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Rapidly Absorbed Solid Oral Formulations of Ibuprofen Using Water-soluble Gelatin

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Abstract—Rapidly absorbed oral dosage forms of ibuprofen using water-soluble gelatin (hydrolysate of common gelatin: mean mol. wt: 6000) have been studied and compared with tablets prepared with common gelatin (mean mol. wt: 100 000) and commercial tablets. Spray-dried and speed-kneaded powders, two types of granules and tablets were prepared with water-soluble gelatin. The in-vitro dissolution rates of water-soluble gelatin preparations were significantly faster than those of commercial tablets, whereas the tablets prepared using common gelatin had slower dissolution rates than commercial tablets. Water-soluble gelatin enhanced the dissolution rate of ibuprofen by improving the wettability of the drug particle surface by water, without any interaction in solution and the solid state. The absorption behaviour of various preparations was evaluated in four beagle dogs. The peak concentration time (t_{max}) of the water-soluble gelatin preparations was significantly shorter than that of tablets prepared with common gelatin and commercial tablets. The maximum concentration (c_{max}) and the area under the serum concentration-time curve ($AUC_{0-10\,h}$) were similar in all cases. The serum concentration profiles of water-soluble gelatin solid preparations were almost the same as those of the solutions. On the other hand, the profiles of the common gelatin tablets were similar to those of the commercial tablets. The mean absorption time (MAT) from water-soluble gelatin preparations was about 0·7 h, while the MAT from commercial tablets and common gelatin tablets was about 1·2 h. The differences in the MAT of water-soluble gelatin preparations and commercial tablets or common gelatin tablets were the same as the differences in mean dissolution time (MDT) in gastrointestinal fluid. The MDTs of the water-soluble gelatin preparations were from 1 to 5 min, so both disintegration and dissolution steps were rapid. The water-soluble gelatin preparations were stable at 40°C and 70% RH for at least 30 days. The results suggest that the water-soluble gelatin is a useful additive to solid ibuprofen formulations as it may initiate a more rapid and uniform dissolution and absorption of the drug.

Ibuprofen, a propionic acid derivative with anti-inflammatory activity, is slightly soluble in water and has poor wettability. However, it is completely bioavailable and is rapidly absorbed after oral administration, to give maximum plasma concentrations within 2 h. There is a variation in the absorption rate between solid oral dosage forms (Gillespie et al 1982; Stead et al 1983), and Wagner et al (1984) have reported that its absorption from tablets is not simple first order as was that from solution. Several carrier systems have been used in formulations to enhance solubility, dissolution rate and bioavailability, and to attain uniform absorption rate. Polymers such as polyvinylpyrrolidone (PVP), polyvinylalcohol and cyclodextrins enhance dissolution (Chow & Karara 1986; Najib et al 1986) and give rapid and uniform dissolution and absorption rates for ibuprofen. However, since the incorporation of these carriers entailed quantities 3- to 6-fold that of drug, there were problems with the preparation of oral dosage forms such as granules and tablets. We have previously reported that water-soluble gelatin in an amount equivalent to that of the drug significantly enhanced the dissolution rate of several drugs (Imai et al 1989). Water-soluble gelatin is a hydrolysate of common gelatin with a mol. wt of 6000; it has a high aqueous solubility (more than 30% in water at 25°C) and is wettable with binding characteristics. Therefore, water-soluble gelatin could be useful in the formulation of granules and tablets. The present study was undertaken to investigate the prospect of water-soluble gelatin as an additive giving rapid and uniform dissolution rates of ibuprofen oral solid dosage forms. The spray-dried and speed-kneaded powders, granules and tablets were prepared using water-soluble gelatin and their relative dissolution and absorption behaviours were examined and compared with commercial tablets and tablets prepared with common gelatin.

