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RESEARCH ARTICLE

Evaluation Optimized Chewing Gum Formulations against Commercial Chlorpheniramine Maleate Tablet Formulation

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ABSTRACT

Oral route is most convenient for the patient, therefore, it is very popular in the society. Chewing gum delivery system is convenient, easy to administer anywhere, anytime and is pleasantly tasting, making it patient acceptable. It is a novel drug delivery system containing masticatory gum base with pharmacologically active ingredient and intended to use for local treatment of mouth diseases or systemic absorption through oral mucosa. Chewing gum is the convenient and effective means of rapidly administering chlorpheniramine maleate (CPM), as it is readily soluble, permeable, and used to relieve symptoms of allergy, hay fever, and common cold. In the present study, medicated chewing gum of CPM has been formulated using gum base, sorbitol, mannitol, magnesium stearate, lecithin, and menthol. This medicated chewing gum was prepared by direct compression method and formulated using various compositions of gum base and lecithin such as 30–35–40% and 5–10–15% accordingly. In the formulation, soya lecithin was used as a plasticizer and it was found that it acted on the drug release to some extent. When concentration of soya lecithin was increased, drug release was also found to be increased.

Keywords: Chlorpheniramine maleate, sorbitol, mannitol, magnesium stearate

INTRODUCTION

Medicated chewing gums are solid, single-dose preparations with a base consisting mainly of gum that is intended to be chewed but not swallowed. They contain one or more active substances which are released by chewing and are intended to be used for local treatment of mouth diseases or systemic delivery after absorption through the buccal mucosa. Medicated chewing gum is a novel drug delivery system containing masticatory gum base with pharmacologically active ingredient and intended to use for local treatment of mouth diseases or systemic absorption through oral mucosa. Chewable tablets and chewing gum have been very well received by the parents for use in children with full dentition. Children in particular may consider chewing gum as a more preferred method of drug administration compared with oral liquids and tablets; hence, attempt is made to prepare medicated chewing gum to increase compliance. The use of medicated chewing gum is feasible in local treatment of diseases of oral cavity as well as treatment of systemic conditions. Chewing gum has been used for centuries to clean the mouth and freshen the breath. The first patent for the production of chewing gum was filed in 1869 and was issued to WF Semple in Ohio under US patent no. 98,304. A medicated chewing gum containing acetyl salicylic acid was commercially introduced in 1928. In 1991, chewing gum was approved as a term for pharmaceutical dosage form by the Commission of European Council.[1]

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Chlorpheniramine maleate (CPM) is a histamine H1 antagonist used in allergic reactions, hay fever, rhinitis, urticaria, and asthma. It has also been used in veterinary applications. One of the most widely used of the classical antihistaminics, it generally causes less drowsiness and sedation than promethazine. The mechanism of the action of CPM is, it binds to the histamine H1 receptor. This blocks the action of endogenous histamine, which subsequently leads to temporary relief of the negative symptoms brought on by histamine. Chlorpheniramine is a histamine H1 antagonist (or more correctly, an inverse histamine agonist) of the alkylamine class. It competes with histamine for the normal H_1-receptor sites on effector cells of the gastrointestinal tract, blood vessels, and respiratory tract. It provides effective, temporary relief of sneezing, watery and itchy eyes, and runny nose due to hay fever and other upper respiratory allergies.[2] The CPM is available in tablet and syrup form. The half-life of CPM is 21–27 h, so need to be formulated into fast release formulation. The protein binding of drug is 72%.[3]

MATERIALS AND METHODS

The CPM was obtained as a gift sample from Meditab Ltd., Satara. Lecithin was obtained as a gift sample from Perfect Laboratories, Nagpur. Gum base was obtained as a gift sample from Cafosa SPA, Spain. All other chemicals and solvents used were of analytical grade.[4]

Method of preparation

Direct compression method was used to prepare the chewing gum tablet. Weighed quantity of gum base powder and active ingredient was mixed well in mortar the ratio of different materials have been shoen in Table 1. To it, accurately weighed soya lecithin, sorbitol, and L-menthol were added. The sorbitol was added as sweetening agent.[5] After thorough mixing, the lubricant and glidant were also mixed. The powder was compressed into tablets using flat faced punches of 15 mm diameter by keeping hardness between 1 and 2 kg/cm^2 using 12 station multitooling tablet compression machine (Rimerk II Karnavati Engg. Ltd., Ahmedabad, India).

