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Studies on the In Vitro Release of Theophylline from Polyethylene Glycol–Polyvinyl Acetate Mixtures Liquid Filled into Hard Gelatin Capsules

M. A. Shehab and J. H. Richards

Department of Pharmaceutical Sciences, De Montfort University, Leicester, LE1 9BH, U.K.

ABSTRACT

The release of theophylline from mixtures of polyethylene glycol (PEG) with polyvinyl acetate (PVAc) liquid filled into hard gelatin capsules has been studied in vitro. Results indicate that theophylline release can be controlled over a relative wide range by varying the concentration of PVAc, and that the reproducibility of the release profile is improved considerably if the PVAc concentration exceeds 2% w/w. Other results show that drug load, molecular weight of PEG, and pH of the dissolution medium also affect release profiles. In general, the experimental data are well described by a simple equation derived from Fickian diffusion kinetics, thus supporting the suggestion that drug release from this type of formulation is controlled by diffusion in solution through water-filled pores in a network of precipitated PVAc.

INTRODUCTION

The potential advantages of liquid-filled capsules have been described previously (1–3). Modification of these bases provides an opportunity for controlling drug release rates from the encapsulated dosage forms. Part of a previous study (1) indicated that mixtures of polyethylene glycol (PEG) 1500 and polyvinyl acetate (PVAc) might be useful in this respect. Information on factors which influence the in vitro release characteristics of bases is important in the selection of formulations for use in subsequent in vivo experiments (4). This study is concerned, therefore, with an investigation of the effects of some factors which might affect the release of theophylline from PEG/PVAc bases contained within hard gelatin capsules. The selected factors were the proportion of PVAc, the unit dose of theophylline, the molecular weight of the PEG, and the pH of the dissolution medium.

MATERIALS

Materials were obtained from the following sources: Sigma Chemical Co. (USA) for theophylline (1,3-dimethyl xanthine); BDH Chemicals Ltd. (Poole, England) for polyethylene glycols 1000, 1500, 3000, 4000, and 6000 and polyvinyl acetate with molecular weight of approximately 45,000; Davacaps (Monmouth, Gwent, Wales) for hard gelatin capsules.

METHODS

Preparation of Capsules

The general composition of the contents of the various liquid-filled capsules investigated in this study can be described by the following formula:

Theophylline: x mg
Base consisting of y% PVAc in PEG of mol. wt. z: to 600 mg

In the specific formulas, x = 50, 100, or 200; y = 0, 1, 2, 3, 4, 5, 6, or 10; and z = 1000, 1500, 3000, 4000, or 6000. (Note. In order to avoid considerable repetition, henceforth in this report the molecular weight of PEG is given only when the value differs from 1500).

PVAc was stirred into molten PEG until it dissolved completely. During this step the temperature was not allowed to rise above 130°C. Theophylline, previously sieved through a 250-μm mesh screen, was mixed gradually into the molten mass until a homogeneous dispersion was obtained. The hot melt was filled into hard gelatin capsules (size 0), giving each a total fill weight of 600 mg, which included the required dose of theophylline, i.e., 50, 100, or 200 mg. The contents of the capsules were allowed to cool and solidify at room temperature, and the filled capsules were stored overnight in screw-capped jars before being tested.

Determination of Uniformity of Weight and Contents of Active Ingredient

The methods described in the British Pharmacopoeia (5) for these determinations were followed. The theophylline content of the capsules was determined by dissolving the contents of each capsule in 900 cm^3 of 0.1 mole dm^{-3} HCl and assaying spectrophotometrically against a blank of 0.1 mole dm^{-3} HCl using a Pye-Unicam SP8-400 UV/visible spectrophotometer at 270 nm. (Previous experiments showed that this assay was unaffected by the presence of appropriate concentrations of PEG or gelatin.)

