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HIGH PERFORMANCE LIQUID CHROMATOGRAPHIC ANALYSIS AND DISSOLUTION OF DEXTROPROPOXYPHENE NAPSYLATE WITH OTHER ANALGESICS IN CAPSULE FORMULATIONS

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ABSTRACT

A reversed phase high-performance liquid chromatographic method was developed for simultaneous quantitation of dextropropoxyphene napsylate in three different formulations. The first contains caffeine and aspirin while the others are combinations with acetaminophene. The mobile phase consisted of acetonitrile (30%) in acetate buffer. The assay was carried at 280nm wavelength. The method is precise and does not require sample manipulation prior to analysis. The applicability of the assay procedure in studying dissolution rate of capsule formulations is described.

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INTRODUCTION

Dextropropoxyphene is a mild analgesic structurally related to narcotic methadone. The safety of the drug was a subject to considerable concern, since death following ingestion of quantities slightly larger than the recommended therepeutic dose was reported (1). Dextropropoxyphene is used in pharmaceutical formulations either as napsylate or hydrochloride salt. Combinations of this drug with other mild analgesics like aspirin, caffeine and acetaminophene are commercially available. Various methods were reported for the quantitative analysis of dextropropexyphene (2). The USP XXI recommends non-aqueous titration for the drug alone and gas chromatography for it's combination with other analgesics (3). Pharmacokinetic studies of propoxyphene were carried out by GLC (4,5). High performance liquid chromatographic methods were reported for the determination of diastereomeric purity (6,7), and quantitative determination using ion-pair procedure (8).

The analytical method described in this report involves the use of reverse phase high performance liquid chromatography for the quantitation of dextropropoxyphene napsylate (I) in the presence of other analgesics. Three different capsule formulations were used, the first contained aspirin and caffeine,

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while the others were a combination of (I) and acetaminophene in different concentrations. The procedure was used foı the determination of dissolution rates of (I), aspirin, caffeine and acetaminophene in their respective capsule formulations.

EXPERIMENTAL

Apparatus: A Beckman chromatographic system consisted of the following components: 114A pump, injection head with 10µl sample loop and a variable wave length detector 165, which was connected to spectraphysics integrator 4270. The column used was 5 micron Altex Ultrasphere^{R} C-18, provided with a guard column.

Chemicals and Reagents: Dextropropoxyphene napsylate, aspirin, caffeine, acetaminophene and acetanilide were of pharmacopeial standards. Acetonitrile was HPLC grade (J.T. Baker, U.S.A.). Water was glass distilled and demineralized. Sodium acetate was analar grade (BDH, Pool, Dorset, U.K.).

Chromatographic Conditions: The mobile phase used consisted of 0.0IM Sodium acetate buffer adjusted to pH 4.0, mixed with acetonitrile (30%), flowing at a rate of 1 ml/min. Injection volume was 10µl, and detection was carried at 280nm. The mobile phase was always filtered using 0.45µ membrane filters and degassed by refluxing prior to use.

Dosage Forms: Three commercially available capsule

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dosage forms designated as A, B, and C were used. The label on each indicates the following composition.

A: Dextropropoxyphene napsylate (I) 50mg, Caffeine 30mg and Aspirin 375mg.

B: Dextropropoxyphene napsylate (I) 50mg, and Acetaminophene 325mg.

C: Dextropropoxyphene napsylate (I) 100mg and Acetaminophene 325mg.

Preparation of Standard Solutions:

a. Internal standard solution: 0.2 mg/ml solution of acetanilide in mobile phase was prepared and stored in a tightly covered flask. One ml aliqcutes were added to assay solution before injection.

b. Standard solution for linearity: The concentrations of stock solutions for (I), aspirin, caffeine and acetaminophene were 0.1 mg/ml, 0.5 mg/ml, 0.03 mg/ml and 0.1 mg/ml respectively. Appropriate volumes were measured and diluted to 10 ml after the addition of 1 ml of the internal standard solution. The linearity was established over concentration ranges utilized in the assay procedure.

