μm). An equal volume of fresh medium was replaced immediately.

Each test solution was analyzed for PAS with a ultraviolet (U.V.) spectrophotometer at 300 nm. Also, the absorbance of solution of different concentration of pure PAS was measured after filteration through a membrane filter to obtain a calibration curve for PAS. Experiments were done in triplicate, and the mean values were obtained.

RESULT AND DISCUSSION

Powder X-ray diffraction patterns of PAS are shown in Fig. 1, 2. Pure PAS showed diffraction peaks at 2θ degree of 16.8, 25.8, 26.6, 27.5 etc., indicating the presence of crystalline PAS. The physical mixture also showed sharp diffraction peaks derived from the remaining crystalline PAS.

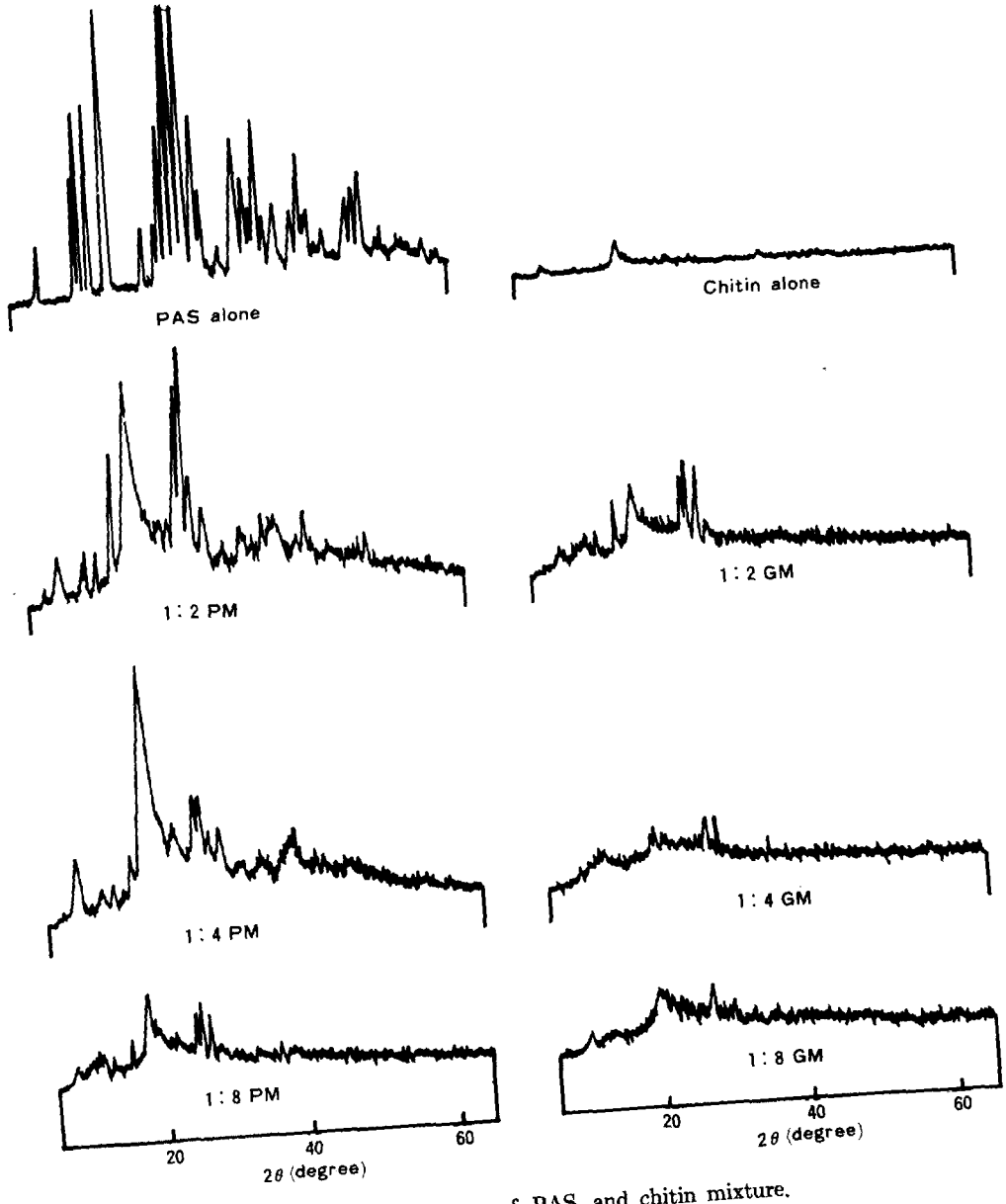

Fig. 1. Powder X-ray diffraction patterns of PAS and chitin mixture. PM : physical mixture, GM : ground mixture

However the diffraction intensity of PAS in the ground mixture was smaller than that of a physical mixture, suggesting a relative decrease in the size of the crystals of PAS in the ground mixture.

Fig. 3 shows the endothermic peak of melting of PAS obtained by differential scanning calorimetry for pure PAS, mixtures with chitin or chitosan. Pure PAS showed the endothermic peak of melting at 146℃. The peak due to the fusion of PAS in the chitin mixture appeared near 150℃, while it appeared at 148℃ 162℃ in physical mixture and ground mixture with chitosan.