Drug Release Studies

The method was based on the "flask-stirrer method." A 2-liter, wide-mouthed, round-bottomed flask with a lid comprising four side ports and one central port was used. A two-bladed, 8.1 cm diameter, glass stirrer was placed into the central port, located in a standard position relative to the bottom of the flask (i.e. 5 cm from the bottom of the flask), and connected to an electric motor (Citenco Ltd.), which rotated the stirrer in a counterclockwise direction at 50 rpm. The flask was placed in a water bath maintained at 37.0°C ± 0.1°C. A plastic cannula, connected to a syringe for sampling, was placed at a constant height and positioned into the dissolution medium through one of the other side ports. At zero time and while the stirrer was in motion, one capsule, which was wrapped loosely in a stainless steel wire, was introduced into the flask containing 900 cm^c of either 0.1 mole dm^{-3} HCl or Sorensen's phosphate buffer (pH 5.5 or 7.5), which had already been allowed to reach the operating temperature of 37°C. The pH of the dissolution medium was monitored throughout the course of each dissolution study. In all cases it remained constant at the desired value of either 1.0, 5.5, or 7.5. Samples, 5 cm^3 were withdrawn from the flask at various times and replaced immediately by an equal volume of dissolution medium previously maintained at 37°C. The contents of the syringe were ejected through a Millipore Swinnex adaptor, fitted with a Millipore HA 0.45-μm pore size filter, into a clean, dry, labeled test tube. The concentration of theophylline in each sample was determined spectrophotometrically using the method described previously but with appropriate modifications to allow for the effects of pH of the dissolution medium on the assay. The theophylline concentrations were corrected in order to account for the effect of replacing samples by fresh dissolution medium. Control experiments, during which release of 270 nm absorbing material from bases consisting of either PEG or PEG plus PVAc was studied, showed that interference with the assay for theophylline was very low, i.e., equivalent to a total amount of ≤ 0.1 mg of theophylline.

X-ray Diffraction Analysis

Samples for x-ray diffraction analysis were taken from the center and outer surfaces of various matrices of PEG or PEG/PVAc and theophylline together with

samples of pure theophylline and pure PEG. A small amount of each sample was mounted on a glass capillary, which was fastened into a sample holder. The latter was placed in a Debye–Scherrer x-ray powder camera (radius 57.415 mm) using a Philips PW 1010 x-ray generator and exposed to CuK_α radiation for approximately 1.5 hr. The x-ray pattern was recorded using a Kodak x-ray direct film. The *d*-spacings (*d*), i.e., the distances between each set of atomic planes of a crystal lattice, were determined from the film negative using a vernier microscope.

RESULTS AND DISCUSSION

Uniformity of Capsule Fill Weight and Theophylline Content

The average fill weights (± *SD*) of two series of 20 capsules containing target doses of 200 mg of theophylline and 400 mg of base comprising either PEG or PEG with 4% w/v PVAc were 608 mg (± 14 mg) and 599 mg (± 16 mg), respectively. In addition, the average theophylline content (± *SD*) of two further series of similar capsules were 208 mg (± 4 mg) and 205 mg (± 4.5 mg), respectively. The reproducibilities indicated by these results were considered to be satisfactory for the purposes of the present investigation.

Effect of PVA Concentration on Theophylline Release

The release rate curves of theophylline from encapsulated bases consisting of PEG and various concentrations of PVAc and containing 200 mg of theophylline are shown in Fig. 1. (The effects of PVAc concentrations on drug release from capsules containing smaller initial loads of theophylline are described in the next section.)

As expected, the release of theophylline from a base comprising PEG alone is rapid, the dose of drug being completely released within 40 min. The inclusion of 1% w/w PVA in the formulation leads to a marked reduction in the release rate by raising the time required for theophylline to be completely released to approximately 90 min, and 2% w/w PVA extends this time to 4 hr. When the PVA concentration is increased from 3% to 10% there is a relatively small reduction in the amount of theophylline released after 3 hr. Beyond this point the release curves for the 6% and 10% w/w PVA systems are almost superimposable and have lower gradients than those given by the 3%, 4%, and 5% systems.

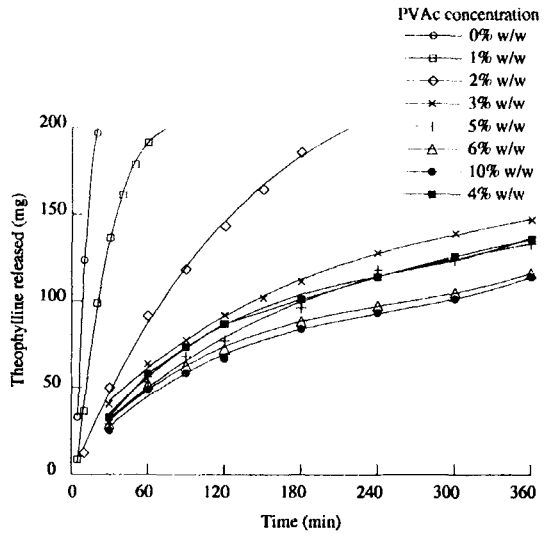

Figure 1. Effect of PVAc concentration on theophylline release from PEG/PVAc bases (drug load = 200 mg; dissolution medium = 0.1 mole dm^{-3} HCl).