Sample Preparation:

a. Content Uniformity: The content of individual capsules were emptied, weighed and crushed. An amount equivalent to 1/4th the weight of one capsule contents was weighed accurately. The powder was dissolved in

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25 ml of the mobile phase and sonicated for 5 minutes to assure complete dissolution. The concentration of (I) in A and B capsule solutions was 0.5 mg/ml and double the value (1 mg/ml) in solution C. For capsule B and C acetaminophene concentration was 3.25 mg/ml. The concentration of aspirin and caffeine (Capsule A solution) were 3.75 mg/ml and 0.3 mg/ml, respectively. Dilutions were carried by pipetting 2 ml of solution A and 1 ml of solutions B and C into 10 ml volumetric flasks. The volume was completed to the mark with the mobile phase. Further dilution was carried by measuring 2 ml of each solution, adding 1 ml of the internal standard solution (0.2 mg/ml) and completing the volume to 10 ml with the mobile phase, injection volume was 10 µl.

b. Average: The average weight of individual capsule contents was calculated by weighing the contents of ten capsules. The powder was mixed thoroughly. The weight equivalent to 1/4th the average weight was measured and subjected to the same procedure reported under content uniformity.

c. Recovery from Spiked Samples: The weight equivalent to 1/4th the capsule contents was weighed out of mixed powder representing 10 capsule contents. To the powder, the indicated amounts of pure components were added, the resulting powder was dissolved in 25 ml of the mobile

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phase and the assay procedure was repeated as indicated for the content uniformity.

Determination of Dissolution Rate: Pharmacopeial method for determining dissolution rate for both combinations were followed (USP XXI). The dissolution media for dosage form A was 500 ml of acetate buffer (0.05M), the pH was adjusted to 4.5 with acetic acid. For dosage forms B and C, 700 ml of the same dissolution medium were used. At defined time intervals, 5 ml were withdrawn and replaced by buffer solution. Of this volume, 4 ml, 3 ml, and 2 ml were taken for dosage forms A, B and C respectively, 1 ml of internal standard solution was added to each flask and the volume was completed to 10 ml with mobile phase. 10µl was injected. Standard solutions were prepared by dissolving one capsule (A) in 500 ml of buffer and one capsule of each B and C, in 700 ml of buffer, solutions were sonicated to ensure 100% dissolution. Assay procedure was carried as described above.

Calculations: Standards of equivalent concentrations were prepared, the ratio of the peak area of each component to that of the internal standard was calculated (R_a). The same ratio was calculated for the standard solution (R_s).

$$\text{Percent recovery} = \frac{R_a}{R_s} \times 100$$

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Assay and standard solutions were injected sequentially. Standard solutions for dissolution rate determination were prepared on the assumption of 100% release.

RESULTS AND DISCUSSION

Pharmacopeial method for the analysis of (I) in combination dosage forms involves extraction and sample manipulation before carrying a gas chromatographic analysis. By using reverse phase HPLC the sample preparation was reduced to a minimum. The method would therefore be more suitable for quality control purposes. Dosage forms containing weakly acidic components, along with neutral or weakly basic components, were analysed. The buffer used for the separation was 0.01M acetate buffer, the pH was adjusted to 4.0. Raising the pH to 7.0 did not effect elution times or resolution pattern considerably. Acetonitrile (30%) was used as a cosolvent. One of the problems in carrying the analysis was the wide variation in the concentrations of dosage form compositions. The detection wave length was set at 280nm which seemed to be a compromise wave length where all components could be analysed simultaneously. The choice of internal standard (acetanilide) was based on it's similarity in structure with other analgesics analysed and it's reproducible peak under the chromatographic conditions. Typical chromatograms for both combinations are shown in Figure 1. Acetanilide eluted