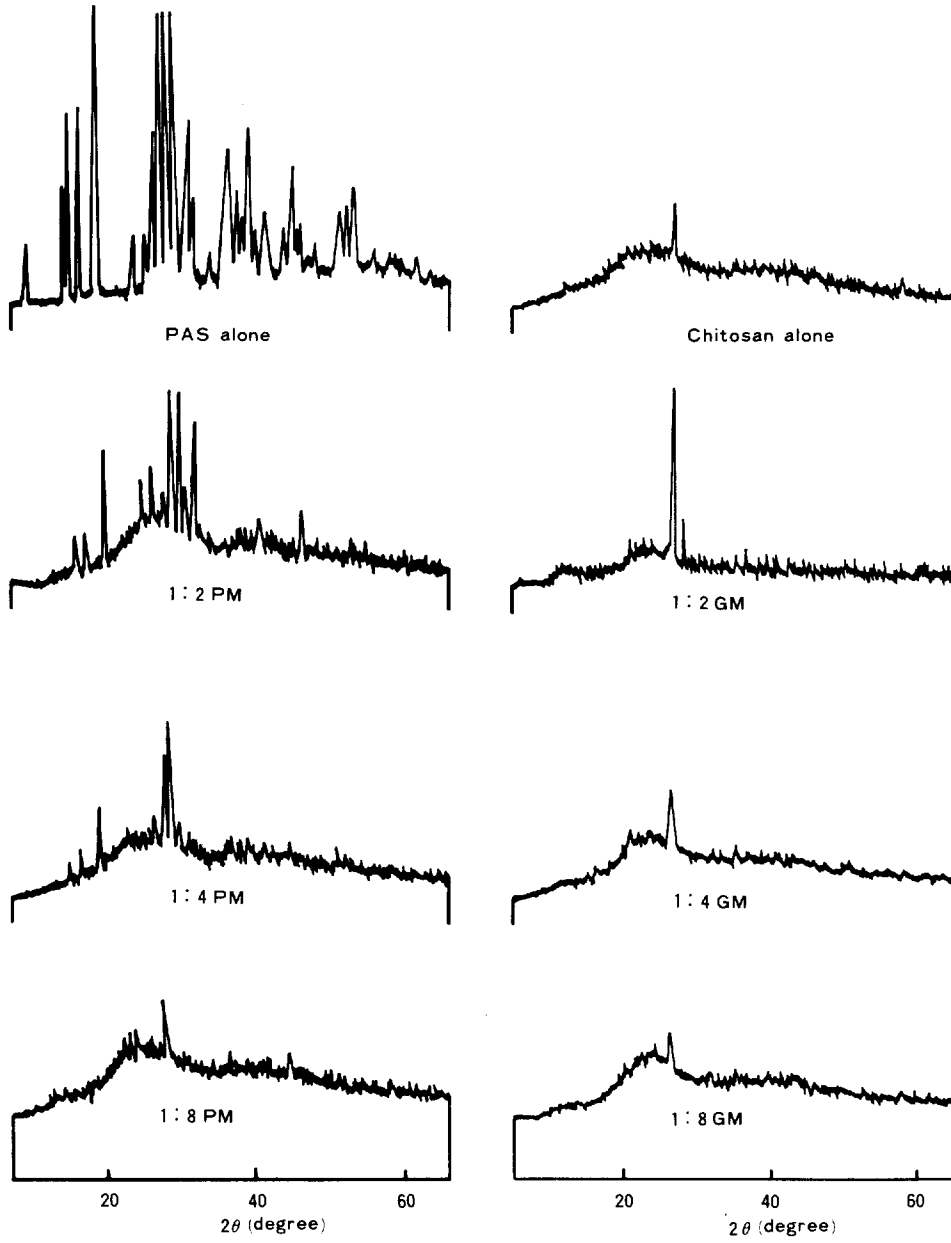

Fig. 2. Powder X-ray diffraction patterns of PAS and chitosan mixture.
PM : physical mixture, GM : ground mixture

Also, the relative enthalpy change of melting of PAS is shown in Table 1. This relative enthalpy change may be considered to correspond to the apparent degree of crystallinity. Table 1 indicates clearly that the relative enthalpy change of chitosan mixture is smaller than that of chitin mixture in 1 : 2 mixing ratio, but the relative enthalpy change of mixtures with the greater ratio of excipient was not determined, because the endothermic peak of PAS was not recorded on the thermograms

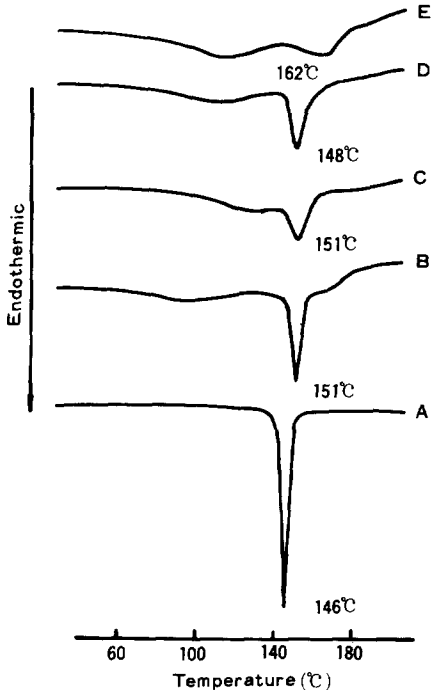

Fig. 3. DSC thermograms of PAS, physical mixture and ground mixture in 1 : 2 mixing ratio. A : PAS alone, B : PAS-chitin PM, C : PAS-chitin GM. D : PAS-chitosan PM, E : PAS-chitosan GM