The range of $t_{50\%}$ values shown in Table 1 illustrates the wide degree of control of theophylline release that can be achieved by the addition of a relatively small amount, i.e., ≤6% w/w, of PVAc.

It has been suggested (1) that precipitation of PVAc in the form of a porous matrix occurs as PEG and drug are leached out of the mixture and water enters. The retarding effect of PVAc on drug release from PEG is therefore considered to arise from time taken for drug to diffuse in solution through the water-filled pores in the PVAc matrix. This suggestion would obviously pro-

Table 1

$t_{50\%}$ Values for Theophylline Release from PEG/PVAc Bases into 0.1 mole dm^{-3} HCL

PVAc Concentration (% w/w)	$t_{50\%}$ Mean[a] (min)	$t_{50\%}$ *SD* (min)	Coefficient of Variation (%)
0	9.0	0.8	8.9
1	21.0	2.6	17.1
2	74.0	8.6	11.7
3	157.0	2.6	1.6
4	177.5	1.9	1.1
5	209.0	5.3	2.5
6	290.0	4.1	1.4
10	292.5	4.4	1.5

[a]Mean of 4 replicates.

vide explanations for both the decrease in release rate of drug and the increase in lifetime of the matrix with increase in concentration of PVAc. The reproducibility of theophylline release is also affected by the PVAc content of the base. Reference to the coefficients of variation of the $t_{50\%}$ values listed in Table 1 shows that release from bases containing PVAc contents of ≥3% w/w is more reproducible than from the other systems, probably because the former retain their shape during most of the release process. The bases containing 0% and 1% w/v PVAc tend to break up into smaller pieces in an uncontrolled manner.

Effect on Drug Loading on Theophylline Release

As indicated earlier, the effect of initial drug load was tested utilizing the general formula with theophylline contents of 50, 100, and 200 mg incorporated into systems containing 0%, 1%, 2%, 3%, and 4% w/w PVAc. Plots of the amount of drug released versus time for the two lower theophylline contents are shown in Figs. 2 and 3. These show that the effect of PVAc content is qualitatively similar to that observed with the capsules containing 200 mg of drug (see Fig. 1).

Effect of Molecular Weight of PEG on Theophylline Release

The effect of this variable on the release rate of theophylline was studied using capsules containing 200 mg theophylline in a PEG base containing 4% w/w PVAc. The release rate curves shown in Fig. 4 indicate that capsules containing PEG 1000 give a higher release rate than the other systems, and that generally the release rate decreases as the molecular weight of PEG increases. Similar findings have been reported for PEG systems with diazepam (6), sulphadimidine (7), digoxin (8), bendrofluazide (9), hydroflumethiazide (10) and theophylline (11).

The results obtained are consistent with the physicochemical properties of PEGs. As the polymer chains in the PEGs become longer the ether linkages become more numerous and exert more influence on the overall properties. The decrease in dissolution rate of PEG with increase in its molecular weight (11), as expected

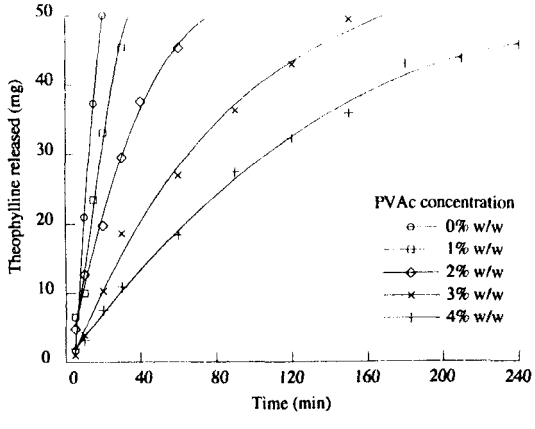

Figure 2. Effect of PVAc concentration on theophylline release from PEG/PVAc bases (drug load = 50 mg; dissolution medium = 0.1 mole dm^{-3} HCl).

