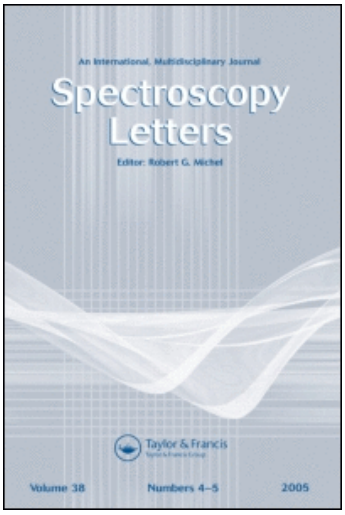

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Spectrophotometric Determination of Timolol and Other β-adrenergic Blocking Drugs and in Pharmaceutical Preparations

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Spectrophotometric Determination of Timolol and Other β-adrenergic Blocking Drugs and in Pharmaceutical Preparations

Key Words: Timolol, Carazolol, Pindolol and Metropolol, U.V. Spectrophotometric analysis in bulk and pharmaceutical forms.

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Introduction:

β-adrenergic blocking drugs are presently used for the treatment of diseases characterised by excess sympathetic nervous acitivity. These illnesses range from cardiac arrhythmia, sinus tachycardia, angina pectoris, hypertension to migraine.

In this work, a direct UV spectrophotometric assay is adopted for four of such drugs; namely Timolol (I) (-)-1-(tert-butylamino)-3-[(4-morpholino-1,2,5 thiadiazol-3-yi)oxy]-2-propanol maleate, Carazolol (II) 1-(carbazol-4-yloxy)-3-(isopropylamino)-2-propanol, Pindolol (III) 1-(indol-4-yloxy)3-isopropylamino-2-propanol and Metropolol (IV) 1-isopropylamino-3-(p-(2 methoxyethylphenoxy)-2-propanol tartarate.

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Timolol (I) was determined in dosage form by adopting high-pressure liquid chromatography (HPLC)[1]; however, a gas liquid chromatographic (GLC[2]) and mass fragmentographic[3] methods were applied to assay the drug in biological fluids.

Carazolol (II) was also assayed by HPLC[8] and spectrofluorometric methods[9] whereas for Pindolol (III) nonaqueous titrimetric[4], GLC[5,6] and an indirect fluorometric[7] methods were adopted for its analysis in pharmaceutical forms and in biological fluids.

Metropolol was also assayed in biological fluids and in dosage forms by GLC methods[10].

The objective of this investigation is to develop a spectrophotometric assay for the four prementioned drugs in their pharmaceutical formulations. It was deemed of interest to adopt such procedure due to its well known simplicity, high accuracy and precission.

Experimental:

Apparatus:

The U.V. - visible spectrophotometer used in this study was model SP8-100, Pye Unicam Ltd, Cambridge, England.

Materials and Methods:

Materials:

Authentic timolol maleate (I) (Batch No. L-714-503-01T12) was kindly received from Merck Sharp & Dohme Research Laboratory, RAHWAY, N.J., U.S.A. Timolol eye-drops (Timptol(R)) preparation was purchased from local pharmacies. Authentic carazolol (II) sample (Batch No. 02-770-508076) and carazolol tablets (Conducton(R)) were kindly donated by KLINGE PHARMA GmbH & Co., West Germany. Authentic pindolol (III) sample used (Batch No. 80002) was the product obtained from

