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Mima et al.

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[54] **PHARMACEUTICAL PREPARATIONS OF PENICILLIN COMPOUNDS FOR RECTAL USE**

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[58] **Field of Search** 424/271

[56] **References Cited**

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[57] **ABSTRACT**

Pharmaceutical compositions for rectal administration, containing an alkali metal disalt of sulbenicillin or carbenicillin, a specified amount of an oily or fatty suppository base and a specified amount of a nonionic surfactant, for example, a polyoxyethylene higher alcohol ether.

10 Claims, No Drawings

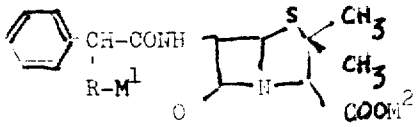
PHARMACEUTICAL PREPARATIONS OF PENICILLIN COMPOUNDS FOR RECTAL USE

This invention relates to pharmaceutical preparations of penicillin compounds for rectal use.

While a number of penicillin compounds have been put on the market, most of them find no other administration forms than parenteral, particularly when systemic effects are expected, because their absorbability by oral administration is very low.

It has been generally known that water-soluble and oil-insoluble compounds are hardly absorbed through the rectal tract, and most of the penicillin compounds so far put on the market are of such nature as above. Thus, it has been believed in this art that rectal administration of penicillin compounds is not effective for systemic effects.

Exhaustive studies by the present inventors to find a penicillin product for rectal use have brought quite a new and astonishing result that certain water-soluble and oil-insoluble penicillin compounds are well absorbed into the body even through the rectum and can give high concentrations in blood enough to achieve systemic effects when administered in the presence of certain nonionic surfactants and fatty or oily bases. The new finding is not only unexpected for even those skilled in the art but also very interesting in the biopharmacy. These penicillin compounds are represented by the following formula (I)



(I)

wherein R stands for $-SO_2-O-$ group or $-CO-O-$ group and M^1 and M^2 stand for, the same or different from each other, alkali metal such as sodium and potassium. The compound (I) wherein R is $-SO_2-O-$ group is named as "sulbenicillin dialkali metal salt" and the compound (I) wherein R is $-CO-O-$ group is named as "carbenicillin dialkali metal salt."

According to this invention, the pharmaceutical preparations of the penicillin compounds can be administered through the rectal tract, which gives no substantial pain, although the injections of penicillin compounds are generally accompanied by a strong pain. Another advantage is to make the administration feasible by anyone without resorting to administration by a physician. Needless to state, they all have merits of a pharmaceutical preparation for rectal use and a suppository.

This invention is concerned with the said pharmaceutical composition for rectal use prepared by dispersing the penicillin compounds (I) in the particular mixture of oily or fatty base of 0.5 to 15 times the weight relative to the said penicillin compounds (I) and at least one species of nonionic surfactants selected from a polyoxyethylene higher alcohol ether, a polyoxyethylene fatty acid ester and polyoxyethylene sorbitan fatty acid ester of 0.01 to 0.5 time the weight relative to the said oily or fatty base. Hydrophile-Lipophile Balance [calculated based on W. C. Griffin's equation] (hereinafter abbreviated as HLB) of the nonionic surfactants is within the range of 7 to 18.

In the compound represented by the formula [I], the compounds wherein both of M^1 and M^2 are sodium are desirably employed in this invention.

The oily or fatty base employable in this invention includes any of the bases which are commonly used in the manufacture of ointments, suppositories, etc. Such an oily or fatty base is exemplified by sesame oil, olive oil, soybean oil, rapeseed oil, cottonseed oil, linseed oil (from *Lini Semen*), castor oil, rice bran oil, tsubaki oil (from *Camellia japonica* L.), corn oil, arachis oil, coconut oil, poppyseed oil, almond oil, avocado oil, palm oil, palm kernel oil, kaya oil (from *Torreya nucifera S* and *Z*) tung oil, kapok oil, kuromoji oil (from *Lindera umbellata*), sasanqua oil (from *Camellia sasanqua*), teaseed oil, perilla oil, cocoa butter, Isocacao MO-5 (registered by KAO-SOAP Com.Ltd.: Higher saturated fatty acid triglyceride), cinnamon butter (from *Cinnamomum japonicum* S.EB.). laurin butter, beef tallow, lard, wool fat, turtle oil, squalene, etc.; materials obtainable by the modification of the fats and oils mentioned above, by such procedures as hydrogenation, interesterification, acetylation, fractional extraction, etc.; mineral oils such as vaseline, paraffin, silicone oils, etc.; esters of fatty acids having 6 to 30 carbon atoms with glycerol, such as glyceryl palmitate, glyceryl laurate, glyceryl stearate, glyceryl myristate, etc.; waxes such as esters of fatty acids having 6 to 30 carbon atoms with alcohols having 2 to 8 carbon atoms, e.g., isopropyl myristate, butyl stearate, diisopropyl adipate, diethyl sebacate, etc.; higher fatty acids of 6 to 30 carbon atoms, e.g., stearic acid, oleic acid, etc.; and so forth. These oily and fatty bases may be employed either singly or as mixtures of two or more. Particularly preferred oily and fatty bases are corn oil, cocoa butter, Isocacao MO-5, interesterified fats and oils (e.g., palmitic acid, stearic acid, etc.), artificial suppository base (e.g., Witepsol (Dynamit Nobel Aktiengesellschaft:Triglyceride of saturated vegitable fatty acids with monoglycerides).