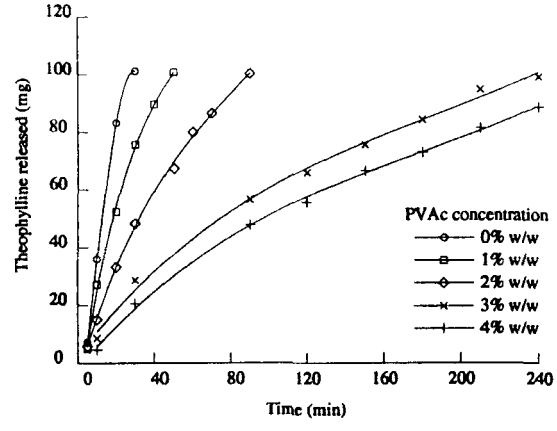

Figure 3. Effect of PVAc concentration on theophylline release from PEG/PVAc bases (drug load = 100 mg; dissolution medium = 0.1 mole dm^{-3} HCl).

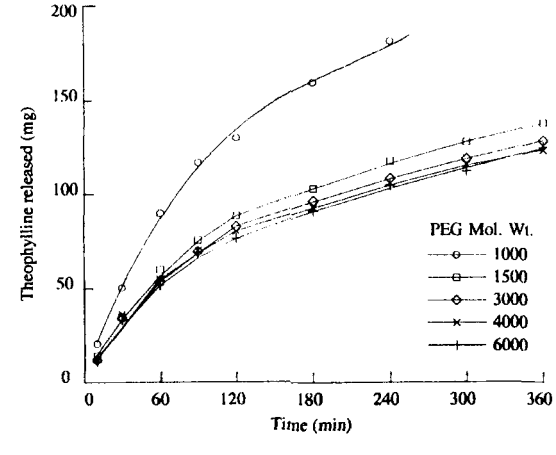

Figure 4. Effect of molecular weight of PEG on theophylline release from PEG/PVAc bases (drug load = 200 mg; dissolution medium = 0.1 mole dm^{-3} HCl; PVAc concn. = 4 % w/w).

from the decreasing solubilities of the larger molecules, is likely to be the major reason for the general trend in the release profiles shown in Fig. 4.

However, Ford (12) concluded that the melting point of a PEG/drug system is also important and suggested that the tendency of lower molecular weight PEGs to show greater degrees of supercooling might aid release. Although, as stated previously, many workers have shown that the release of drugs decreases as the molecular weight of PEG increases, others have shown an opposite result (13–16). Furthermore, Geneidi et al. (17) showed that release of glibenclamide from PEG dispersions was independent of PEG molecular weight whereas Kassem et al. (18) obtained higher rates of chloramphenicol release from PEG 6000 dispersions than from either PEG 12,000 or PEG 4,000 dispersions. Thus, the effect of the molecular weight of PEG on drug release does not appear to be a general one.

Effect of pH of Dissolution Medium on Theophylline Release

It can be seen from Fig. 5 that the release rates of theophylline are higher at pHs 5.5 and 7.5 than at pH 1.0, and that only a relatively small difference exists between the release profiles at the two higher pHs. The release rate of theophylline from PEG/PVAc bases is therefore pH dependent. The relative insensitivity of theophylline solubility to changes in pH over the range 1–7.5 (19) suggests that the pH dependency of release is linked to some effect on the bases themselves, similar, perhaps, to that observed in a recent study of theophylline release from partly esterified alginic acid matrices (20).

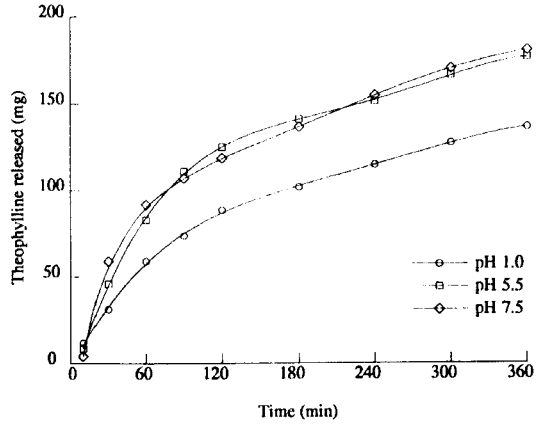

Figure 5. Effect of pH of dissolution medium on theophylline release from PEG/PVAc bases (drug load = 200 mg; PVAc concn. = 4% w/w).

