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Research Article

Solid Dispersion Incorporated Fast Dissolving Oral Wafers of Cinnarizine: Development and Evaluation

Deepthi O, Akhil Hari*, Deepthi K

National College of Pharmacy, Kozhikode, Kerala, India

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ABSTRACT

Cinnarizine is a piperazine derivative, antiallergic with antihistamine, sedative, and calcium-channel blocking activity. It is used for the symptomatic treatment of nausea and vertigo caused by Meniere's disease and other vestibular disorders and for the prevention and treatment of motion sickness. The present study is focused on making fast dissolving wafers of solid dispersion incorporated Cinnarizine to enhance the bioavailability, dissolution of the drug and increasing the patient compliance. Fast dissolving films of Cinnarizine can be considered suitable for clinical use in the treatment of allergic rhinitis and other conditions of allergies, where a quicker onset of action is desirable along with the convenience of administration. Seven formulations of fast releasing wafers of solid dispersion incorporated Cinnarizine, dispersed in two different polymers; HPMC and PVA by solvent casting method were prepared. Solid dispersion was prepared by solvent evaporation method to enhance the solubility, dissolution rate and consequently, the bioavailability of Cinnarizine. These wafers were evaluated for various parameters like thickness uniformity, weight uniformity, folding endurance, swelling index, percentage moisture absorption, content uniformity, ex vivo permeation studies etc. The cumulative percentage amount of drug diffused was higher for fast releasing wafer made of 3% HPMC. The release kinetics data indicates that the release of drug from fast releasing wafer F4 follows first order release kinetics and model fits to Higuchi which is indicative of the diffusion mechanism of drug release. The mechanism of drug release was found to be non-Fickian. From all of these findings it was concluded that HPMC K4M is the best fast releasing wafer forming polymer.

Keywords: Cinnarizine, Fast releasing wafers, Solid dispersion, HPMC, PVA.

INTRODUCTION

Fast dissolving drug delivery system were first introduced in 1970 as an alternative to conventional delivery systems, which rapidly disintegrate and dissolve in saliva and easily swallowed without need of water[1]. Nearly 35-50% of the general population, especially the elderly and children suffer from dysphagia or difficulty in swallowing, which results in high incidence of non-compliance and ineffective therapy. Swallowing problems also are very common in young individuals because of their poorly developed muscular and nervous systems. Other groups who may experience problems in swallowing conventional oral dosage forms are the patients with tremors of extremities, mentally ill, developmentally disabled, non-cooperative and patients with reduced liquid intake or patients suffering from nausea, as well as patients travelling or who do not have access to water[2]. Oral thin Wafer drug delivery systems are solid dosage forms, which dissolve in a short period of time when placed in the mouth without drinking water or chewing. These are also referred as fast dissolving oral wafers, wafers, buccal films or oral strips[3].

Cinnarizine is a piperazine derivative, antiallergic, antihistamine, sedative, and calcium-channel blocking activity. It is used for the symptomatic treatment of nausea and vertigo caused by Meniere's disease and other vestibular disorders and for the prevention and treatment of motion sickness. Cinnarizine absorption is taking place from gastrointestinal tract, peak plasma concentrations occurring 2 to 4 hours after oral doses. It has a half-life of 3 to 4 hours. The dose for vertigo and vestibular disorders is 30 mg three times daily by mouth and for motion sickness a dose of 30 mg is taken 2 hours before the start of the journey and 15 mg every 8 hours during the journey if necessary[4]. The available marketed dosage form of cinnarizine is 25 mg and 75 mg conventional tablets which can be given according to the requirement.

There is always been a need of better drug delivery system of cinnarizine which satisfies immediate action, uniform plasma concentration profile and enhanced patient compliance. Thus, the current study is focused on formulating fast dissolving drug delivery system of cinnarizine to enhance its bioavailability, thereby increasing the patient compliance. Fast dissolving films of cinnarizine can be considered suitable for the treatment of allergic rhinitis and other conditions of allergies, where a quicker onset of action is desirable along with the ease of administration. Cinnarizine is poorly water soluble (750 mg/L) class II basic drug and very sensitive to pH changes. Many techniques are employed to improve dissolution and bioavailability of BCS class II drugs, which includes the surfactants, micronization, solid dispersion etc.[5] In the

*Author for Correspondence: akilhari@gmail.com

Working formula for cinnarizine solid dispersion incorporated fast releasing wafers.