Identification of chlorpheniramine

Melting point of CPM was determined by microcontrolled based melting point apparatus (Chemiline-CL 726). The temperature at which the drug started melting was noted. Average of three results was noted as the melting point of drug. λ_{max} determination ultraviolet (UV) spectrum of pure CPM was taken in phosphate buffer solution (PBS) of pH 6.4 as per procedure described in I.P. 2007. Drug (10 mg) was dissolved in 100 ml PBS pH 6.4 to obtain the stock solution of concentration 100 μg/ml.[6] From this stock solution, 1 ml was withdrawn and diluted to 10 ml. Absorbance was checked using UV spectrophotometer. It gives one peak corresponding to its λ_{max} at 261 nm.

Calibration curve of CPM in PBS pH 6.4

Calibration curve of CPM has been carried out in PBS pH 6.4. Ten milligrams of drug were dissolved in 100 ml of dissolution medium to obtain stock solution of concentration 100 μg/ml. From this, 1 ml, 2 ml, 3 ml, 4 ml, 5 ml, 6 ml, and 7 ml aliquots were withdrawn and diluted to 10 ml to give the solutions of concentration 10–70 μg/ml. Absorbances were recorded at 261 nm using UV spectrophotometer (Pharmaspec 1700, Shimadzu, Japan) and standard curve was plotted and values of slope, intercept, and coefficient of correlation were calculated.

Infrared (IR) spectroscopy

IR study was carried out to check purity of drug. It was determined by Fourier transform IR (FTIR) spectrophotometer (FTIR Alpha E Bruker, Germany). The baseline correction was done by blank background measurement. The scanning range was 400–4000 cm^{-1}.

Differential scanning calorimetry (DSC)

Thermograms of pure CPM, physical mixture, and optimized formulation were recorded using Mettler-Toledo DSC 821e instrument equipped with an intracooler (Mettler-Toledo, Switzerland). Samples were sealed in aluminum pans and heated

at the rate of 10°C/min from 30°C to 300°C under nitrogen atmosphere of flow rate 10 ml/min.

RESULTS AND DISCUSSION

Melting point

Melting point was checked using capillary method. It was found to be in the range of 130–135°C which is close to the melting point of the drug (133°C).

λ_{max} determination

The standard solution of CPM of concentration 10 g/ml showed maximum absorbance of 0.1549 at 261 nm wavelength in PBS pH 6.4.[7] shown in Figure 1.

Calibration curve of CPM

The Beer–Lambert law was found to be obeyed over the range of 0–70 µg/ml.

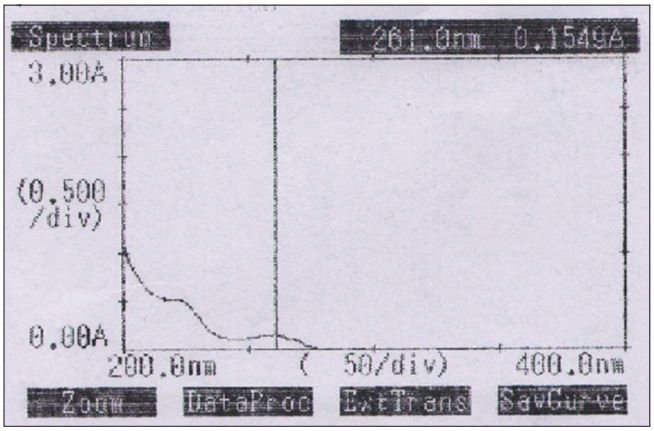

Figure 1: UV spectrum of chlorpheniramine maleate in PBS pH 6.4

FTIR spectroscopy

The FTIR spectrum of pure CPM, physical mixtures, and optimized formulation is shown in Figure 3. To determine possible interaction between drugs with carrier, FTIR was used. The CPM shows characteristic peak of N-H stretching vibration at 2350.92^{cm-1}, C=O stretching 1697.92^{cm-1}, C=N stretch 1576.97^{cm-1}, carboxylate 1353.31^{cm-1}, and maleate 860.78^{cm-1} shown in Figures 2 and 3. The FTIR spectra of optimized formulation showed same peak as that of pure drug CPM. From FTIR spectra, it was observed that there was no any incompatibility between drug and carrier.[8]

