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Research

Formulation and in vitro evaluation of timolol maleate of sustained release matrix tablets by using different polymers

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Abstract

The main objective of present work was to formulate and evaluate sustained release matrix tablet of Timolol Maleate using different polymers like Fenugreek, Tamarind gum and Grewia Gum. Formulation of matrix tablets was prepared by using powder blend of different ratios of polymer to get desirable drug release profile. Direct compression method was used to formulate tablets. The evaluation of physical properties of tablet were done the in vitro drug release study was performed in 0.1N HCL for 2hours and in phosphate buffer PH 6.8 up to 10 hours. Evaluation parameters of formulated matrix tablets were hardness, friability, thickness, drug content, weight variation and the in vitro drug release rate pattern results indicated that the formulation F5 was the most promising formulation as the drug release from this formulation was high compared to other formulations. In formulation F5 percentage drug release of Timolol Maleate sustained release was 99.64 % 12hrs.

Keywords: Timolol Maleate, Fenugreek, Tamarind gum and Grewia Gum

INTRODUCTION

Now a day's conventional dosage forms of drugs are rapidly being replaced by the new and the novel drug delivery systems. Amongst, these the controlled release/sustained release dosage forms have been extremely popular in modern therapeutics. Matrix system is the release system which prolongs and controls the release of the drug, which is dissolved or dispersed. A matrix is defined as a well-mixed composite of one or more drugs with gelling agent i.e. hydrophilic polymers. Introduction of matrix tablet as sustained release (SR) has given a new breakthrough for novel drug delivery system in the field of Pharmaceutical technology[1.] Sustained release constitutes any dosage from that provides medication over an extended time or denotes that the system is able to provide some actual therapeutic control whether this is of a temporal nature, spatial nature or both. Sustained release system generally do not attain zero order type release and usually try to mimic zero order release by providing drug in a slow first order[2.] Repeat action table are an alternative method of sustained release in which multiple doses of drug are an alternative method of sustained release, in which, multiple doses are contained within a dosage form and each dose is released at a periodic interval[13.] Sustained release dosage forms provide a

better control of plasma drug levels, less dosage frequency, less side effect, increased efficacy and constant delivery. There are certain consideration for the preparation of extended release formulations:

- ✓ If the active compound has a long half-life, it is sustained on its own,
- ✓ If the pharmacological activity of the active is not directly related to its blood levels,
- ✓ If the absorption of the drug involves an active transport and
- ✓ If the active compound has very short half-life then it would require a large amount of drug to maintain a prolonged effective dose.

The above factors need serious review prior to design.

Introduction of matrix tablet as sustained release (SR) has given a new breakthrough for novel drug system in the field of Pharmaceutical technology[4]. It excludes complex production procedures such as coating and Pelletization during manufacturing and drug release rate from the dosage form is controlled mainly by type and proportion of polymer used in the preparations. Hydrophilic polymer matrix is widely used for formulating an SR dosage form. Because of increased complication and expense involved in marketing of new drug entities, has focused greater attention on development of sustained release or controlled release drug delivery systems. Matrix systems are widely used for the purpose of sustained release. It is the release system which prolongs and controls the release of the drug that is dissolved or dispersed[5].

In fact, a matrix is defined as a well-mixed composite of one or more drugs with gelling agent i.e. hydrophilic polymers. By the sustained release method therapeutically effective concentration can be achieved in the system circulation over an extended period of time, thus achieving better compliance of patients. Numerous SR oral dosage forms such as membrane controlled system, matrices with water soluble/insoluble polymer or waxes and osmotic system have been developed, intense research has recently focused on the designation of SR systems for poorly water soluble drugs.

Rational for extended release dosage forms

Some drugs are inherently long lasting and require only once-a-day oral dosing to sustain adequate drug blood levels and the desired therapeutic effect. These drugs are formulated in the conventional manner in immediate release dosage forms. However, many other drugs are not inherently long lasting and require multiple daily dosing to achieve the desired therapeutic results. Multiple daily dosing is inconvenient for the patient and can result in missed doses, made up doses and noncompliance with the regimen[6,7]. When conventional immediate-release dosage forms are taken on schedule and more than once daily, they cause sequential therapeutic blood level peaks and valleys (troughs) associated with the taking of each dose. However, when doses are not administered on schedule, the resulting peaks and valleys reflect less than optimum drug therapy. For example, if doses are administrated too frequently, minimum toxic concentrations of drug may be reached, with toxic side effects resulting. If doses are missed, periods of sub therapeutic drug blood levels or those below the minimum effective concentration may result, with no benefit to the patient. Extended release tablets and capsules are commonly taken only once or twice daily, compared with counterpart conventional forms that may have to be taken three or four times daily to achieve the same therapeutic effect.