Kinetics of Theophylline Release

Although x-ray diffraction analysis revealed that considerable overlapping of the diffraction patterns of theophylline and PEG occurs and the amorphous PVAc gives a diffuse bond with an approximate *d*-spacing of 4.7 Å, three bands with *d*-spacings of 3.46, 7.00, and 12.10–12.30 Å, respectively, appear to be solely due to the presence of theophylline. These three bands were evident in all of the samples taken from the edges and centers of systems comprising PEG containing 4% w/w PVAc and theophylline at the three drug loadings used in this study.

As indicated earlier in this report, it has been suggested that theophylline release is controlled by its rate of diffusion through the water-filled pores in a network of precipitated PVAc. If this is so and the diffusion is Fickian, then in view of the x-ray diffraction results, all of the PEG/PVAc/theophylline systems would be expected to be represented by case 4 in the classification of Langer and Peppas (21). In this case the amount of drug released per unit area in time t (Q_t) from a matrix with planar geometry may be described by Eq. (1).

$$Q_t = \frac{M_t}{A} = [2CD_eC_m t]^{1/2} \quad (1)$$

where M_t is the amount of drug released in time t from a planar matrix with a surface area A, C is the total amount of drug present in the matrix per unit volume, C_m is the solubility of the drug in the water-filled pores, and D_e is the effective diffusion coefficient of the drug. The latter term is described by the relationship $D_e = D_m\varepsilon/\gamma$, where D_m is the diffusion coefficient of the drug in liquid which fills the pores, ε is the porosity of the matrix, and γ is a factor which accounts for the affect of the tortuosity of the pores. It should be noted that Eq. (1) is a simplified version, which is only applicable when $C \gg \varepsilon C_m$.

Although Eq. (1) describes release from a slab-shaped matrix, it can also be used to describe release from other shapes such as spheres and cylinders, at least in the early stages, e.g., $M_t/M_\infty < 0.5$ (22,23). In fact, Eq. (1) provides a good description of the complete release profiles of theophylline from the formulations which contained 50 and 100 mg drug loadings, as indicated by the correlation coefficients of the linear plots of M_t versus $t^{1/2}$ given in Tables 2 and 3 together with

Table 2

Effect of PVAc Concentration on M_t versus $t^{1/2}$ Plots (theophylline load = 50 mg; dissolution medium = 0.1 mole dm^{-3} HCl)

PVAc Concentration (% w/w)	Slope (mg $min^{-1/2}$)	Intercept (mg)	Correlation Coefficient
0	21.65	-47.26	0.999
1	12.77	-26.71	0.992
2	7.13	-10.41	0.996
3	4.89	-10.36	0.996
4	3.57	-7.50	0.996

Table 3

Effect of PVAc Concentration on M_t versus $t^{1/2}$ Plots (theophylline load = 100 mg; dissolution medium = 0.1 mole dm^{-3} HCl)

PVAc Concentration (% w/w)	Slope (mg $min^{-1/2}$)	Intercept (mg)	Correlation Coefficient
0	31.09	-61.20	0.995
1	20.46	-38.84	0.999
2	13.09	-24.55	0.999
3	7.42	-14.29	0.996
4	6.51	-14.65	0.998

the slopes and intercepts resulting from linear regression analyses.

In general, M_t versus $t^{1/2}$ plots of release data obtained from formulations containing 200 mg of theophylline consist of two linear portions (phases 1 and 2), which intersect at approximately the 90-min point. The slopes, intercepts, and correlation coefficients of these lines are given in Tables 4–6.