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Materials and Methods

Materials

Water-soluble gelatin (mean mol. wt: 6000) and common gelatin (mean mol. wt: 100 000) were kindly supplied by Nitta Gelatin Co. Ltd (Osaka, Japan). Ibuprofen (10 μm; Nisshin Flour Milling Co. Ltd, Tokyo, Japan), Perfiller-101 (Mixture of synthetic aluminium silicate 20%, hydroxypropylstarch 60% and crystalline cellulose 20%; Freund Ind. Co. Ltd, Tokyo, Japan), carboxymethylcellulose (Shin-Etsu Chem. Co. Ltd, Tokyo, Japan), magnesium stearate (Nakarai Tesque Co. Ltd, Kyoto, Japan), macrogol 6000 (Wako Pure Chem., Osaka, Japan), titanium oxide (Freund Ind. Co. Ltd, Tokyo, Japan) and hydroxypropylmethylcellulose (Shin-Etsu Chem. Co. Ltd, Tokyo, Japan) were used. Tablets containing 80 mg of ibuprofen, prepared in the same way as Ibuprocin (Nisshin Chem. Tokyo, Japan), were used as commercial tablets. All other reagents and solvents were of analytical grade.

Spray-dried powder

A laboratory spray-dryer, with drying chamber 80 cm in diameter equipped with a centrifugal wheel atomizer (Ohkawara, L8 type, Yokohama, Japan) was used. Water-soluble gelatin (100 g) was dissolved in 20% ethanol (400 g). Ibuprofen (100 g) was added and homogenized at 8000 rev min^{-1} for 5 min. The suspension was then fed to a spray-dryer having an inlet and outlet temperature of 80 and 45°C, respectively; the flow rate of the suspension was 55 g min^{-1} and the rotation speed of the atomizer was 20 000 rev min^{-1}.

Speed-kneaded powder

Ibuprofen (100 g) and water-soluble gelatin (100 g) were mixed at 750 rev min^{-1} for 60 min using a high speed mixer (Fuji Sangyo, NSK-150 type, Osaka, Japan).

Granules

Two kinds of granules were prepared by wet granulation. For granules A, ibuprofen (40 g), water-soluble gelatin (12 g), Perfiller-101 (27 g) and carboxymethylcellulose (CMC, 15 g) were mixed and the mixture was kneaded with water (51 mL) and granulated through a 10 mesh sieve. The granules were sieved through 32 mesh after being dried at 50°C for 4 h. The granules were coated with a mixture of CMC (5 g) and magnesium stearate (1 g). For granules B, a mixture of ibuprofen, Perfiller-101 (27 g) and CMC (15 g) was kneaded with 24·5% water-soluble gelatin solution (49 mL). Subsequently granules B were prepared as for granules A. Although the two batches of granules contained the same excipients in exactly the same amount, the method of incorporating the water-soluble gelatin differed.

Tablets

Granules A and B (200 mg; equivalent to 80 mg of ibuprofen) were compressed into cylindrical tablets A, B (diameter: 7 or 8 mm) using a single punch tableting machine (Riken Seiki Co. Ltd, Tokyo, Japan) at a pressure of 150 kg cm^{-2}. The tablets were coated with a solution containing 8% hydroxypropylmethylcellulose 2910, 1·6% macrogol 6000 and 1% titanium oxide. Tablets C containing common gelatin (mean mol. wt: 100 000) were prepared as for tablets A and B, so only the type of gelatin differed. The manufacturing parameters of the tablets are listed in Table 1. The measurements of manufacturing parameters were according to Japanese Pharmacopoeia (JP) XI.

Dissolution studies

The drug dissolution test was performed according to the JP XI, using pH 5·8 phosphate buffer (900 mL) maintained at 37°C and a paddle at 100 rev min^{-1}. Sample powders and granules (equivalent to 80 mg of ibuprofen) were hand-filled into size 0 hard capsules. The capsules and tablets were kept at the bottom of the dissolution flask by means of a sinker. At appropriate intervals, 1 mL samples were removed and filtered through a 0·45 μm membrane filter. The concentration of ibuprofen in the solution was determined by HPLC (apparatus; Hitachi 655, column; LiChrosorb RP-18, mobile phase; acetonitrile–water–phosphoric acid (275:225:0·5), flow rate; 1 mL min^{-1}, detection wavelength 220 nm).

Solubility studies

Solubility measurements were made according to Higuchi & Connors (1965). Excess of ibuprofen was added to aqueous solutions containing various concentrations of water-soluble gelatin and these were vigorously shaken at 25 ± 0·5°C for 24 h. The suspensions were centrifuged and filtered through a 1·0 μm membrane filter. The filtrate (1 mL) was extracted with hexane to remove water-soluble gelatin, and analysed spectrophotometrically.