MATERIALS

Timolol Maleate-Procured From Mylan, Hyderabad. Provided by SURA LABS, Dilsukhnagar, Hyderabad, Fenugreek- Elder Pharmaceuticals Pvt Ltd, Dehradun (India), Tamarind gum -Elder Pharmaceuticals Pvt Ltd, Dehradun (India), Grewia Gum -Elder Pharmaceuticals Pvt Ltd, Dehradun (India), PVP k30-Merck Specialities Pvt Ltd, Mumbai, India, Talc-Merck Specialities Pvt Ltd, Mumbai, India, Magnesium Stearate-S.D. Fine Chem. Ltd. Mumbai, MCC-S.D. Fine Chem. Ltd. Mumbai.

METHODOLOGY

Analytical method development

Determination of Wavelength

10mg of pure drug was dissolved in 10ml methanol (primary stock solution - 1000 µg/ml). From this primary stock solution 1 ml was pipette out into 10 ml volumetric flask and made it up to 10ml with the media (Secondary stock solution – 100µg/ml). From secondary stock solution again 1ml was taken it in to another volumetric flask and made it up to 10 ml with media (working solution - 10µg/ml). The working solution was taken for determining the wavelength.

Determination of Calibration Curve

10mg of pure drug was dissolved in 10ml methanol (primary stock solution - 1000 µg/ml). From this primary stock solution 1 ml was pipette out into 10 ml volumetric flask and made it up to 10ml with the media

(Secondary stock solution – 100µg/ml). From secondary stock solution required concentrations were prepared and those concentrations absorbance were found out at required wavelength.

Pre formulation parameters

The quality of tablet, once formulated by rule, is generally dictated by the quality of physicochemical properties of blends. There are many formulations and process variables involved in mixing and all these can affect the characteristics of blends produced. The various characteristics of blends tested as per Pharmacopoeia.

Angle of repose

The frictional force in a loose powder can be measured by the angle of repose. It is defined as, the maximum angle possible between the surface of the pile of the powder and the horizontal plane. If more powder is added to the pile, it slides down the sides of the pile until the mutual friction of the particles producing a surface angle, is in equilibrium with the gravitational force. The fixed funnel method was employed to measure the angle of repose. A funnel was secured with its tip at a given height (h), above a graph paper that is placed on a flat horizontal surface. The blend was carefully pored through the funnel until the apex of the conical pile just touches the tip of the funnel. The radius (r) of the base of the conical pile was measured. The angle of repose was calculated using the following formula:

$\tan \theta = h / r$ $\tan \theta$ = Angle of repose

h = Height of the cone,

r = Radius of the cone base

Bulk density

Density is defined as weight per unit volume. Bulk density, is defined as the mass of the powder divided by the bulk volume and is expressed as gm/cm^3. The bulk density of a powder primarily depends on particle size distribution, particle shape and the tendency of particles to adhere together. Bulk density is very important in the size of containers needed for handling, shipping, and storage of raw material and blend. It is also important in size blending equipment. 10 gm powder blend was sieved and introduced into a dry 20 ml cylinder, without compacting. The powder was carefully leveled without compacting and the unsettled apparent volume, Vo, was read.