Table 1: Working formula for fast releasing wafers of cinnarizine.

Formulation code	F1	F2	F3	F4	F5	F6	F7
Cinnarizine solid dispersion (equivalent to 15mg drug)	170mg	170mg	170mg	170mg	170mg	170mg	170mg
PVA	2%	_	3%	_	2%	3%	3%
HPMC K4M	_	2%	_	3%	2%	3%	2%
PEG 4000	2%	2%	2%	2%	2%	2%	2%

Drug Excipient Compatibility Study

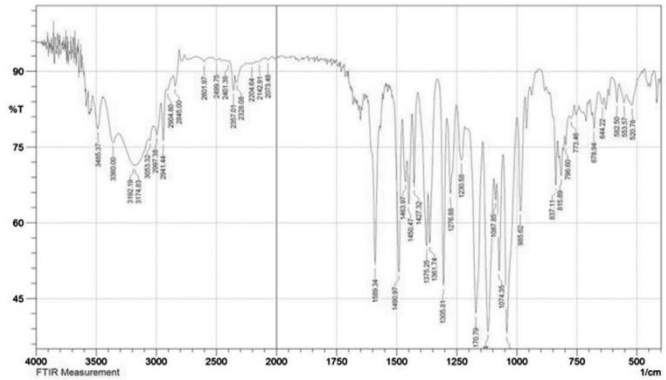

Figure 1: FTIR of Cinnarizine

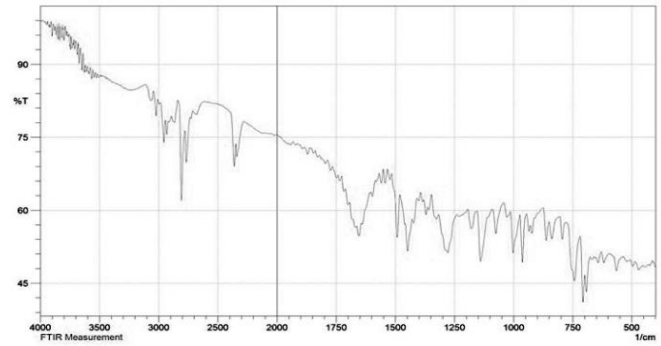

Figure 2: FTIR of cinnarizine solid dispersion with PVP K30

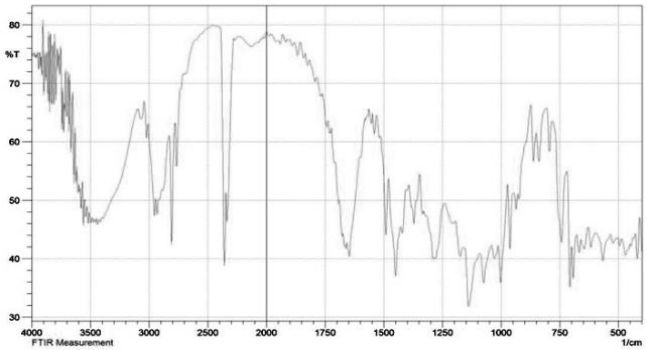

Figure 3: FTIR of cinnarizine with PVA and HPMC

present work solid dispersion of cinnarizine were prepared with PVP K30 by using solvent evaporation method in the 1:3 ratio of drug and carrier respectively. The fast dissolving films were prepared by solvent casting method.

MATERIALS AND METHODS

Materials

Cinnarizine, PVP K30, PEG 4000, HPMC K4M were obtained from Yarrow Chem Products, Mumbai. PVA obtained from Loba Chem Ltd, Mumbai. All other reagents used were of analytical grade.

Methodology

Drug excipient compatibility studies

FTIR absorption spectra of pure drug and physical mixture were recorded in the range of 400 to 4000 cm-1 by KBr

Calibration curve of cinnarizine in pH 6.8 Phosphate Buffer Solution.

Table 2: Spectrophotometric data for the estimation of cinnarizine

Concentration, µg/ml	Absorbance
1	0.07
2	0.138
3	0.201
4	0.26
5	0.316

disc method using FTIR spectrophotometer. FTIR study was carried out individually for drug and polymers and physical mixture of drug with all polymers. FTIR spectra of physical mixture of drug with all polymers were compared with FTIR spectra of pure drug and polymers.