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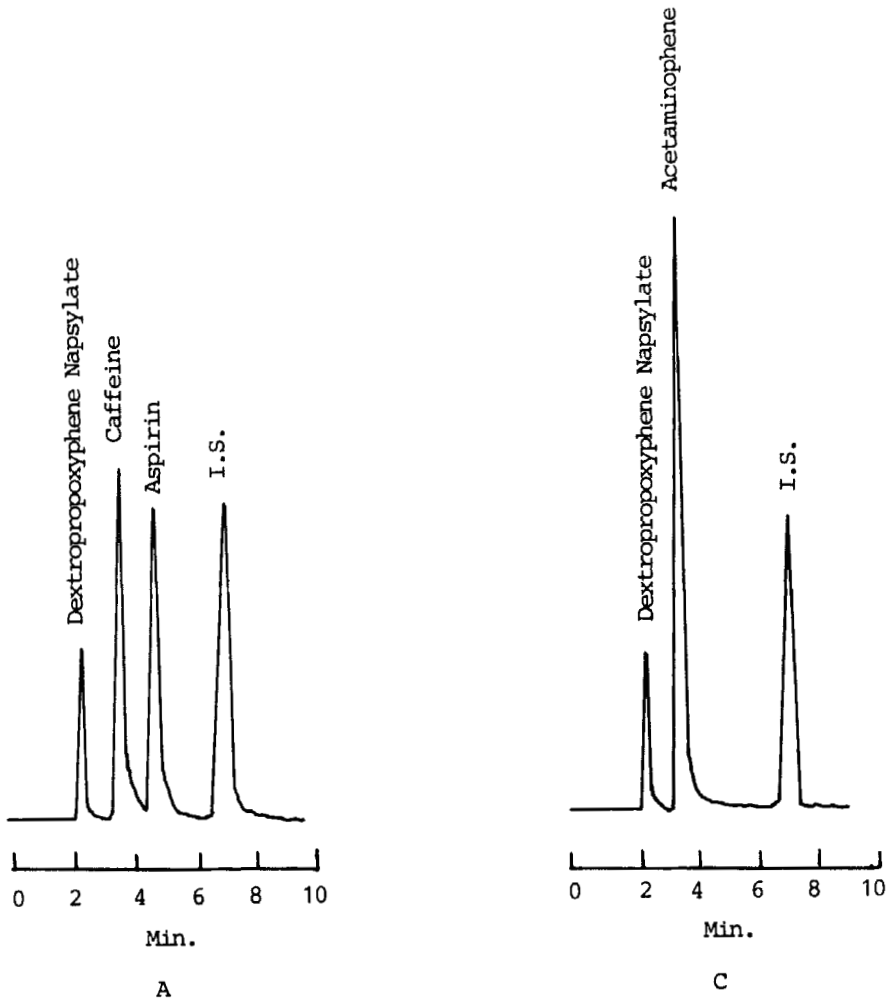

FIGURE 1

Typical chromatograms of dosage forms A and C. Dextropropoxyphene napsylate (0.02 mg/ml) caffeine (0.012 mg/ml), aspirin (0.15 mg/ml) and acetaminophene (0.065 mg/ml).

at 7.1 ± 0.02 minutes after the latest component, aspirin (Rt 5.25). Delayed elution of internal standard offers the advantage of further utilization of the analytical procedure for other combinations. Table 1 shows Rt values for several drugs using similar chromatographic conditions.

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TABLE 1

Retention Times of Dosage Forms Components and Other Drugs Under the Described Chromatographic Conditions

Drug	Rt (min)
Dextropropoxyphene napsylate	2.45 ± 0.05
Aspirin	5.25 ± 0.03
Caffeine	3.67 ± 0.03
Acetaminophene	3.49 ± 0.02
Salicylic acid	4.4 ± 0.03
Salicylamide	9.37 ± 0.02
Chlorpheneramine maleate	2.1 ± 0.05
Indomethacine	2.73 ± 0.01
Pseudoephedrine HCl	9.41 ± 0.02

TABLE 2

Statistical Data for the Calibration Curves of Dextropropoxyphene, Caffeine, Aspirin and Acetaminophene

Drug (mg/ml)	Correlation Coefficient	Slope	Intercept
Dextropropoxyphene Napsylate (0.01-0.05)	0.999	9.701	-0.005
Caffeine (0.003-0.015)	0.996	56.919	0.114
Aspirin (0.1-0.3)	0.999	4.116	-0.221
Acetominophene (0.03-0.07)	0.999	17.624	-0.033

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TABLE 3

Content Uniformity of Dextropropoxyphene Napsylate, Caffeine and Aspirin Expressed as % of Label Claim.