The amount of such oily and fatty bases to be employed is 0.5 to 15 times the weight relative to the penicillin compounds [I] to be dispersed therein, and preferably 1 to 5 times on the same basis.

The nonionic surfactants of this invention have an HLB value of 7 to 18, desirably 9 to 14. In such nonionic surfactants, polyoxyethylene (hereinafter referred to as POE) higher alcohol ether, wherein the higher alcohol has 8 to 18 carbon atoms, and of which the average number of POE units (hereinafter referred to as *n*) is 5 to 30, is exemplified by POE.cetyl ether(HLB=8.8, *n*=7), POE.cetyl ether(HLB=10.6, *n*=10), POE.cetyl ether(HLB=11.5, *n*=12), POE.cetyl ether(HLB=12.8, *n*=15), POE.cetyl ether(HLB=13.6, *n*=17), POE.cetyl ether(HLB=14.1, *n*=20), POE.oleyl ether(HLB=8.9, *n*=8), POE.oleyl ether(HLB=10.0, *n*=10), POE.oleyl ether(HLB=11.0, *n*=12), POE.oleyl ether(HLB=11.6, *n*=15), POE.oleyl ether(HLB=13.6, *n*=20), POE.oleyl ether(HLB=14.6, *n*=25), POE.stearyl ether(HLB=8.9, *n*=8), POE.stearyl ether(HLB=10.6, *n*=11), POE.stearyl ether(HLB=12.2, *n*=15), POE.stearyl ether(HLB=13.6, *n*=20), POE.stearyl ether(HLB=14.5, *n*=20), POE.lauryl ether(HLB=8.6, *n*=5), POE.lauryl ether(HLB=10.9, *n*=8), POE.lauryl ether(HLB=11.5, *n*=9), POE.lauryl ether(HLB=12.1, *n*=10), POE.lauryl ether(HLB=13.0, *n*=12), POE.lauryl ether(HLB=14.1, *n*=15), POE.lauryl

ether(HLB=14.8, n=17), POE.lauryl ether(HLB=15.5, n=20), POE.octyl ether(HLB=13.9, n=10), POE.octyl ether(HLB=15.8, n=15), POE fatty acid ester, wherein the fatty acid has 12 to 18 carbon atoms and whose n is 5 to 30, is exemplified by POE.monostearate (HLB=10.6, n=10), POE.monostearate (HLB=13.0, n=13), POE.monostearate(HLB=13.9, n=20), POE.-monostearate(HLB= 15.9, n=30), POE.monos-tearate(HLB=15.2, n=25), POE.-monooleate(HLB=9.5, n=8), POE.-monooleate(HLB=10.7, n=10), POE.-monooleate(HLB=10.7, n=10), POE.-monooleate(HLB=13.6, n=15), POE.-monolaurate(HLB=12.6, n=10); POE sorbitan fatty acid ester, wherein the fatty acid has 12 to 18 carbon atoms, whose n is 4, 5 or 20, is exemplified by POE.sorbitan monooleate (POE=10.0, n=5), POE.sorbitan monolaurate(HLB=13.3, n=4), POE.sorbitan monolaurate(HLB=16.7, n=20), POE.sorbitan monopalmitate(HLB=15.6, n=20), POE.sorbitan monostearate(HLB=9.6, n=4), POE.sorbitan monostearate(HLB=14.9, n=20), POE.sorbitan monooleate(HLB=10.0, n=5), POE.sorbitan monooleate(HLB=15.0, n=20).

When the nonionic surfactant is used in the amount less than 0.01 time the weight relative to the oily and fatty bases being used, the penicillin compounds [I] are hardly absorbed, while when the amount of nonionic surfactant is more than 0.5 time the weight relative to the oily and fatty bases being used, the penicillin compounds [I] decompose gradually, and, therefore, the amount to be used is 0.01 to 0.5 time the weight relative to the oily and fatty bases, preferably, 0.01 to 0.3 time on the same bases.

The nonionic surfactants may be employed either singly or as a mixture of two or more. Particularly preferred surfactants are, for example, POE.higher alcohol ether and the mixture of POE.higher alcohol ether and POE.fatty acid ester.