Table 1. Relative Enthalpy Change of Melting of PAS[a] at Various Mixing Ratios

PAS-excipient	1 : 2	1 : 4	1 : 8
PAS-chitin	0.74	—	—
PAS-chitosan	0.58	—	—

[a] $\frac{\triangle H \text{ of GM}}{\triangle H \text{ of PM}}$ ($\triangle H$: enthalpy change of melting obtained by DSC)

of the ground mixture with chitin or chitosan. This result indicates that the interaction between PAS and chitosan is greater than that of PAS and chitin in ground mixture.

The calibration curve for pure PAS by using U.V.-spectrophotometer at 300 nm is shown in Fig. 4.

The dissolution patterns of PAS from the 1:2 PAS-chitin ground mixture and the same ratio

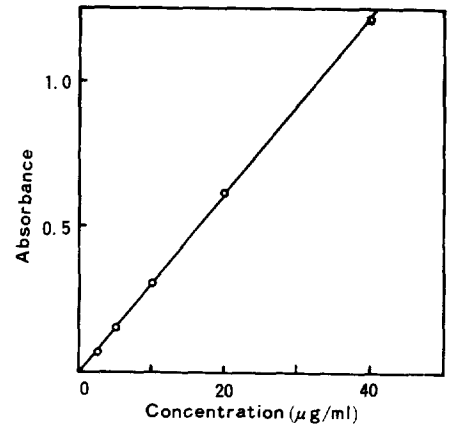

Fig. 4. Calibration curve for pure PAS in disintegration medium(pH=1.2) at 37℃.