(Dosage Form A)

Capsule No.	Dextropropoxyphene Napsylate	Caffeine	Aspirin
1	100.43	100.97	103.25
2	100.75	100.53	100.63
3	101.02	101.39	100.95
4	100.91	99.75	101.78
5	99.63	101.68	100.05
6	100.34	100.08	102.61
7	99.57	100.09	100.23
8	100.53	102.70	100.58
9	100.05	100.63	101.07
10	101.07	100.12	100.98

To determine the linearity of the detector response, standard solutions of drugs used in the analysis were prepared as described in the text. Ratios of peak areas vs concentrations were plotted. Statistical data for calibration curves are shown in Table 2.

The recent pharmacopeial requirement (3) for content uniformity testing is to analyse for content when the active material comprises 50% or less of the total

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TABLE 4

Content Uniformity of Dextropropoxyphene Napsylate and Acetaminophene, Expressed as % of Label Claim (Dosage Form B, C).

Capsule No.	Dextropropoxyphene Napsylate		Acetaminophene	
	B	C	B	C
1	101.35	99.95	100.35	101.05
2	100.62	100.13	100.77	100.81
3	100.75	100.66	102.33	101.35
4	102.11	101.88	105.09	100.99
5	101.29	100.30	103.43	102.12
6	100.63	102.37	100.98	103.60
7	100.95	100.08	101.59	99.22
8	100.81	101.12	103.31	101.85
9	103.69	98.45	100.43	100.97
10	100.33	100.55	102.91	98.73

weight, Consequently, the analytical procedure was applied to determine the content uniformity of (I) and other analgesics. Percentage recoveries for individual capsules are listed in Tables 3 and 4. Additionally, samples corresponding to the average weight of capsule were analysed and the percentage recoveries of label

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TABLE 5

Analysis of Dextropropoxyphene Napsylate, Caffeine, Aspirin and Acetaminophene in Average Weight (Dosage Form A, B, C)

	Mean* (% Label Claim)	S.D.	% C.V.
Dextropropoxyphene Napsylate			
A	99.926	± 0.9609	± 0.9616
B	100.543	± 0.7677	± 0.7635
C	100.731	± 0.9010	± 0.8945
Acetaminophene			
B	100.460	± 0.5115	± 0.5091
C	100.757	± 0.8192	± 0.8131
Caffeine			
A	100.481	± 0.4086	± 0.4066
Aspirin			
A	100.074	± 0.5816	± 0.5812

* An average of 8 determinations.

claim are presented in Table 5 for the three capsule formulations.

The accuracy of the method was tested by adding known amounts of each components to the powder formula-

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TABLE 6

Recovery of Dextropropoxyphene Napsylate, Caffeine and Aspirin from Spiked Samples (Dosage Form A)

	% Recovery[a]
Dextropropoxyphene (mg added)	
6	100.517 ± 0.5542
12	100.497 ± 0.4077
18	100.576 ± 0.7187
Caffeine (mg added)	
6	100.561 ± 0.5362
8	100.247 ± 0.3661
10	100.341 ± 0.4526
Aspirin (mg added)	
25	100.509 ± 0.4164
50	100.427 ± 0.4379
75	100.286 ± 0.5207

[a]Mean ± % C.V. for 8 determinations

tion. Recovery from spiked samples were determined and % C.V. was calculated. The low values of C.V. ranging from 0.366 to 1.087 indicate the reproducibility of the method,(Table 6 and 7).