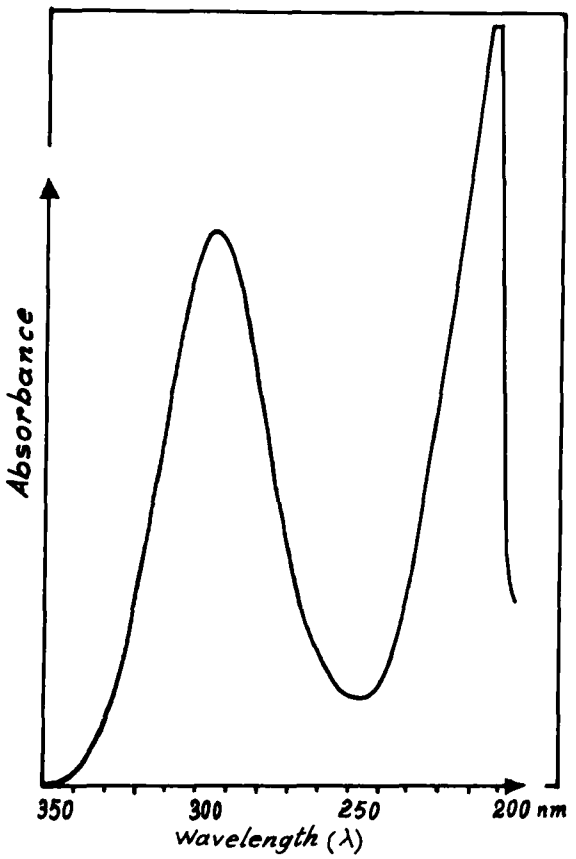


Fig.1 U.V. Absorption Spectrum of Timolol.

Sandoz Ltd., Basle, Switzerland. Pindolol tablets (Visken$^{(R)}$) were purchased from local market. Authentic metropolol tartrate (IV) (Batch No. 375) was granted by Hässle, Mölndal , Sweden. Metropolol tablets (Lopresor $^{(R)}$50) produced by Giegy (Ciba-Geigy Limited), Basle, Switzerland, were obtained from local market. Dilute hydrochloric acid solution (0.1 N) was used as solvent.

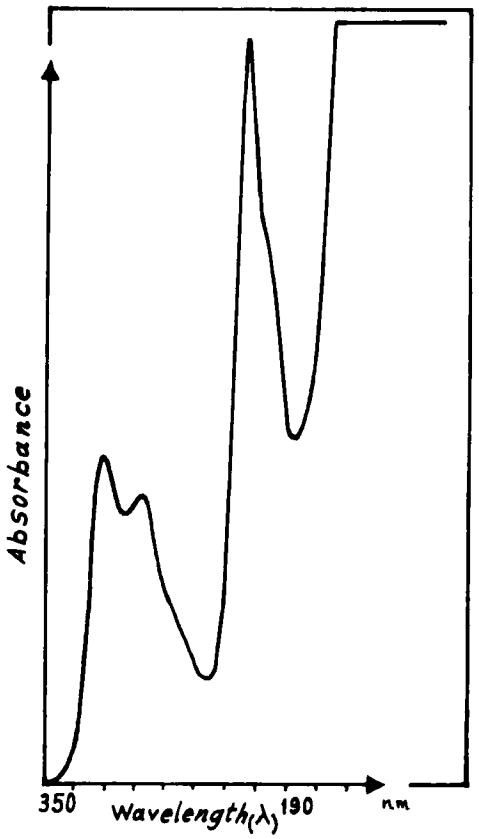


Fig. 2 U.V. Absorption Spectrum of Carazolol.

Methods:

(a) Preparation of Standard Stock Solution: From the authentic sample weigh accurately about 100 mg and dissolve in 100 ml 0.1 N - HCl using 100 ml - volumetric flasks.

(b) Sample Preparation: For tablets weigh accurately twenty tablets of each drug and calculate the average weight of tablet. Grind a satisfactory number of tablets, by trituration and weigh