Powder X-ray diffraction studies

The powder X-ray diffraction patterns were obtained (1° min^{-1} through the 2θ angle) on a Rigaku Denki Geiger Flex-2012 diffractometer (Tokyo, Japan), using Cu-Kα radiation.

Wettability

The sample powder was compressed into cylindrical tablets (diameter 2 cm) using a single punch tableting machine (Riken Seiki Co. Ltd, Tokyo, Japan) at a pressure of 100 kg cm^{-2} for 5 min. A 50 μL drop of water was added to the flat tablet surface using a microlitre syringe. After 2 s the drop was photographed, and the contact angle measured from the photographs.

Stability studies

The samples were stored at 40°C and 70% RH. After 7, 14, 21 and 30 days, change of colour and smell as well as dissolution behaviour were observed for each sample.

In-vivo absorption studies

Four beagle dogs (11–13 kg, 2–4 years old) were used at intervals more than 10 days apart. After they were fed 500 g day^{-1} of soft diet (Besvion: Snow Brand Milk Product Co. Ltd, Tokyo, Japan) for two days, they were fasted for 24 h before drug administration. The granules and powders (80 mg equivalent to ibuprofen) were filled in 0 size hard capsules and capsules and tablets were administered orally with 20 mL water. Blood samples (4 mL) were taken at 10, 20, 30, 45, 60, 90, 120, 180, 300, 420 and 600 min after oral administration. The samples were centrifuged (3000 rev min^{-1}, 15 min) and serum was stored in the refrigerator until assayed. To 1 mL of serum was added 1 mL of 1 M HCl, and the serum was then extracted with 5 mL of cyclohexane containing 3 μg mL^{-1} of flurbiprofen as an internal standard. After centrifugation (3000 rev min^{-1}, 10 min), the organic phase (4 mL) was transferred to a new tube, and the solvent evaporated. The residue was dissolved in 100 μL of acetonitrile, and assayed by HPLC as before.

Results and Discussion

In-vitro studies

Fig. 1 shows the dissolution profiles of ibuprofen from the preparations made with water-soluble gelatin and common gelatin in pH 5·8 phosphate buffer at 37 C, compared with the profile of commercial tablets. It is evident that preparations made with water-soluble gelatin dissolved much more rapidly than the commercial samples. The granules and tablets prepared with water-soluble gelatin dissolved as fast as the samples prepared by speed-kneading and spray-

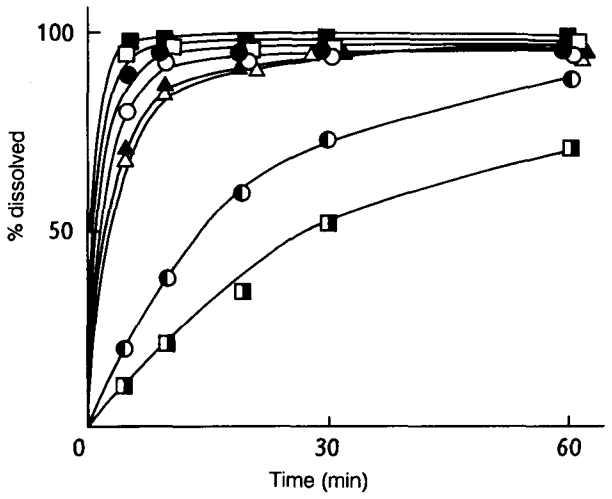

FIG. 1. Dissolution profiles of ibuprofen from test preparations. ○ spray-dried powder, ● speed-kneaded powder, □ granules A, ■ granules B, △ tablets A, ▲ tablets B, ◨ tablets C, ◐ commercial tablets.