To investigate the possibility of using the analytical method for quality control purposes, the

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TABLE 7

Recovery of Dextropropoxyphene Napsylate, and Acetaminophene from Spiked Samples (Dosage Form B, C)

		% Recovery[a]	
		B	C
Dextropropoxyphene Napsylate Amount Added (mg)			
B	C		
12	6	100.663 ± 0.5712	100.543 ± 0.5899
18	12	99.911 ± 0.6929	100.821 ± 0.7052
24	18	101.003 ± 1.087	100.291 ± 0.7294
Acetaminophene Amount Added (mg)			
B	C		
10	5	100.382 ± 0.4628	100.595 ± 0.7764
20	10	100.157 ± 0.6550	100.631 ± 0.5431
30	15	100.262 ± 0.8828	100.567 ± 0.5324

[a]Mean ± % C.V. for 8 determinations.

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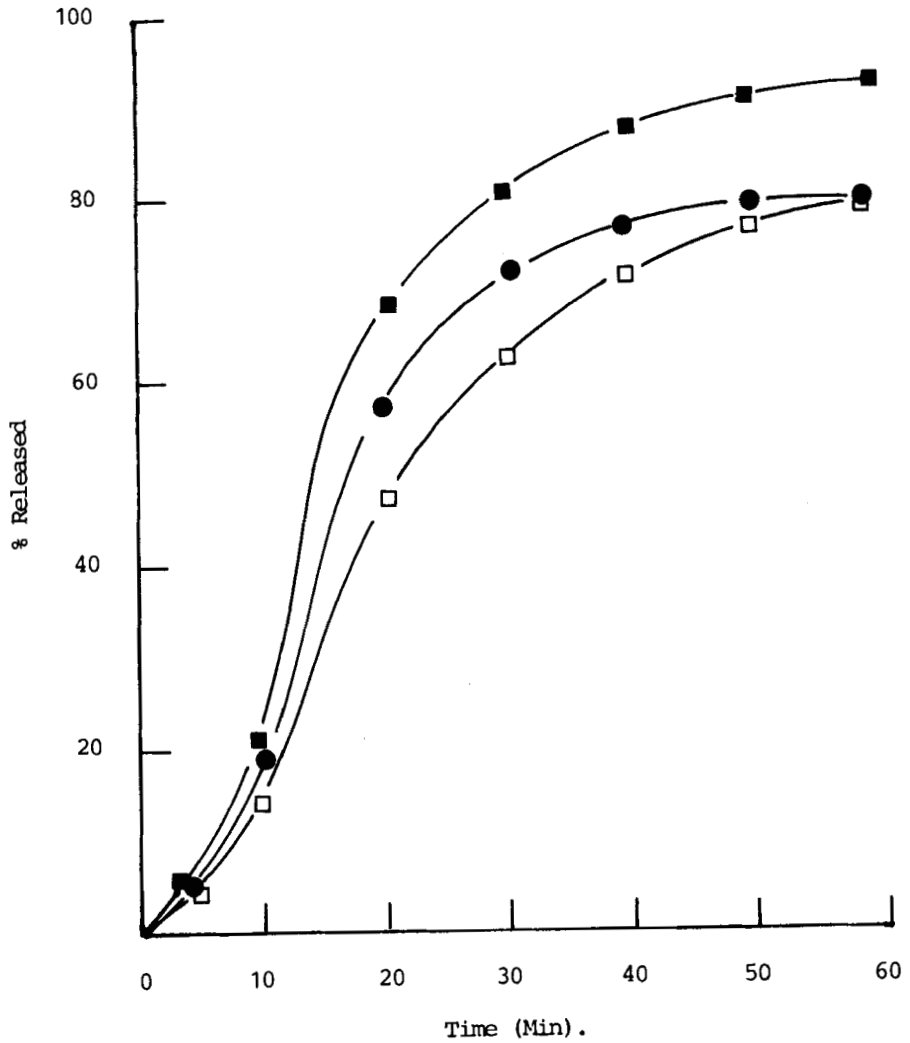