Preparation of calibration curve of cinnarizine in phosphate buffer pH 6.8.

Preparation of standard stock solution of cinnarizine in phosphate buffer (pH 6.8)

Standard stock solution of cinnarizine was prepared by dissolving accurately weighing 100 mg drug in little quantity of glacial acetic acid in 100 ml volumetric flask. The volume was then made up to 100 ml by using phosphate buffer (pH 6.8) to obtain stock solution of 1000 µg/ml.

Preparation of calibration curve of cinnarizine

From stock solution (1000µg/ml), 1ml is diluted to 10ml using 6.8 pH phosphate buffer solutions (100µg/ml). From this solution 1ml is diluted to 10ml using 6.8 pH phosphate buffer solution (10µg/ml). Series of solutions with concentration range of 1,2,3,4,5 µg/ml were prepared by pipetting 1,2,3,4,5 ml from above solution and made up to 10ml with buffer solution. Absorbance of the resulting solutions was measured at λmax 254nm. Calibration curve was prepared using absorption maxima method.

Formulation of solid dispersion of cinnarizine[6].

Solid dispersion of cinnarizine were prepared by solvent evaporation method. Drug was weighed and taken in a china dish, dissolved in 5ml chloroform and then carrier was weighed (PVP k30 in ratio of1:3) and taken in an another china dish, dissolved in 5ml chloroform. The two solutions are mixed and solvent was evaporated at room temperature and dried in hot air oven at 50^0 C for 4 hours. The resultant mass was passed through sieve no. 60 and stored in desiccator.

Formulation of fast releasing wafers of solid dispersion incoporated cinnarizine.

Polymers HPMC K4M and PVA (2%, 3%,) were weighed accurately and dispersed separately in 5ml water. Then 0.5ml 2% plasticizer (PEG 4000) was added to each

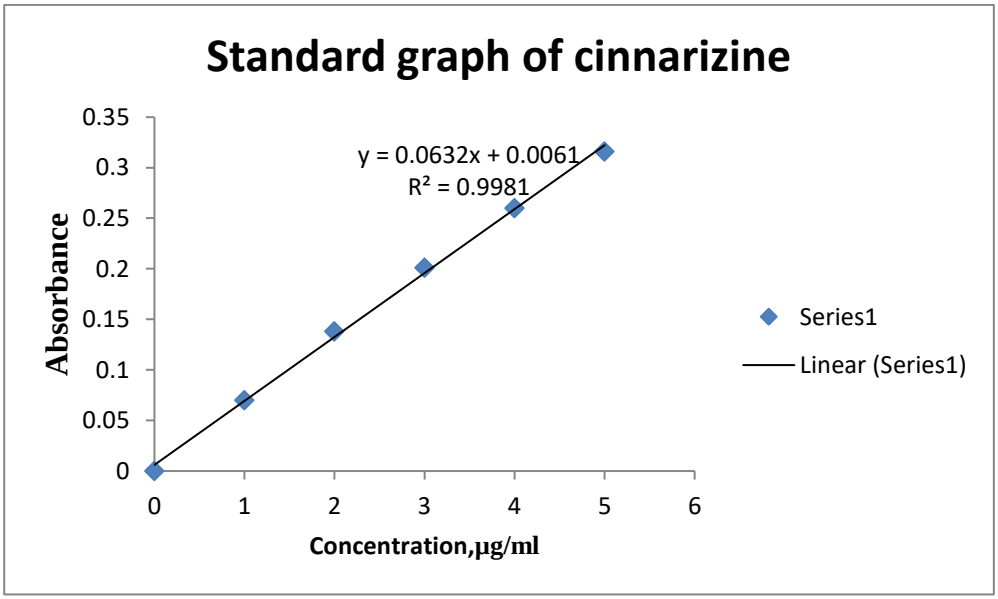

Figure 4: Standard plot of cinnarizine in pH 6.8 phosphate buffer.

Table 3: Values of evaluation parameters.