The bulk density was calculated using the formula:

Bulk Density = M / V_o

Where, M = weight of sample

V_o = apparent volume of powder

Tapped density

After carrying out the procedure as given in the measurement of bulk density the cylinder containing the sample was tapped using a suitable mechanical tapped density tester that provides 100 drops per minute and this was repeated until difference between succeeding measurement is less than 2 % and then tapped volume, V measured, to the nearest graduated unit. The tapped density was calculated, in gm per L, using the formula:

Tap = M / V

Where, Tap= Tapped Density

M = Weight of sample

V= Tapped volume of powder

Measures of powder compressibility

The Compressibility Index (Carr's Index) is a measure of the propensity of a powder to be compressed. It is determined from the bulk and tapped densities. In theory, the less compressible a material the more flowable it is. As such, it is measures of the relative importance of interparticulate interactions. In a free- flowing powder, such interactions are generally less significant, and the bulk and tapped densities will be closer in value. For poorer flowing materials, there are frequently greater interparticle interactions, and a greater difference between the bulk and tapped densities will be observed. These differences are reflected in the Compressibility Index which is calculated using the following formulas:

Carr's Index = $[(tap - b) / tap] \times 100$

Where, b = Bulk Density

Tap = Tapped Density

Formulation development of Tablets

All the formulations were prepared by direct compression. The compositions of different formulations are given in Table 7.3.The tablets were prepared as per the procedure given below and aim is to prolong the release of Timolol Maleate. Total weight of the tablet was considered as 120 mg.

Procedure

- Timolol Maleate and all other ingredients were individually passed through sieve no ≠ 60.
- All the ingredients were mixed thoroughly by triturating up to 15 min.
- The powder mixture was lubricated with talc.
- The tablets were prepared by using direct compression method.

Table 1: Formulation composition for tablets

Ingrediants	TM1	TM2	TM3	TM4	TM5	TM6	TM7	TM8	TM9
Timolol Maleate	20	20	20	20	20	20	20	20	20
Fenugreek	20	40	60	-	-	-	-	-	-
Tamarind gum	-	-	-	20	40	60	-	-	-
Grewia Gum	-	-	-	-	-	-	20	40	60
PVP k30	6	6	6	6	6	6	6	6	6
Talc	6	6	6	6	6	6	6	6	6
Magnesium stearate	3	3	3	3	3	3	3	3	3
MCC	65	45	25	65	45	25	65	45	25
Total weight	120	120	120	120	120	120	120	120	120

All the quantities were in mg

RESULTS AND DISCUSSION

The present study was aimed to developing Sustained release tablets of Timolol Maleate using various polymers. All the formulations were evaluated for physicochemical properties and *in vitro* drug release studies.

Analytical Method

Graphs of Timolol Maleate were taken in 0.1N HCl and in pH 6.8 phosphate buffer at 294 nm and 296 nm respectively.

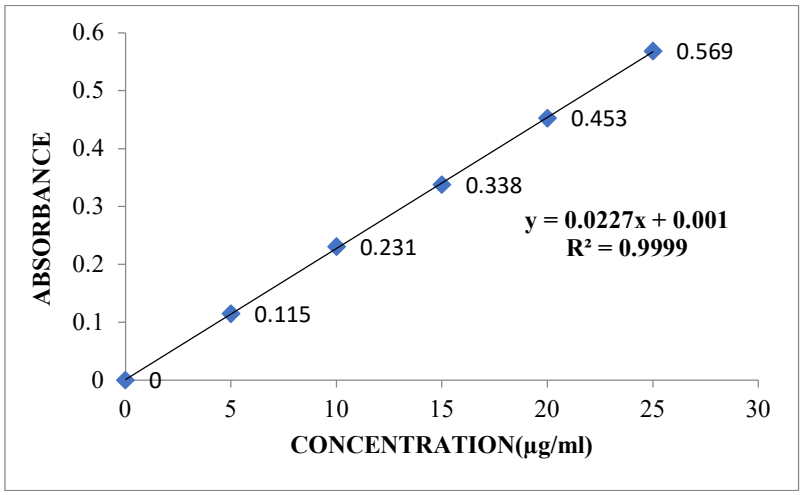

Fig 1: Standard graph of Timolol Maleate in 0.1N HCl (294nm)