DSC

The DSC curves obtained for pure CPM and optimized formulation are shown in Figure. DSC analysis of crystalline CPM showed single sharp endothermic peak at 134.13°C correspondence to its melting point. It is revealed from DSC thermogram of optimized formulation showed sharp endothermic peak at 133.25°C correspondence to melting point of pure drug. From both of the DSC thermogram, it was concluded that there was no any interaction between drug entity and excipients[9] shown in Figures 4 and 5.

Evaluation of powder blends

Bulk densities of powder blends were found between 0.47 and 0.58 g/ml.[10,11] Tap densities of powder blends were found between 0.55 and

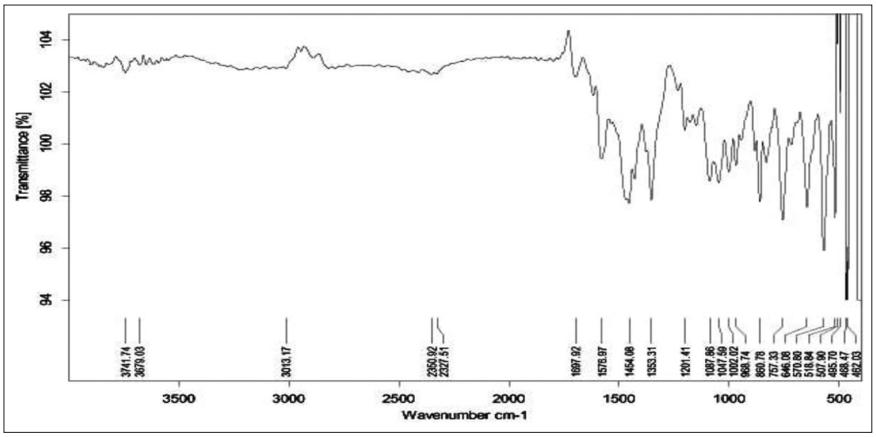

Figure 2: Infrared of optimized formulation (F3)