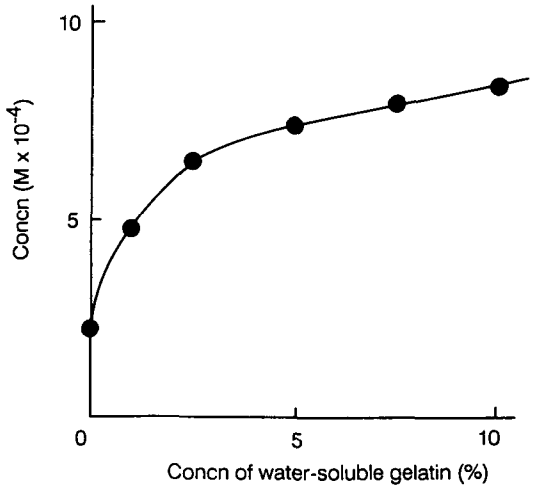

FIG. 2. Phase solubility diagram of the ibuprofen–water-soluble gelatin system.

drying, though the dissolution of tablets and granules involved disintegration and dispersion steps. Although the granules prepared with CMC might be expected to have a slower dissolution rate because of the retarding drug release property of CMC (Finholt et al 1966), the granules prepared with CMC and water-soluble gelatin had an accelerated dissolution rate. The dissolution rate was not affected by the manner of incorporating the water-soluble gelatin (granules A, B and tablets A, B). Common gelatin is considered to be an excellent granulating agent giving a fast dissolution rate of drug from granules and tablets by making the surface of the drug powder hydrophilic (Solvang & Finholt 1970). However, the ibuprofen dissolution rate from tablet C was slower than that from commercial tablets. One factor relating to dissolution rate is the disintegration time of tablets. The disintegration time of tablets prepared with water-soluble gelatin was significantly shorter than that of tablets prepared with common gelatin (Table 1) and there was a significantly faster dissolution rate than obtained with common gelatin. This suggests that the water-soluble gelatin has the ability to make the surface of a powder hydrophilic compared with common gelatin. The results suggest that water-soluble gelatin could give faster dissolution rates and more rapid absorption in-vivo. We reported previously that the dissolution rates of kneaded mixtures of some acidic and basic drugs with water-soluble gelatin were increased, owing to the improvement of wettability, without any interaction or reduction of crystallinity (Imai et al 1989). Though the enhancement of the dissolution rate of ibuprofen by water-soluble gelatin may be due to the increase in wettability of ibuprofen to water, other factors such as increase of solubility and decrease in crystallinity of the drug and the diffusion layer on dissolution may be related to improvement of dissolution.

Table 1. Manufacturing parameters of tablets.

Parameter	Tablet A	Tablet B	Tablet C
Weight (mg)	203–205	203–205	200–202
Diameter (mm)	7·11–7·12	8·10–8·12	8·09–8·11
Thickness (mm)	5·70–5·85	5·08–5·15	5·01–5·11
Hardness (kg cm^{-2})	5·7–6·6	5·5–6·3	5·0–5·5
Disintegration time (min)	3·6–3·9	3·8–4·2	9·1–12·3

The interactions of ibuprofen with water-soluble gelatin in solution and in the solid state were also studied. Fig. 2 shows the phase solubility diagrams for ibuprofen with the water-soluble gelatin. The solubility of ibuprofen increased with increase in water-soluble gelatin. However, the solubility of ibuprofen in 10% water-soluble gelatin solution (pH 5·0) was only about four times that of its aqueous solubility, which corresponds almost to its solubility ($7{\cdot}5 \times 10^{-4}$ M) in pH 5·0 buffer. Furthermore, no interaction of ibuprofen with water-soluble gelatin was observed spectroscopically in aqueous solution. The enhanced solubility of ibuprofen may be due to the buffer effect of the water-soluble gelatin. Thus, the solubility of ibuprofen may not be affected by the water-soluble gelatin, because of the small amount of gelatin (equivalent in amount to ibuprofen) in each preparation.

The crystallinity of ibuprofen in the preparations was also compared with that of drug powder as determined by the powder X-ray diffraction. Fig. 3 shows the diffraction pattern of ibuprofen in each preparation. The diffraction peaks in the physical mixture were identical to those of ibuprofen powder, since the diffraction pattern of the water-soluble gelatin showed only a halo. The diffraction patterns of spray-dried and speed-kneaded powder and granules were almost the same as those of the physical mixture. Therefore the crystallinity of ibuprofen did not appear affected by the methods of preparation. The above results indicate that the enhanced dissolution rate caused by water-soluble gelatin was not due to an increase in solubility and/or a decrease in crystallinity, rather that it made the surface of the drug powder hydrophilic in a similar manner to other acidic and basic drugs, because water-soluble gelatin has surface activity and high aqueous solubility.