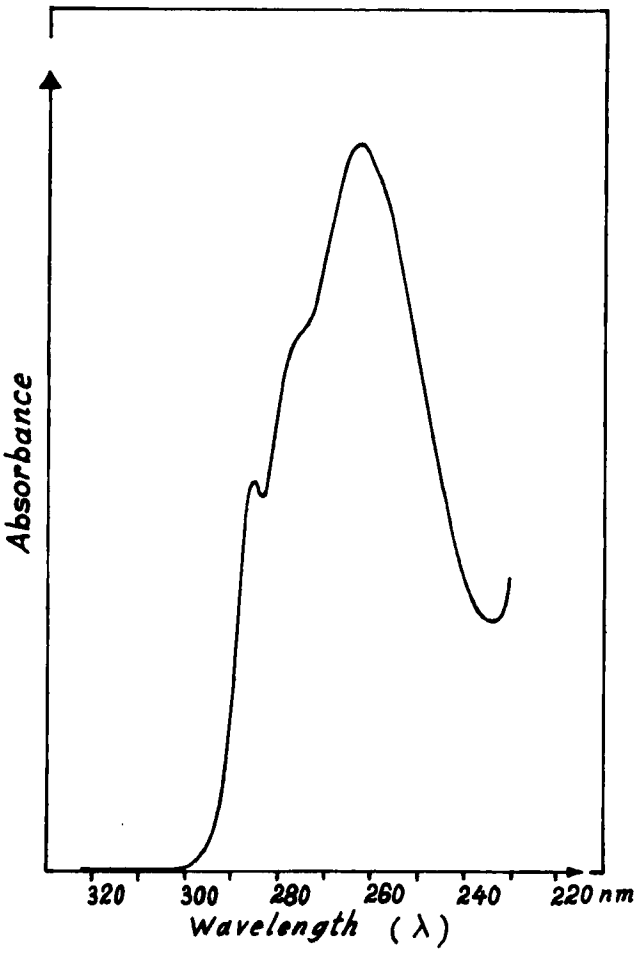


Fig. 3 U.V. Absorption Spectrum of Pindolol.

accurately aliquot portions of the powdered drug containing an amount of active ingredient ranging between 10 to 50 mg. Transfer quantitatively into 100 ml volumetric flasks; and add about 80 ml 0.1 N - HCl. Shake the suspension for about fifteen minutes and finally adjust to volume. Allow the system to settle down, and filter using Whatmann filter paper No. 5. Reject the first few millilitres of the filterate.

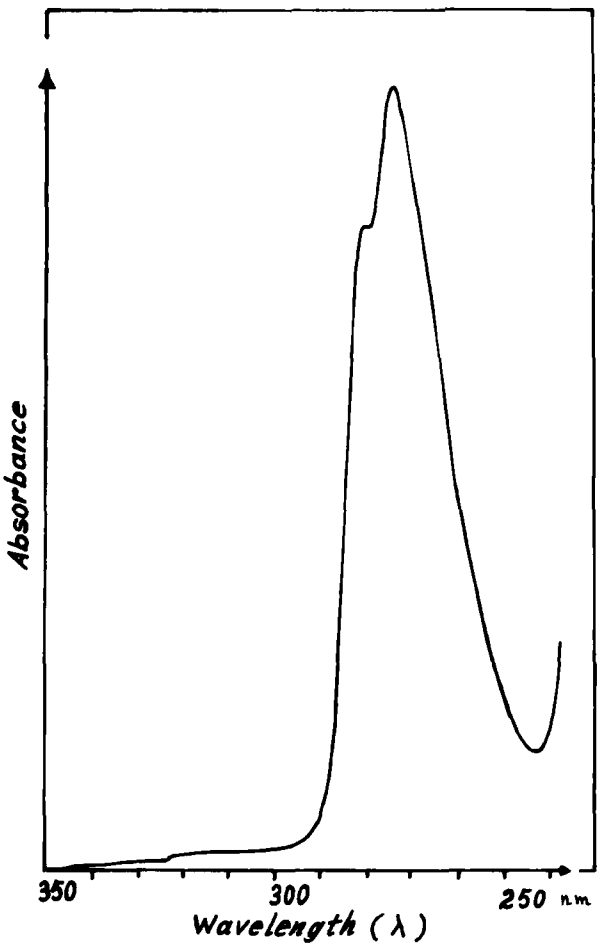


Fig. 4 U.V. Absorption Spectrum of Metoprolol.

Procedure

1. Absorption spectra of the compounds: Standard solutions of the authentic compounds in 0.1 N HCl (0.005% w/v) were scanned in the U.V. range (200-400 nm) and the spectra are given in Figs (1-4)- from which λmax (s) were deduced.
2. Establishment of calibration curves and calculation of $E^{1\%}_{1\ cm}$ for the compounds: Prepare a standard series of each drug in concent-