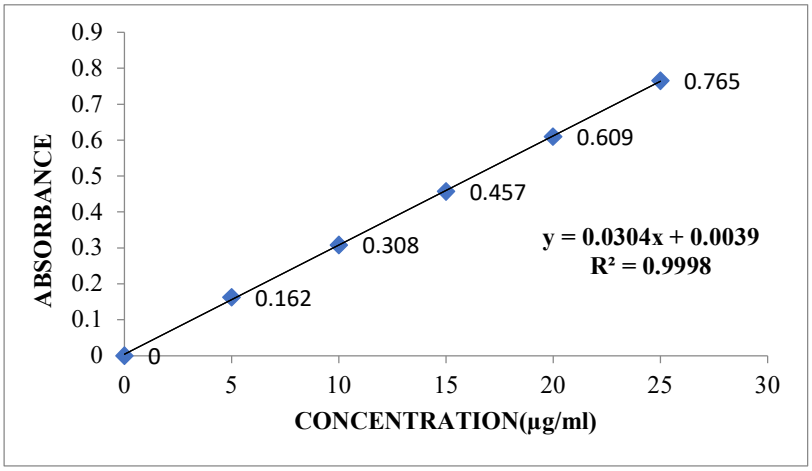

Fig 2: Standard graph of Timolol Maleate pH 6.8 phosphate buffer (296 nm)

Preformulation parameters of powder blend

Table 2: Pre-formulation parameters of Core blend

Formulation Code	Angle of Repose	Bulk density (gm/ml)	Tapped density (gm/ml)	Carr's index (%)	Hausner's Ratio
TM1	19.29	0.434	0.497	12.67	1.14
TM2	26.43	0.375	0.442	15.15	1.17
TM3	30.45	0.386	0.473	18.39	1.22
TM4	28.73	0.362	0.428	15.42	1.18
TM5	29.58	0.331	0.393	15.77	1.18
TM6	28.19	0.559	0.649	13.94	1.16
TM7	26.42	0.439	0.521	15.73	1.18
TM8	24.77	0.488	0.537	9.12	1.10
TM9	26.43	0.412	0.483	14.69	1.17

Tablet powder blend was subjected to various pre-formulation parameters. The angle of repose values indicates that the powder blend has good flow properties. The bulk density of all the formulations was found to be in the range of 0.331 to 0.559 (gm/cm3) showing that the powder has good flow properties. The tapped density of all the formulations was found to be in the range of 0.393 to 0.649 showing the powder has good flow properties. The compressibility index of all the formulations was found to be below 25 which show that the powder has good flow properties. All the formulations has shown the hausner ratio below 1.333 indicating the powder has good flow properties.

Quality Control Parameters For tablets

Tablet quality control tests such as weight variation, hardness, and friability, thickness, and drug release studies in different media were performed on the compression coated tablet.

Table 3: *In vitro* quality control parameters for tablets

Formulation codes	Average weight(mg)	Hardness(kg/cm2)	Friability (%loss)	Thickness (mm)	Drug content (%)
TM1	119.24	2.75	0.43	1.58	98.49
TM2	118.38	2.83	0.38	1.62	99.38
TM3	121.22	2.61	0.41	1.43	97.22
TM4	122.08	2.81	0.25	1.73	98.52
TM5	120.12	2.59	0.21	1.54	99.12
TM6	119.31	2.67	0.36	1.69	98.69
TM7	120.56	2.77	0.28	1.58	97.48

TM8	118.93	2.74	0.33	1.67	99.38
TM9	121.42	2.67	0.38	1.61	98.35

Weight variation test

Tablets of each batch were subjected to weight variation test, difference in weight and percent deviation was calculated for each tablet and was shown in the Table 8.4. The average weight of the tablet is approximately in range of 118.38 to 122.08 mg, so the permissible limit is ±7.5% (>120 mg). The results of the test showed that, the tablet weights were within the pharmacopoeia limit.

Hardness test

Hardness of the three tablets of each batch was checked by using Pfizer hardness tester and the data's were shown in Table 8.4. The results showed that the hardness of the tablets is in range of 2.59 to 2.83 kg/cm^2, which was within IP limits.

Thickness

Thickness of three tablets of each batch was checked by using Micrometer and data shown in Table-8.4. The result showed that thickness of the tablet is raging from 1.43 to 1.73 mm.

Friability

Tablets of each batch were evaluated for percentage friability and the data were shown in the Table 8.4. The average friability of all the formulations was less than 1% as per official requirement of IP indicating a good mechanical resistance of tablets.

Drug content

Drug content studies were performed for the prepared formulations. From the drug content studies it was concluded that all the formulations were showing the % drug content values within 97.22 - 99.38 %. All the parameters such as weight variation, friability, hardness, thickness and drug content were found to be within limits.