Formulation code	Thickness(mm)	Weight uniformity(gm)	Folding endurance	Swelling property	Transparency
F1	0.0425	0.018	380.5	6.835	2.8225
F2	0.03	0.0115	394.25	11.3325	0.484
F3	0.0475	0.018	373	10.74	7.4375
F4	0.0325	0.0158	364.75	12.4275	10.255
F5	0.0675	0.021	368	8.685	4.93
F6	0.0875	0.0313	343	8.305	4.285
F7	0.07	0.0228	356.5	6.555	5.125

Table 4: Values of evaluation parameters.

Formulation code	Percentage moisture absorption	Percentage moisture loss	Percentage drug content	Disintegration time (sec)
F1	1.365	1.41	96.17	13.75
F2	1.535	1.3525	96.13	12.5
F3	1.73	1.1975	98.33	17
F4	1.85	1.25	97.67	14.75
F5	1.84	1.5325	96.6	18
F6	1.845	1.42	97.33	20
F7	1.52	1.5	97.77	18

Ex vivo Permeation studies

Table 5: Percentage cumulative amount of drug diffused data of all formulations

Formulations / Time	% Cumulative amount of drug diffused						
	F1	F2	F3	F4	F5	F6	F7
0	0	0	0	0	0	0	0
2	6.53	7.47	9.73	11.6	6.4	6.87	5.07
4	19.33	20.67	24.4	29.47	18.2	19.8	11.67
6	34.87	37.07	42.8	49.54	31.73	36.33	24.07
8	55.53	59.53	66.67	70.67	51.47	58.47	44.13
10	85.33	92.67	94	98	82.67	90.67	74.67

solution and mixed well till clear solution was obtained. Then the solid dispersion of drug was dissolved in the mixture of glacial acetic acid and water (3.5:1.5). Then two solutions were mixed and poured into a clean and dry glass petri dish and allowed to dry. The dried films were carefully removed from the petri dish, checked for any imperfections or air bubbles and cut in to pieces of 4 cm^2.

Evaluation of Fast Releasing Wafers of Solid Dispersion Incoporated Cinnarizine

Organoleptic evaluation

Organoleptic properties like colour and appearance were evaluated.

Mechanical properties

Thickness

The thickness of wafer can be measured by micrometer screw gauge at different strategic locations. This is essential to ascertain uniformity in the thickness of the Wafer as this is directly related to the accuracy of dose in the wafer.

Weight uniformity[7]

Weight variation of 4 cm2 of the film was measured by cut at three different places from the casted film. The weight of each film was taken and weight variation was calculated.

Percent Elongation

When stress is applied, wafer sample stretches and this is referred to as strain. Strain is the deformation of strip divided by original dimension of the sample. Generally elongation of wafer increases as the plasticizer content increases.

$$\% \textbf{ Elongation } = \frac{\{\textbf{Increase in length of wafer} \times \textbf{100}\}}{\{\textbf{Initial length of wafer}\}}$$

Folding Endurance

Folding endurance is determined by repeated folding of the strip at the same place till the strip breaks. The number of times the wafer is folded without breaking is computed as the folding endurance value.

Swelling property

Wafer swelling study is conducted using pH 6.8 phosphate buffer. The wafer sample is weighed and placed in a stainless steel wire mesh. The mesh containing wafer sample is submerged into 15ml medium in a plastic container. Increase in the weight of the wafer is determined at predetermined time interval until a constant weight is observed. The degree of swelling is calculated using formula- $\alpha = (w_t - w_o)/w_o$, w^t is weight of Wafer at time t, and w^o is weight of Wafer at time zero.

Transparency

The transparency of the Wafers can be determined using a simple UV spectrophotometer. Cut the Wafer samples into rectangles and placed on the internal side of the spectrophotometer cell. Determine the transmittance of wafers at 600 nm. The transparency of the wafers can be calculated as follows:

Transparency = (logT600)/b = - €c

Where, T600 is the transmittance at 600 nm, b is the Wafer thickness (mm), c is concentration

Percentage moisture absorption (PMA)[8]

The percentage moisture absorption test was carried out to check the physical stability of the mouth dissolving film at high humid conditions. Three films were taken, weighed accurately and placed in a desiccator containing saturated solution of aluminium chloride, keeping the humidity inside the desiccators at 79.5 %. The films were taken out after 72 hours, weighed and percentage moisture absorption was calculated by using the formula

$$\textbf{PMA} = \frac{\text{Final weight} - \text{Initial weight}}{\text{Initial weight}} \text{X100}$$