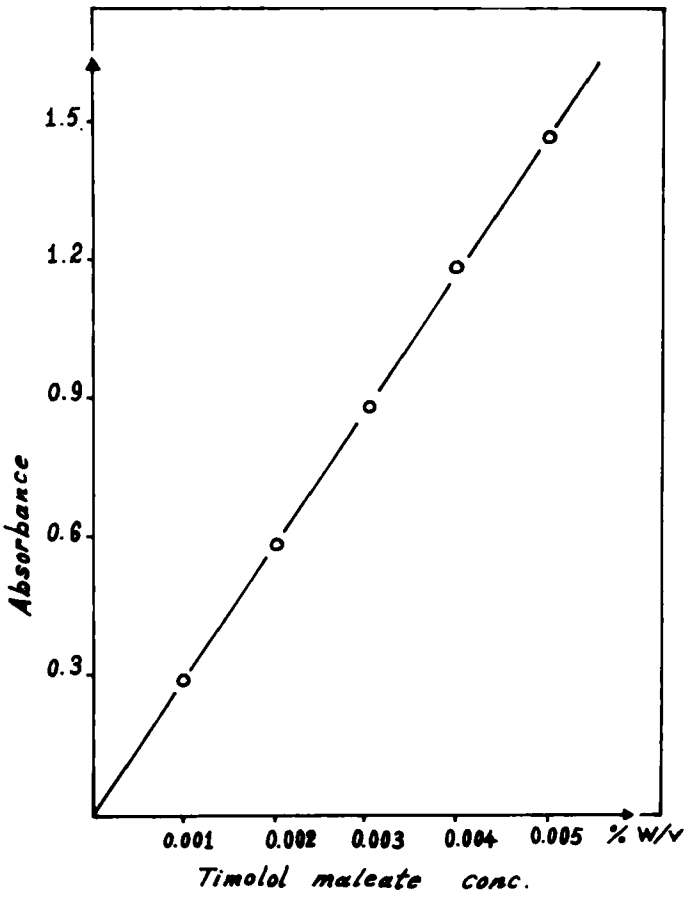


Fig. 5 Timolol maleate standard curve.

rations ranging between 0.001 to 0.005% w/v from the authentic stock solution, measuring the absorbances at the specified λmax for each drug. The results were plotted (Figs.5-8) and thus $E^{1\%}_{1\ cm}$ were calculated.

3. Spectrophotometric determinations: Measure the absorbance of a suitable aliquot of the prepared sample solutions each at its specific λmax and determine the percentage of the drug in the

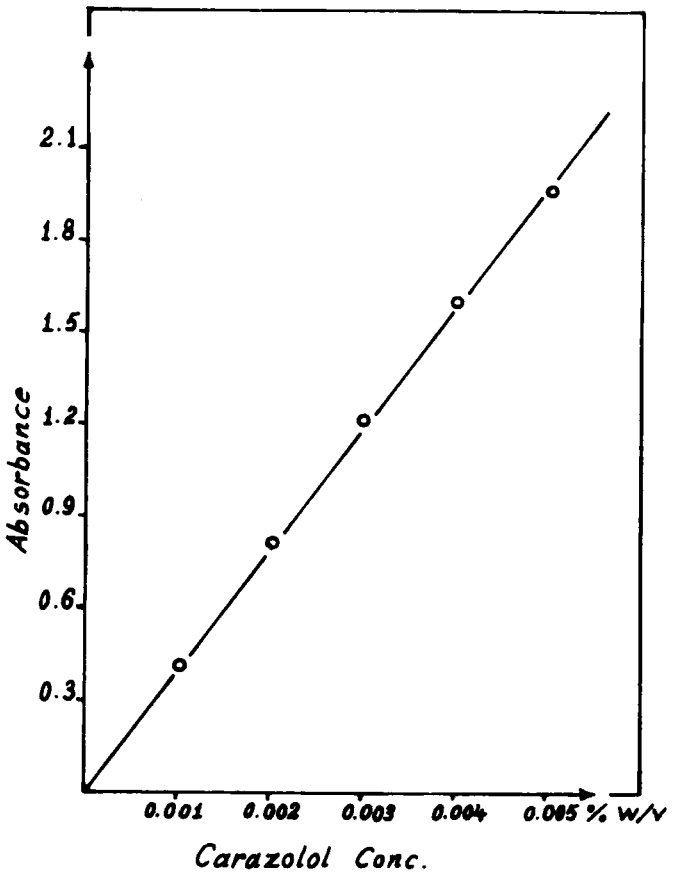


Fig.6 Carazolol standard curve.

tablets or eye-drops by adopting the following expression

$$\text{Percentage of the drug in dosage form} = \frac{E^{1\%}_{1\ cm} \text{ of authentic material}}{E^{1\%}_{1\ cm} \text{ of prepared solution from pharmaceutical form.}} \times 100$$

where the $E^{1\%}_{1\ cm}$ of the solution from the pharmaceutical formulation is calculated under the same conditions for the authentic material.