***In-Vitro* Drug Release Studies**

Table 4: Dissolution Data of Timolol Maleate Tablets

TIME(Hrs)	TM1	TM2	TM3	TM4	TM5	TM6	TM7	TM8	TM9
0	0	0	0	0	0	0	0	0	0
0.5	09.12	14.83	17.52	12.72	18.49	15.37	11.24	19.42	21.44
1	12.22	18.62	24.48	19.94	27.42	24.51	22.52	26.83	23.76
2	17.34	25.47	33.33	26.88	35.05	32.17	26.64	32.68	29.84
3	22.31	31.63	42.74	33.43	42.79	37.80	34.77	38.03	35.98
4	28.08	37.88	48.61	44.77	53.52	42.98	42.68	43.62	39.79
5	35.12	46.69	55.11	52.74	58.33	49.79	48.89	52.92	45.14
6	39.68	53.42	62.48	59.15	62.16	54.53	51.38	57.65	52.25
7	47.43	59.18	68.26	65.24	71.87	63.05	58.74	64.97	54.37
8	56.35	62.22	74.35	72.44	79.54	72.23	63.59	72.58	68.67
9	64.92	71.72	82.07	78.21	88.37	81.55	69.47	77.86	73.83
10	77.26	85.53	88.66	84.71	92.34	84.16	73.18	86.48	81.67
11	83.35	91.68	93.19	93.43	96.51	89.43	79.69	91.79	88.48
12	89.72	94.83	97.62	98.22	99.64	95.37	85.31	95.27	92.24

From the dissolution data it was evident that the formulations prepared with Fenugreek as polymer were retard the drug release up to desired time period i.e., 12 hours and showed maximum of (TM3) 97.62 % in 12 hours with good retardation. From the dissolution data it was evident that the formulations prepared with Tamarind gum as polymer were retard the drug release up to desired time period i.e., 12 hours and showed maximum of (TM5) 99.64 % in 12 hours with good retardation. From the dissolution data it was evident that the formulations prepared with Grewia Gum as polymer were retard the drug release up to desired time period i.e., 12 hours and showed maximum of (TM8) 95.27 % in 12 hours with good retardation. Among all 9 formulations TM5 formulation showed good drug permeation from the patch. Among all *in vitro* evaluation parameters TM5 formulation passed all evaluation parameter.

Application of Release Rate Kinetics to Dissolution Data

Various models were tested for explaining the kinetics of drug release. To analyze the mechanism of the drug release rate kinetics of the dosage form, the obtained data were fitted into zero-order, first order, Higuchi, and Korsmeyer-Peppas release model.

Table 5: Release Rate Kinetics to Dissolution Data

CUMULATIVE(%) RELEASE Q	TIME (T)	ROOT (T)	LOG(%) RELEASE	LOG (T)	LOG (%) REMAIN	RELEASE RATE (CUMULATIVE % RELEASE / t)	1/CUM% RELEASE	PEPPAS log Q/100	% Drug Remaining	Q01/3	Qt1/3	Q01/3-Qt1/3
0	**0**	0			2.000				100	4.642	4.642	0.000
18.49	0.5	0.707	1.267	-0.301	1.911	36.980	0.0541	-0.733	81.51	4.642	4.336	0.306
27.42	1	1.000	1.438	0.000	1.861	27.420	0.0365	-0.562	72.58	4.642	4.171	0.470
35.05	2	1.414	1.545	0.301	1.813	17.525	0.0285	-0.455	64.95	4.642	4.020	0.622
42.79	3	1.732	1.631	0.477	1.757	14.263	0.0234	-0.369	57.21	4.642	3.853	0.788
53.52	4	2.000	1.729	0.602	1.667	13.380	0.0187	-0.271	46.48	4.642	3.595	1.046
58.33	5	2.236	1.766	0.699	1.620	11.666	0.0171	-0.234	41.67	4.642	3.467	1.175
62.16	6	2.449	1.794	0.778	1.578	10.360	0.0161	-0.206	37.84	4.642	3.357	1.284
71.87	7	2.646	1.857	0.845	1.449	10.267	0.0139	-0.143	28.13	4.642	3.041	1.600
79.54	8	2.828	1.901	0.903	1.311	9.943	0.0126	-0.099	20.46	4.642	2.735	1.907
88.37	9	3.000	1.946	0.954	1.066	9.819	0.0113	-0.054	11.63	4.642	2.266	2.376
92.34	10	3.162	1.965	1.000	0.884	9.234	0.0108	-0.035	7.66	4.642	1.971	2.670
96.51	11	3.317	1.985	1.041	0.543	8.774	0.0104	-0.015	3.49	4.642	1.517	3.125
99.64	12	3.464	1.998	1.079	-0.444	8.303	0.0100	-0.002	0.36	4.642	0.711	3.930