Percentage moisture loss (PML)

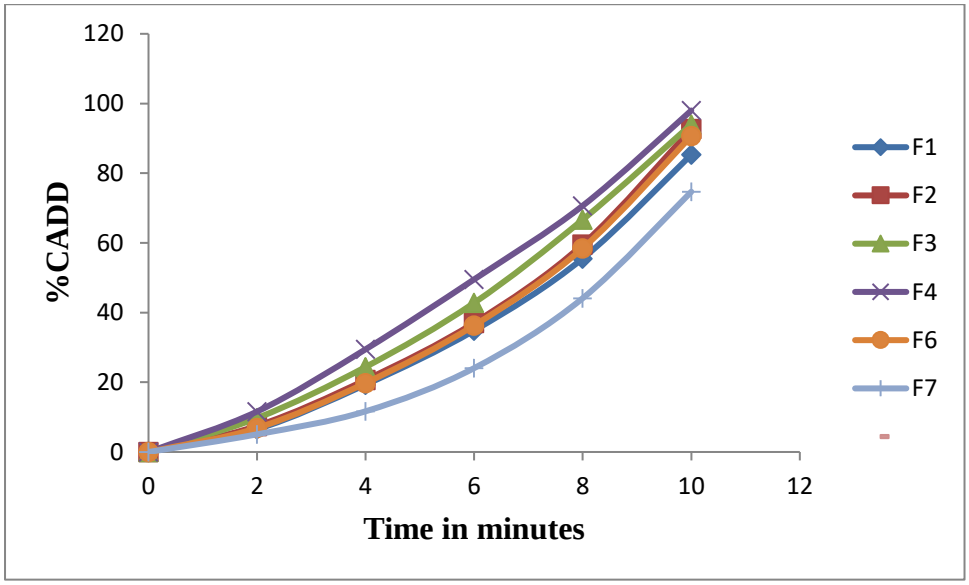

Figure 5: % cumulative amount of drug diffused.

Percentage moisture loss was calculated to test the integrity of films at dry condition. Three 1cm square films was cut out and weighed accurately and kept in desiccators containing fused anhydrous calcium chloride. After 72 hours the films were removed and weighed. The percentage moisture loss was calculated by using the following formula.

$$PML = \frac{\text{Initial weight} - \text{Final weight}}{\text{Initial weight}} \text{ X100}$$

Assay/ Content uniformity[7]

Drug content determination of the film was done by dissolving the film of 4 cm2 in 100 ml of pH 6.8 phosphate buffer using magnetic stirrer for 1 hour. The drug content was then evaluated spectrophotometrically at λmax of 254 nm. The determination was carried out in three times for all the formulations and average with standard deviation was recorded. Limit of content uniformity is 85– 115 percentage.

Disintegration Time

In vitro disintegration time was evaluated visually in a petri dish containing 25 ml of phosphate buffer pH 6.8 with swirling every 10 sec. The disintegration time is the time when the film starts to disintegrates. Typical disintegration time for strips is 5–30 s.

Ex vivo permeation studies[9]

Buccal tissue was taken from pigs at a slaughter-house. It was collected within 10 minutes after slaughter of the pig and tissue was kept in buffer solution. It was transported immediately to the laboratory and was mounted within 2 hours of isolation of buccal tissue. The tissue was washed thoroughly using phosphate buffer saline to remove any adherent material. The buccal membrane from the tissue was isolated using surgical procedure. Buccal membrane was isolated and buccal epithelium was carefully separated from the underlying connective tissue. Sufficient care was taken to prevent any damage to the buccal epithelium.

Permeation studies should be carried out even though permeability of oral mucosa is 4-1000 times greater than that of skin. To study the permeability, modified Franz diffusion cell can be used along with porcine buccal mucosa. The Franz diffusion cell consists of a donor and a receptor compartment. In between the two compartments, mucosa is mounted and the size of the mucosa should be of the same size as that of the head of the receptor compartment. The receptor compartment is filled with buffer and maintained at 37 ± 0.2^0C and to maintain thermodynamics a magnetic bead stirring at a speed of 50 rpm is used. A film specimen moistened with a few drops of simulated saliva should be kept in contact with mucosal surface. The donor compartment should consist of 1ml simulated saliva fluid of p^H 6.8. At particular interval, samples are withdrawn and replaced by same amount of fresh medium. By suitable analytical method, percentage of drug permeated can be determined.