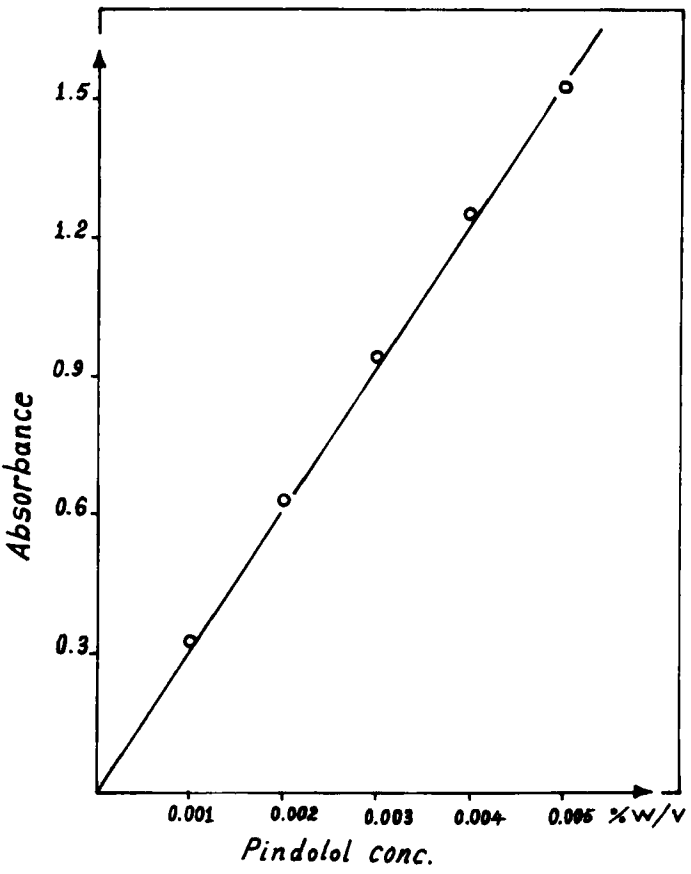


Fig.7 Pindolol Standard Curve.

Results and Discussion:

Timolol (I) is a thia 2,5-diazole derivative which has two Π - bonds conjugated to non-bonding electrons of nitrogen, sulphur and oxygen; and hence a relatively large bathochromic shift is observed.

The structural formulae of carazolol (II) and pindolol (III) consist of substituted heterocyclic aromatic rings. Carazolol (II) possesses a carbazole ring with more extended conjugated

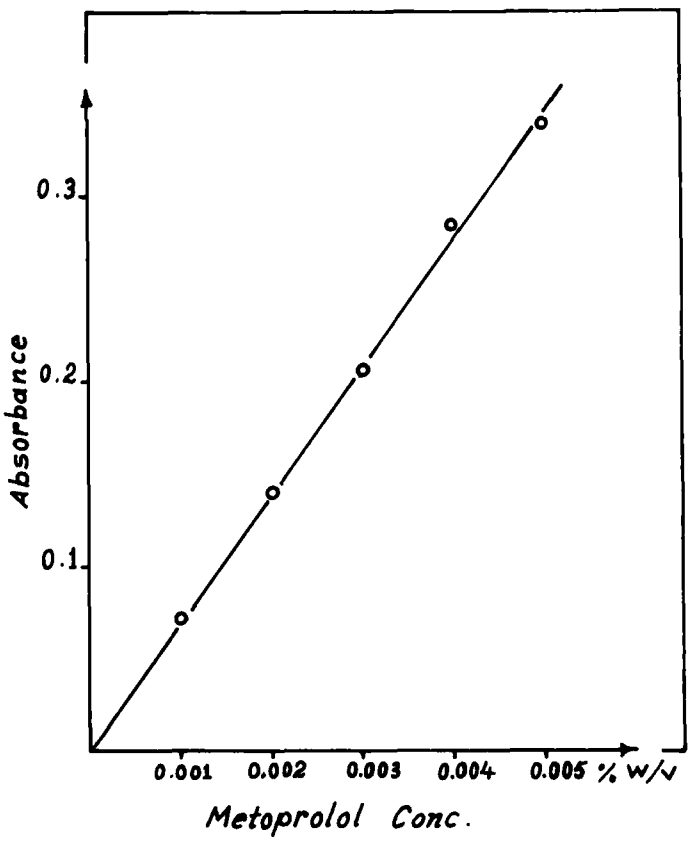
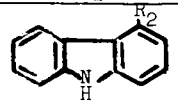
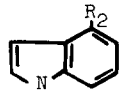
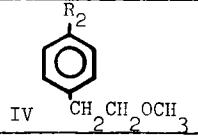