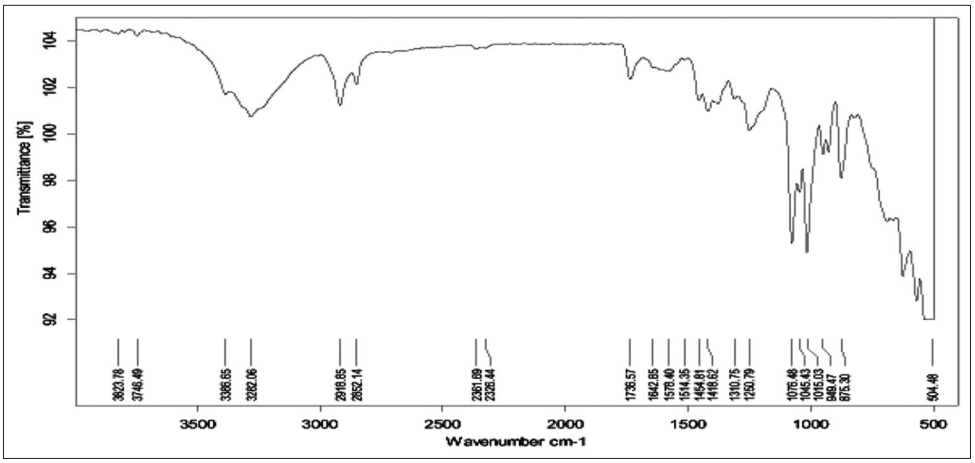

Figure 3: Infrared of pure chlorpheniramine maleate

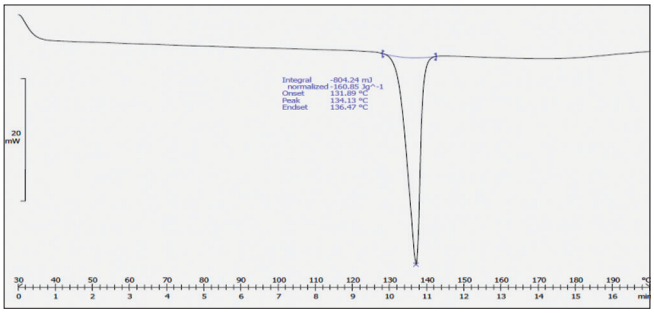

Figure 4: Differential scanning calorimetry of chlorpheniramine maleate

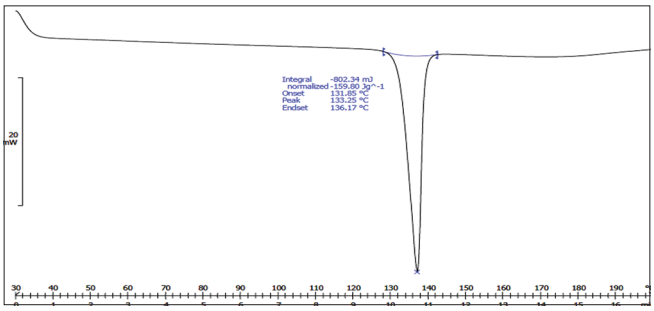

Figure 5: Differential scanning calorimetry of optimized formulation

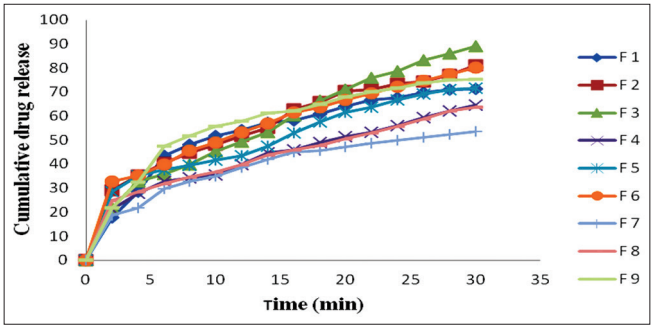

Figure 6a: %Cumulative drug release of various formulations

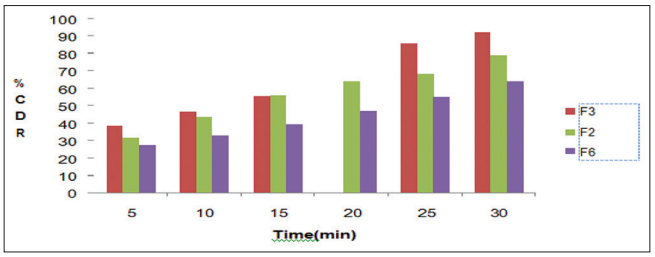

Figure 6b: % Cumulative drug release profiles of optimized formulations

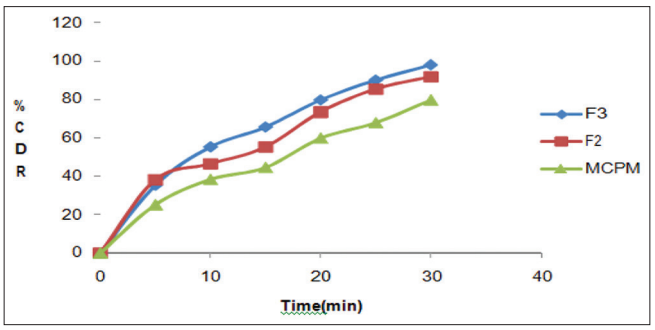

Figure 6c: Comparison of % cumulative drug release profiles of optimized formulations with marketed formulation

0.66 g/ml. The angle of repose values varied from 20.75° to 24.07°. Carr's index values varied from 10.06% to 15.02%. From these values, it was observed that all these blends had good flow properties[12,13] the results are shown in Table 2 and Figure 6b and 6c.