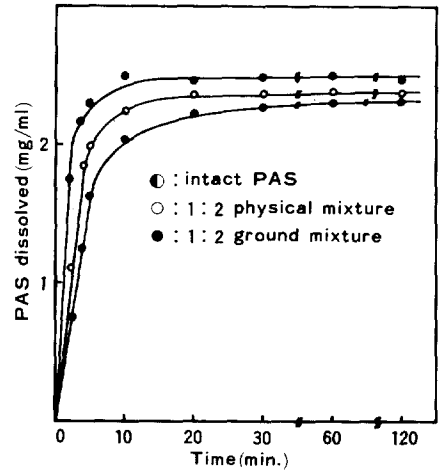

Fig. 5. Dissolution of PAS from mixture(1 : 2 ratio) with chitin in 500 ml of disintegration medium (pH=1.2) at 37℃.

physical mixture are shown in Fig. 5. Also, those from the 1:2 PAS-chitosan test systems are shown in Fig. 6. The dissolution rate of PAS from the physical mixture with chitin was observed to be a little slower than that from the intact PAS, while the dissolution rate from the ground mixture with chitin or chitosan was slower than that from the physical mixture of the same ratio. This result indicates that chitin or chitosan in the ground mixture than these in the physical mixture is responsible for the prolonged dissolution rate of

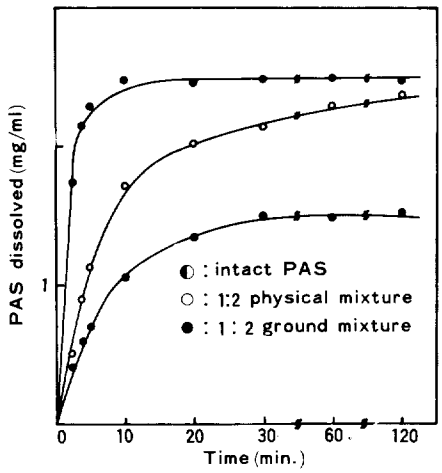

Fig. 6. Dissolution of PAS from mixture(1:2 ratio) with chitosan in 500 ml of disintegration medium (pH=1.2) at 37℃.

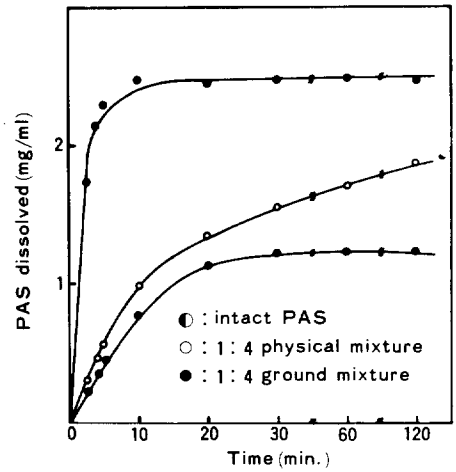

Fig. 8. Dissolution of PAS from mixture(1 : 4 ratio) with chitosan in 500 ml of disintegration medium (pH=1.2) at 37℃.

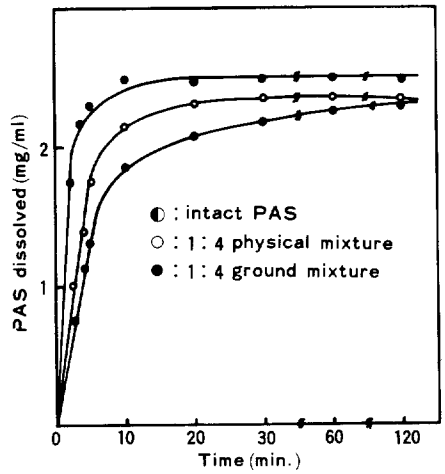

Fig. 7. Dissolution of PAS from mixture(1 : 4 ratio) with chitin in 500 ml of disintegration medium (pH=1.2) at 37℃.