The wettability of ibuprofen powder was also increased by the addition of water-soluble gelatin. The contact angle of

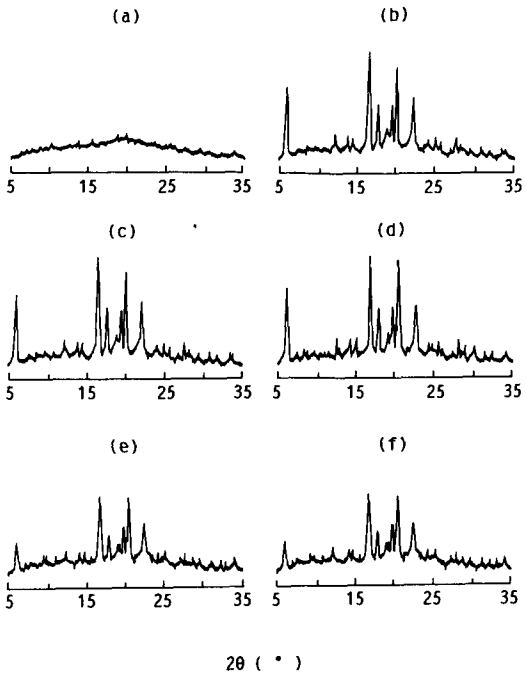

FIG. 3. X-ray diffraction patterns of ibuprofen preparations. a: water-soluble gelatin, b: physical mixture of ibuprofen and water-soluble gelatin (1:1 w/w), c: spray-dried powder, d: speed-kneaded powder, e: granules A, f: granules B.

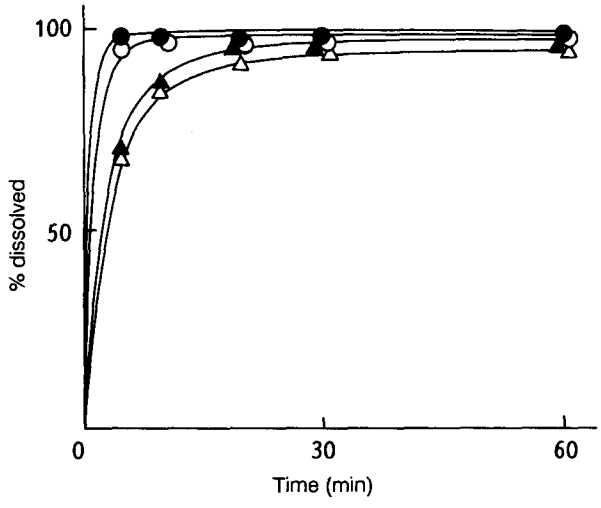

FIG. 4. Dissolution profiles of ibuprofen from granules and tablets after storage for 30 days at 40°C and 70% RH. ○ granules A, ● granules B, △ tablets A, ▲ tablets B.

the speed-kneaded powder decreased to 34°, about one-half the value for ibuprofen alone (62°). It is clear that the formulation process with water-soluble gelatin made the surface of drug particles hydrophilic.

Long-term stability of tablets

The long-term stability of tablets and granules was evaluated from dissolution behaviour, appearance, smell and colour. The tablets and granules did not show any change in appearance after at least 30 days at 40°C and 70% RH. Fig. 4 shows the dissolution behaviour of ibuprofen from tablets and granules after storage for 30 days. Their dissolution profiles were almost the same as those before storage (shown in Fig. 1). These results suggested that the water-soluble gelatin is stable for long-term storage.

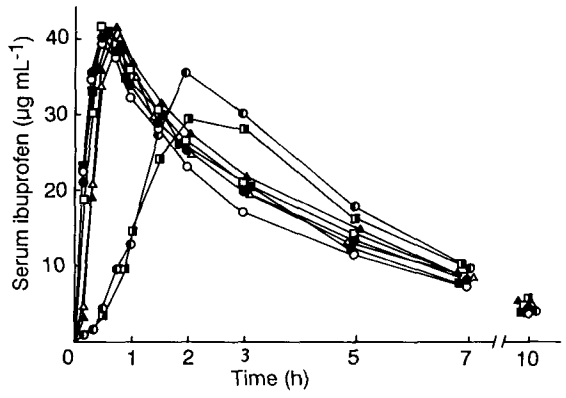

FIG. 5. Serum concentrations of ibuprofen following the oral administration of ibuprofen preparations (Equivalent to 80 mg ibuprofen) to four beagle dogs. ○ spray-dried powder, ● speed-kneaded powder, □ granules A, ■ granules B, △ tablets A, ▲ tablets B, □ tablets C, ○ commercial tablets.