In vitro drug release

The medicated chewing gum tablet mainly consisted of gum base, active ingredient,

Table 1: Ingredients of medicated chewing gum tablets

Ingredient	Formulations*								
	F1	F2	F3	F4	F5	F6	F7	F8	F9
Chlor. maleate	10	10	10	10	10	10	10	10	10
Gum base	300	300	300	350	350	350	400	400	400
Sorbitol	400	400	400	400	400	400	400	400	400
Lecithin	250	250	300	200	250	300	200	250	300
L-menthol	10	10	10	10	10	10	10	10	10
Mannitol	200	200	150	200	150	100	150	100	50
Mg. stearate	10	10	10	10	10	10	10	10	10
Aerosil	10	10	10	10	10	10	10	10	10
Sodium Saccharin	10	10	10	10	10	10	10	10	10
Total	1200	1200	1200	1200	1200	1200	1200	1200	1200

Table 2: Evaluation of powder blend (F1–F9)

Batch	Bulk density (g/cc)	Tapped density (g/cc)	Carr's index (%)	Hausner's ratio	Angle of repose (θo)
F1	0.5867±0.0023	0.6883±0.0023	12.21±0.64	1.13±0.008	21.3±0.32
F2	0.5540±0.0017	0.6236±0.0023	11.17±0.05	1.12±0.0006	23.39±1.38
F3	0.5013±0.0012	0.59±0.0017	15.02±0.05	1.17±0.0007	24.07±0.005
F4	0.5860±0.0035	0.6696±0.0023	12.49±0.71	1.14±0.009	20.75±0.56
F5	0.5540±0.0071	0.6243±0.0011	11.26±0.11	1.12±0.001	23.46±1.28
F6	0.4767±0.0012	0.5536±0.0015	13.90±0.44	1.16±0.0059	23.23±0.44
F7	0.5270±0.0017	0.5860±0.0034	10.06±0.83	1.11±0.010	22.66±1.03
F8	0.5890±0.0017	0.6646±0.0023	11.38±0.28	1.12±0.003	23.37±0.704
F9	0.5496±0.0017	0.5866±0.0023	10.51±0.05	1.11±0.0007	23.63±1.004

Table 3: Cumulative % drug release of formulations F1–F9

Time	F1	F2	F3	F4	F5	F6	F7	F8	F9
0	0±0	0±0	0±0	0±0	0±0	0±0	0±0	0±0	0±0
2	17.83±0.46	29.33±0.46	21.90±0.61	21.22±0.18	28.42±0.47	37.87±0.28	18.65±0.18	24.92±0.49	21.75±0.48
4	28.50±0.44	35.33±0.23	32.82±0.32	28.00±0.20	35.20±0.25	35.17±0.21	21.83±1.05	28.60±0.26	32.42±0.41
6	43.37±0.55	40.40±0.26	35.80±0.18	32.62±0.24	37.60±0.09	39.72±0.25	29.65±0.18	31.85±0.13	47.30±0.53
8	47.93±0.13	44.78±0.30	39.77±0.24	34.40±0.05	39.43±0.30	42.65±0.28	22.62±0.24	34.50±0.20	51.85±0.10
10	51.80±0.22	47.95±0.66	45.15±0.18	35.50±0.30	41.52±0.30	48.98±0.21	35.03±0.24	36.60±0.33	55.72±0.19
12	54.03±0.13	51.82±0.61	49.25±0.19	39.73±0.13	43.33±0.29	53.27±0.38	38.68±0.36	39.67±0.33	57.95±0.13
14	57.22±0.28	55.18±0.47	53.20±0.15	44.65±0.23	47.58±0.35	56.78±0.23	41.87±0.23	43.80±0.35	61.13±0.30
16	58.28±0.08	62.78±0.29	60.33±0.25	45.82±0.13	53.03±0.25	61.48±0.21	44.85±0.17	47.78±0.43	62.22±0.10
18	60.93±0.23	65.85±0.18	65.52±0.20	49.02±0.13	57.55±0.25	63.68±0.16	45.65±0.10	47.62±0.31	64.83±0.23
20	64.10±0.18	70.28±0.15	71.00±0.38	51.42±0.13	61.23±0.13	66.78±0.25	47.10±0.15	50.50±0.18	68.03±0.20
22	66.63±0.14	71.07±0.20	75.92±0.15	53.22±0.15	63.48±0.13	69.53±0.26	48.68±0.13	53.05±0.33	70.40±0.13
24	67.63±0.58	73.55±0.15	78.68±0.38	55.92±0.26	66.72±0.18	72.27±0.23	49.88±0.10	55.75±0.18	71.45±0.28
26	69.78±0.18	74.32±0.10	83.25±0.20	59.48±0.43	69.10±0.13	74.52±0.16	50.98±0.20	58.62±0.14	73.72±0.18
28	70.87±0.18	77.05±0.18	85.92±0.37	62.15±0.18	70.90±0.20	77.30±0.25	52.40±0.13	62.17±0.19	74.93±0.26
30	71.38±0.08	81.00±0.40	88.98±0.18	64.45±0.35	71.55±0.10	80.07±0.38	53.43±0.34	63.73±0.18	75.30±0.10

plasticizer, sweetening agent, and flavoring agent. In the present formulations,[14] we have varied the concentrations of the gum base and lecithin which act as a base and plasticizer, respectively. All formulations were non sticky in nature. However, the formulation F3 released the drug more than