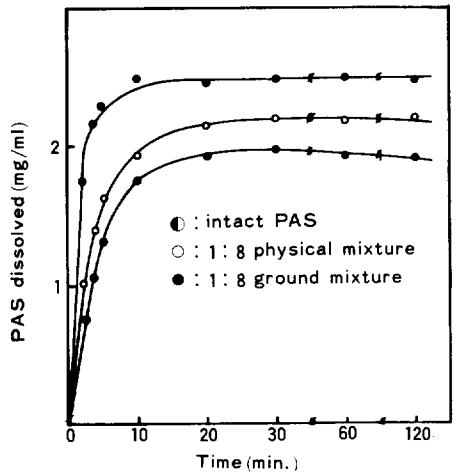

Fig. 9. Dissolution of PAS from mixture(1 : 8 ratio) with chitin in 500 ml of disintegration medium (pH=1.2) at 37℃.

PAS.

The dissolution patterns of PAS from the 1 : 4 PAS-chitin ground mixture and physical mixture of the same ratio are shown in Fig.7. Also, those from the 1 : 4 PAS-chitosan test systems are shown in Fig. 8.

As well dissolution patterns of PAS from the 1 : 8 PAS-chitin mixtures in comparison with that from PAS alone are shown in Fig. 9, and Fig. 10 show the dissolution rate of PAS from the 1 : 8 PAS-chitosan mixture.

As shown in Fig. 7, 8, 9, and 10, the dissolution of PAS from mixtures was significantly slower than that from PAS alone. Consequently, every ground mixture gave slower dissolution than every physical mixture and PAS alone. Specially, ground mixture with chitosan gave the slowest dissolution.

In comparison with the mixing ratio of 1 : 2,

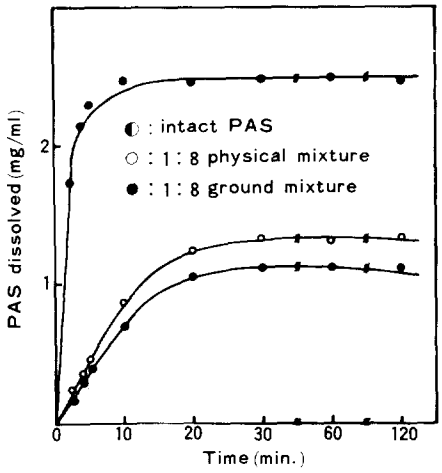

Fig. 10. Dissolution of PAS from mixture(1 : 8 ratio) with chitosan in 500 ml of disintegration medium (pH=1.2) at 37℃.

1 : 4 and 1 : 8 ground mixtures with chitosan showed greatly prolonged dissolution rate. While, the mixtures with chitin showed only slightly prolongation. The difference of dissolution of PAS from ground mixtures, physical mixtures and PAS alone was considered to be simply attributable to the difference in the interaction such as association between PAS-disintegration medium and PAS-chitin or chitosan. Also, the difference of PAS from ground mixture and physical mixture was attributed to the relative decrease in the size of the crystals of PAS in the ground mixture, and was reflected the reducing effect of chitosan on the relative enthalpy change of PAS observed in the DSC study.

In addition, the role of chitin or chitosan in the different prolongation of the PAS dissolution rate between the ground mixture and the corresponding physical mixture is quite interesting. In other words, PAS mixture with chitin act almost independantly in the physical mixture, while chitosan in the physical and ground mixtures alters the physical properties and solubility of PAS.

Considering the usual clinical dose of PAS used in practice, the amount of excipient should be small for formulation. Therefore, the 1 : 2 mixing ratio of PAS-chitosan excipient might be suitable, and the results obtained at this ratio could be practically useful.

In conclusion, co-grounding with chitin and chitosan reduced the size of the crystals of PAS and the dissolution rate of PAS was greatly prolonged.

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