Drug – Excipient compatability studies

Fourier Transform-Infrared Spectroscopy

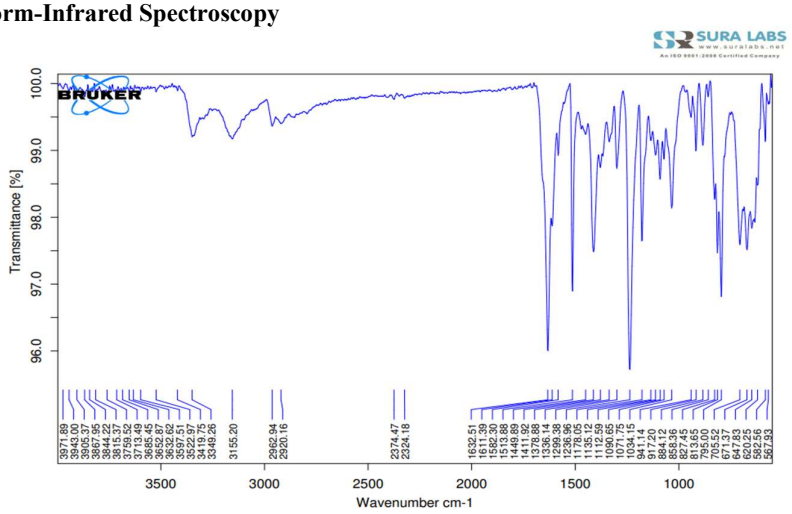

Fig 3: FT-TR Spectrum of Timolol Maleate pure drug.

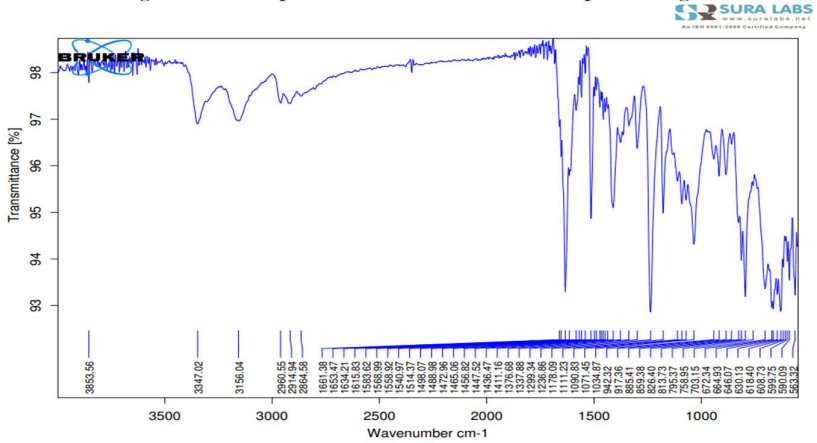

Fig 4: FT-IR Spectrum of Optimised Formulation

From the FTIR data it was evident that the drug and excipients doses not have any interactions. Hence they were compatible.

CONCLUSION

The ultimate aim of the present study was to prepare sustained release Matrix tablets of Timolol Maleate using Different polymers Like Fenugreek ,Tamarind gum and Grewia Gum. They were prepared by direct compression method. The sustained release drug delivery was a promising approach to achieve a prolonged therapeutic action of drug. The amount of drug release for optimized F5 was found to be 99.64 %. The cumulative percentage drug was decreased by increase in polymer concentration. Physiochemical characteristics were used to assess the prepared tablet. The physiochemical analysis of the tablet reveals a white colour, a round smooth look. The formulation F5 as an optimized formulation because of this batch showed satisfactory results of the tablets parameter. Result of in vitro % drug release profile an indicated that formulation F5 was the most promising formulations as the drug release from this formulation was high a compared to other formulations.

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