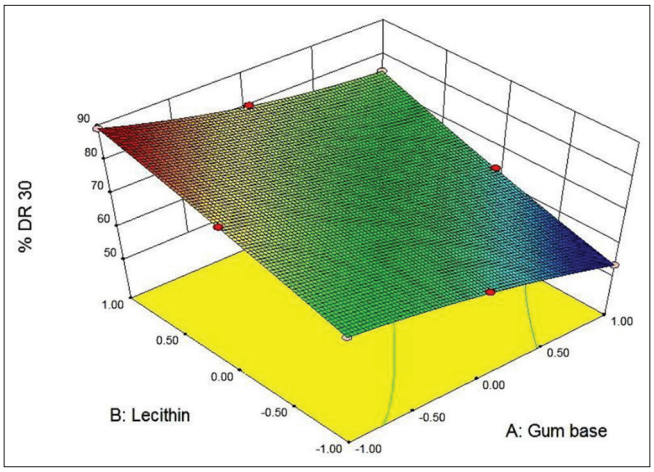

Figure 7: Response 3-D surface plot for percent drug release at 30 min

85% shown in Table 3. This was due to the softness of the formulation F3 developed during the *in vitro* dissolution study[13] shown in Figure 6a, Formulation F3 contained highest amount of soya lecithin and less amount of base. The drug release from various formulations was found to be in the range of 53.43–88.98%. It was found to be least for F1 having the least concentration of both the base and the plasticizer, whereas it was found to be maximum in F3 in which the concentration of both base and the plasticizer was found to be optimum. From the *in vitro* drug release data, it was observed that an increase in the concentration of softener may reduce the hardness of the chewing gum tablet also it was observed that the increase in the concentration of plasticizer and decrease in the concentration of base may increase drug release from formulation.

SUMMARY AND CONCLUSION

In the present work, biting gum definitions were ready in the tablet structure by utilizing lecithin and gum base. This property is fundamental for the biting gum base since it dispenses with the chance of disintegration of gum base in salivation. From the outcomes got in this work, it very well may be presumed that engineered gum base can be utilized as an astounding specialist for detailing of biting gum. For tablet plans, all examinations such as tenacity, weight variety, friability, and *in vitro* discharge test were performed. Every one of the definitions was discovered to be agreed for weight variety and consistency of dynamic substance tests. It was additionally tracked down that the biting gum tablets were not friable which affirmed the uprightness of the definition. *In vitro* discharge test was performed utilizing adjusted breaking down contraption for tablet. From the *in vitro* drug discharge information, it was presumed that medication discharge from the biting gum tablet was agreeable. In the definition, soya lecithin was utilized as a plasticizer and it was discovered that it followed up on the medication delivery partially. At the point, when grouping of soya lecithin was expanded, drug discharge was additionally discovered to be expanded.

FUTURE ANTICIPATION

Moreover, medicated chewing gum can be a desire for kids as chewing gum is fairly customary on this age group. Medicated chewing gum needs to of path be taken into consideration as a drug shipping device and the equal precautions need to be taken as for different shipping systems. Children (>5 years old) might also additionally select chewing gum as a course of drug management than oral beverages or tablets. The use of medicated chewing gum is viable as a nearby remedy of sicknesses or numerous situations of the oral cavity. From a pharmaceutical and medical factor of view, medicated chewing gum will also be an exciting drug shipping device in comparison with the conventional methods of management. There is a unique hobby in acquiring systemic impact by way of medicated chewing gum that till now has best has been hooked up in nicotine remedy for smoking cessation. In the future, new medicated chewing gums are anticipated and can function a manner of drug management.

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