RESULTS

As described in the methodology section the Fourier Transform Infrared spectroscopy studies were carried out for cinnarizine and cinnarizine-polymer physical mixtures. FTIR-spectra of drug and its physical mixture with excipients are exactly same, and there is no shift of peaks or disappearance of principle peaks or modification of the principle peaks indicating that there is no interaction between the drug and excipients

The standard curve of cinnarizine was prepared in pH 6.8 phosphate buffer, the R^2 and slope values were found to be 0.9981 and 0.0632 respectively, which shows a linearity of absorbance between 1-5µg/ml.

Evaluation of Fast Releasing Wafers

Physical appearance

The formulations prepared were opaque, white colour with smooth surface without any grittiness and were found to be flexible and thin in nature.

Mechanical properties

Thickness

The thicknesses of patches were evaluated with the use of a screw gauge and were found to be in the range of 0.03-

0.0875 mm. The thickness was found to be uniform within each formulation.

Weight Uniformity

Fast releasing wafers of cinnarizine ($2\times2cm^2$) were tested for uniformity of weight and were found in the range of 0.0115 to 0.0313gm. The values of weight uniformity of formulations indicated that the films were uniform in weight.

Folding endurance

Folding endurance was found in the range of 343-394. In general, folding endurance of all the film was found to be satisfactory indicating good strength and elasticity.

Swelling property

Degree of swelling of all films was calculated and it was in the range of 6.55-12.42. Degree of swelling increases with increasing concentration of polymer and was found within the range.

Transparency

Transparency of all films was calculated and it was in the range of 0.484-10.255. The value of transparency increases with increasing polymer concentration.

Percentage moisture absorption

The percentage moisture absorption was found to be in the range of 1.365-1.85%. The percentage moisture absorption was found to be increased with increasing polymer concentration.

Percentage moisture loss

The percentage moisture loss was found to be in the range of 1.1975-1.5325. The percentage moisture loss was found to decrease with increasing polymer concentration.

Assay/content uniformity

The drug content in each wafers were analysed spectrophotometrically and it was observed that all the formulations showed satisfactory drug content values ranging from 96.13±0.4726% to 98.33±0.2082.

Disintegration time

The disintegration time was found to be in the range of 12.5-20. It was observed that *in vitro* disintegration time varies for all the formulations. Disintegration time was found to be increased with increasing concentration of polymers.

The cumulative percentage release from the formulations was found in the range of 74.67% – 98.00%. From the seven formulations namely F3 and F4 with 3% PVA and HPMC shows satisfactory release. The *ex vivo* permeation studies of the formulations in pH 6.8 phosphate buffer shows differences depending on their composition. A rapid permeation of all the formulations was observed by the permeation study, in which approximately 80% of cinnarizine diffused within 10 min. The formulation F4 shows maximum drug diffusion of 98% within 10 minutes.

CONCLUSION

Mouth dissolving oral wafers of cinnarizine solid dispersion was prepared successfully using PVA and HPMC K4M polymers individually and in combination by solvent casting method. Solid dispersion of cinnarizine was prepared by solvent evaporation method using PVP K30 as carrier. Solid dispersion with 1:3 ratio of drug and polymer showed enhanced dissolution rate and was further formulated into mouth dissolving wafers. Wafers were prepared with varying concentrations of HPMC K4M, PVA and in combination of the two polymers. The FT-IR spectra revealed that, there was no interaction between polymer and drug. Polymer used was compatible with the drug. Evaluation parameters like thickness, percentage moisture loss, percentage moisture absorption, folding endurance, indicates that films were mechanically stable. Percentage weight variation and content uniformity were found to be uniform in all the films. The *ex vivo* permeation studies of the formulations in pH 6.8 phosphate buffer shows differences depending on their composition. A rapid permeation of all the formulations was observed by the permeation study, in which approximately 80% of cinnarizine diffused within 10 min. The formulation F4 shows maximum drug diffusion of 98% within 10 minutes so it is selected as the best formulation.

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