It is suggested that the difference in the shapes of M_t versus $t^{1/2}$ plots for formulations containing 200 mg of theophylline compared with those with lower drug loads may arise from differences in the relative rates of loss of theophylline and PEG from the formulations. The ratio of movement of boundaries of two noninteracting, soluble solids, A and B, during release of dissolved species of A and B from a matrix is given by Eq. (2) (24):

$$\frac{\text{Boundary A}}{\text{Boundary B}} = \left[\frac{D_A C_{mA} C_B}{D_B C_{mB} C_A}\right]^{1/2} \quad (2)$$

where D is the diffusion coefficient of the component in water, and C_m and C are defined as before. If A and B are taken to be theophylline and PEG, respectively, and if the values of the terms on the right-hand side of Eq. (2) are taken as $D_A = 1.14 \times 10^{-5}$ cm^2 s^{-1} (25), C_A = 13.4 mg cm^{-3} as determined in the present study, D_B = 0.35×10^{-5} cm^2 s^{-1} (estimated from Ref. 26); and C_{mB} = 700 mg cm^{-3} (27), and the values of C_A and C_B are calculated from the amounts of theophylline and PEG in a given formulation and the volume (0.54 cm^3) of the encapsulated system, then the boundary movement rates are as follows:

Drug Load (mg)	Rate of Boundary Movement A/B
50	0.80
100	0.54
200	0.34

The above ratios suggest that in the case of a formulation containing 50 mg of theophylline the two bound-

Table 4

Effect of PVAc Concentration on M_t versus $t^{1/2}$ Plots (theophylline load = 200 mg; dissolution medium = 0.1 mole dm^{-3} HCl)

PVAc Concentration (% w/w)	Slope (mg $min^{-1/2}$)		Intercept (mg)		Correlation Coefficient	
	Phase 1	Phase 2	Phase 1	Phase 2	Phase 1	Phase 2
3	9.99	7.11	-17.08	10.99	0.998	0.997
4	9.71	6.39	-18.23	15.24	0.998	0.999
5	8.60	7.14	-14.87	-1.66	0.997	0.998
6	8.20	5.41	-16.00	9.89	0.993	0.994
10	8.11	5.58	-16.52	7.23	0.994	0.994

Table 5

Effect of Molecular Weight of PEG on M_t versus $t^{1/2}$ Plots (theophylline load = 200 mg; PVAc concentration = 4% w/w; dissolution medium = 0.1 mole dm^{-3} HCl)

Mol. Wt. of PEG	Slope (mg $min^{-1/2}$)		Intercept (mg)		Correlation Coefficient	
	Phase 1	Phase 2	Phase 1	Phase 2	Phase 1	Phase 2
1000	12.67	—	-12.73	—	0.997	—
1500	9.71	6.39	-18.23	15.241	0.998	0.999
3000	8.94	5.70	-14.36	18.676	0.999	0.997
4000	8.52	5.70	-12.14	15.420	0.999	0.999
6000	8.58	5.87	-13.72	11.411	0.999	0.999

Table 6

Effect of pH on M_t versus $t^{1/2}$ Plots (Theophylline Load = 200 mg; PVAc Mol Wt = 1500; PVAC Concentration = 4% w/w; Dissolution Medium = 0.1 mole dm^{-3})

pH of Dissolution Medium	Slope (mg $min^{-1/2}$)		Intercept (mg)		Correlation Coefficient	
	Phase 1	Phase 2	Phase 1	Phase 2	Phase 1	Phase 2
1.0	9.71	6.39	-18.23	15.24	0.998	0.999
5.5	15.77	6.93	-35.07	45.93	0.989	0.998
7.5	16.10	7.63	-44.16	34.91	0.999	0.999

aries are moving at fairly similar rates so that during most of the theophylline release period PEG will be present in the system. In the case of formulations containing 200 mg of theophylline, however, the PEG boundary will move inward 2.4 times faster than the theophylline. Thus, it is possible that in the early stages of theophylline release PEG will be present whereas the later stages may occur in the absence of PEG. Since the presence of PEG may increase the solubility of theophylline and retard the precipitation of PVA as a water-insoluble network, it is possible that the biphasic nature of the M_t versus $t^{1/2}$ plots arises from this difference. The formulations containing 100 mg theophylline lie between the above extremes.

Finally, the general behavior of formulations containing 200 mg of theophylline in yielding biphasic M_t versus $t^{1/2}$ plots was not demonstrated by systems containing either 0%, 1%, or 2% w/w PVAc. The two former systems yielded *S*-shaped plots whereas the 2% w/w PVAc containing system gave a linear plot over its whole range.

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