Fig. 8 Metoprolol tartrate standard curve.

chromophores than pindolol. This explains, at least partly, the bathochromic shifts relative to the secondary benzenoid band which possesses a λmax at about 255 nm.

Metropolol (IV) being a para-disubstituted derivative of benzene has λmax of 274 nm. This relative large bathochromic shift may be attributed[11] to the additive effects of the two para-substituents. Table (1) shows the molar absorptivities ranging between 2,900 - 12,000 indicating highest intensity of absorption for carazolol (II) whose structural formula has the most extended conjugated Π-bonds.

Table (1) Spectrophotometric Determination of Timolol, Carazolol, Pindolol and Metropolol.

Pharmaceutical Formulation	Structural Formula of compound	Working wavelength λnm	Molar absorptivity (ε)	$E^{1\%}_{1\ cm}$	Results* of Assay based on $E^{1\%}_{1\ cm}$	Results of Assay based on non-aqueous titrimetry
Timolol eye-drops (Timptolol(R) 0.5% w/v)	 I	294	11.4×10^3	294	99.1% ± 1.1	101.0%
Carazolol tablets (Conducton(R))	 II	284	12.0×10^3	403	98.8% ± 1.2	99.5%
Pindolol tablets (Visken(R))	 III	264	7.5×10^3	315	101.5% ± 2.1	98.2%
Metropolol tablets (Lopresor(R))	 IV	274	2.9×10^3	70	97.8% ± 0.6	97.5%

* The figure stands for a mean of six runs and standard deviation.

R_1 = O-CH_2-CHOH-CH_2-NHC$(CH_3)_3$

R_2 = O-CH_2-CHOH-CH_2-NHCH$(CH_3)_2$

The litrature in hands does not include spectrophotometric assays for the four compounds under investigation, and hence the purity of the authentic samples was assessed by adopting a non-aqueous potentiometric titration using predried samples and a standard 0.1 N aceteous perchloric acid as a titrant. The results of these assays are given in Table (1).

In order to elaborate standard curves, the absorbance readings were taken for concentrations ranging between 0.001 - 0.005% w/v and are given in Figs. (5-8) and adherence to absorption laws was clearly proved for such concentrations.

To obtain an average value of the $E^{1\%}_{1\ cm}$ for the authentic materials, three readings were taken for each of six individual concentrations in the linear part of the standard curve for each compound and the average $E^{1\%}_{1\ cm}$ was calculated accordingly.

The amounts of active ingredients per tablet in case of pindolol (Visken$^{(R)}$), carazolol (Conducton$^{(R)}$), metropolol (Lopresor$^{(R)}$) and timolol eye-drops (Timptolol eye-drops 0.5% w/v) were determined by calculation using the $E^{1\%}_{1\ cm}$ and the standard curve. The results based on the two methods agree closely; however the use of $E^{1\%}_{1\ cm}$ is simpler.

Timolol eye-drops contains benzalkonium chloride as a preservative in labelled concentration of 0.01% w/v. The U.V. - absorption spectrum of benzalkonium chloride in the concentration range involved in this analysis, does not show interference at 294 nm.

In conclusion the spectrophotometric method reported in this study for the assay pindolol tablets (Visken$^{(R)}$), carazolol tablets (Conducton$^{(R)}$), metropolol tablets (Lopresor$^{(R)}$) and timolol eye-drops (Timptolol 0.5% w/v) is simple, rapid and sensitive.

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