Table 2. Bioavailability parameters of ibuprofen preparations following oral administration to beagle dogs.

Dosage form	$AUC^{a}_{0\ 10\,h}$ (μg mL^{-1} h)	MRT[a] (h)	MAT (h)	MDT (h)
Solution	170·25±24·19	3·19±0·22	0·67	—
Spray-dried powder	154·59±18·55	3·26±0·08	0·74	0·07
Speed-kneaded powder	158·66±24·31	3·28±0·19	0·76	0·09
Granule A	158·24±18·11	3·22±0·19	0·70	0·03
Granule B	156·64±19·82	3·18±0·23	0·69	0·02
Tablet A	151·62±17·75	3·22±0·13	0·70	0·03
Tablet B	152·26±24·24	3·25±0·09	0·72	0·05
Tablet C	152·22±25·26	4·05±0·50	1·53	0·86
Commercial tablets	151·27±17·37	3·76±0·22	1·23	0·56

[a] Values represent the mean ± s.d. (n = 4).

In-vivo absorption studies

The preparations of ibuprofen with water-soluble gelatin were expected to have good bioavailability after oral administration, because of their fast dissolution rate in-vitro. Fig. 5 shows the mean serum concentrations of ibuprofen after oral administration to four beagle dogs. The peak concentration times (t_{max}) after administration of water-soluble gelatin preparations were significantly shorter than those of tablets C and commercial tablets. On the other hand, no differences in the maximum serum concentration (c_{max}) and the area under serum concentration time curves ($AUC_{0\ 10\,h}$) were observed for all samples. At all times, the standard errors of the serum concentration values for the water-soluble gelatin preparations were much smaller than those for commercial tablets and tablets C. The absorption behaviour of water-soluble gelatin preparations was not affected by the manner of preparation, and was almost the same as that of ibuprofen solution. The bioavailability parameters were calculated from the serum concentration-time curve up to 10 h post

administration using moment analysis (Tanigawara et al 1982), and the results are summarized in Table 2. The $AUC_{0\text{-}10\,h}$, the index of the extent of absorption, was almost the same for all the dosage forms. The mean residence time (MRT), the first moment, is the kinetic parameter related to the process which a drug undergoes in the gastrointestinal tract and the body. The mean absorption time (MAT), a useful index of the rate of bioavailability, was estimated by the subtraction of MRT_{iv} (MRT post intravenous injection; 2·52 h) from MRT_{po} (MRT post oral administration). The in-vivo mean dissolution time (MDT) was estimated by the subtraction of MAT_{sol} (MAT from solution) from MAT_{tab} (MAT from tablet), because in-vivo drug absorption involves disintegration and dissolution steps. Absorption rate from the solution was the fastest of all oral dosage forms. Absorption from the water-soluble gelatin preparations was as fast as that from solution, while that from tablets C and the commercial tablets was slower. Before absorption of solid dosage forms through the gastrointestinal wall, the disintegration of tablets and subsequent dispersal of drug must take place in the gastrointestinal tract. The MDTs of all dosage forms prepared with water-soluble gelatin were from 1 to 5 min, so that disintegration and dissolution were rapid. The MDT of tablets C and commercial tablets was about 30 min. The differences in MAT between water-soluble gelatin preparations and commercial tablets or tablets C corresponded to the differences in MDT. These data indicate that the faster absorption rates of water-soluble gelatin preparations were due to rapid dissolution into gastrointestinal fluid and were independent of the preparation method.

The present investigation apparently shows improvement in the dissolution rate of ibuprofen by formulating with water-soluble gelatin, a hydrolysate of common gelatin, with a resultant increase in the rate of bioavailability of drug. Thus, water-soluble gelatin may be useful as an additive to solid ibuprofen formulations as it may facilitate a more rapid and uniform dissolution and absorption of the drug.

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