FIGURE 2

Dissolution profiles of dosage form A in acetate buffer at 37°C. Dextropropoxyphene napsylate (■), caffeine (●) and aspirin (O).

method was utilized in determining the dissolution rates of the studied capsule formulations (Figure 2 and 3). (I) in dosage forms B and C showed slower dissolution as compared to formulation A. Several factors could

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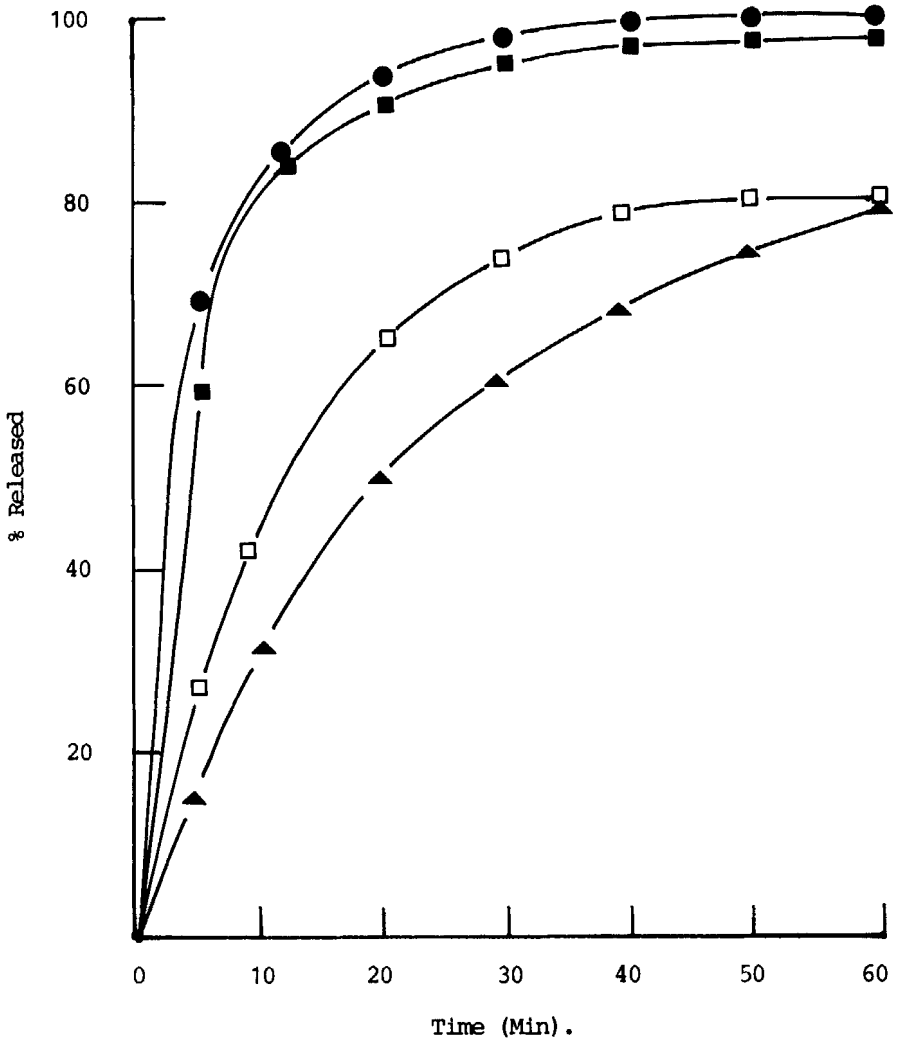

FIGURE 3

Dissolution profiles of dosage forms B and C in acetate buffer at 37°C.

B : Dextropropoxyphene napsylate (□) and acetaminophene (■).

C : Dextropropoxyphene napsylate (▲) and acetaminophene (●).

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cause such a discrepancy including formulation and capsule filling procedure. All formulations, however, met pharmacopeial standard.

In conclusion, the proposed method for the analysis of (I) in presence of other drugs is reliable, accurate and presents a practical alternative to the official G.C. method for quality control purposes.

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