It is also possible to incorporate one or more of such additional ingredients as metallic soaps, waxes, benzoic acid, polyethylene, antioxidants, cellulose derivatives (for example ethyl-cellulose, methyl-cellulose, carboxy-methyl-cellulose), preservatives, and the like in a suitable amount.

The dosage forms which can be adopted in the practice of this invention include suppositories which are solid at room temperature but melt at body temperature, ointments or enema-type preparations. These dosage forms may be achieved by procedures which are commonly followed in the preparation of ointments, suppositories and the like, by melting the oily and fatty bases and surfactant together and evenly dispersing the fine-powdered penicillin compounds [I] in the resulting melt. The preferred particle size of the penicillin powder is within the range of 200μ 1μ.

In a particularly preferred practice embodying the principle of this invention, 6.67 to 200 parts of a powdery penicillin compound [I] in the particle size range not more than 200μ and 1 to 50 parts of a nonionic surfactant with a HLB value of 7 to 18 are uniformly dispersed together in 100 parts of oily and fatty bases of solid or ointment in fused state and, if necessary, the resultant composition is molded.

The dose unit of penicillin compound [I] in these preparations can be adjusted from 500mg. to 5000mg. potency for human adults and from 50mg. to 1500mg. potency for infants including neonates, and these drugs are generally administered once or several times a day.

TEST 1

Blood concentration and percent recovery in urine of penicillins.

1. Test method:

Male, fasted rabbits, weighing about 3 kg. each, were used for examining the rectal absorption and the intramuscular absorption of the test drugs: The former examination was made by administering a test drug in the form of suppository, namely the test drug was inserted into the rectum and pushed about 3cm deep from the anus with a glass rod, or in the form of ointment or enema type preparation, namely the test drug was inserted about 3cm deep from the anus with a small injection syringe. The latter examination was made by injecting the test drug intramuscularly at the thigh of the rabbits.

To determine the concentration of the penicillin compounds [I] in blood, blood samples were taken from the heart at timed intervals and the plasma samples were subjected to quantitative determination by means of biological assay.

On the other hand, urine samples collected for six hours after administration using a cannula were subjected to quantitative determination of penicillin compounds [I] by the same method as above. The urinary recoveries of penicillin compounds [I] (unchanged form) were observed.

2. Drugs employed in the Test:

Dispersions of the penicillin compounds [I] in oily or fatty base of this invention and at least one nonionic surfactant selected from POE.higher alcohol ether, POE.fatty acid ester and POE.sorbitan fatty acid ester (this invention: Test No. 1–12); Dispersions of the penicillin compounds [I] in bases other than the above oily or fatty base (control: Test No. 13–16); Dispersions of penicillin compounds other than the above penicillin compounds [I] in oily or fatty base of this invention and the above surfactant (control: Test No. 17–18); Solution obtained by adding penicillin compounds [I] to distilled water (control: Test No. 19).

3. Preparations of the drugs employed in the Test:

The ointment or enema type preparations (Test No. 1,2,5,6 and 10) which are prepared by dispersing the penicillin compounds [I] in the mixture of oily or fatty base and the nonionic surfactant; The suppository type preparations (Test No. 3, 4, 7, 8, 9, 11 and 12) which are prepared by dispensing evenly the dispersion of the penicillin compounds [I] in the mixture of oily or fatty base and the nonionic surfactant, melted at 40°–45°C, and pouring into the container, and then solidifying with ice-water.

Table 1

The blood concentrations(mcg./ml.) and urinary recoveries(%) of penicillin compounds [I]

(dosage: 400mg./rabbit)

		Test No.	Formulation	Blood concentration(mcg./ml.) 1/4hr.	1/2	1	2	4	6	% Recoveries in urine
Penicillin compounds of this invention	Pharmaceutical preparations for rectal use of this invention	1	Corn oil 54 % POE.lauryl ether (HLB=11.5, n=9) 6 % Disodium sulbenicillin 40 %	205.8	346.5	228.8	32.0	2.4	1.0	62.0
		2	Corn oil 54 % POE.sorbitan monooleate (HLB=15.0, n=20) 6 % Disodium sulbenicillin 40 %	73.2	75.6	34.0	7.6	4.0	2.0	40.6
		3	Corn oil 26.7% Isocacao MO-5® 33.3% POE.sorbitan monooleate (HLB=15.0, n=20) 6.7% Disodium sulbenicillin 33.3%	84.0	34.8	10.0	4.1	1.8	0.6	24.6
		4	Isocacao MO-5® 66.5% POE.monostearate (HLB=13.0, n=13) 3.5% Disodium sulbenicillin 30.0%	108.5	59.7	38.2	5.0	1.3	0.8	28.3
		5	Liquid paraffin 63.0% POE.monostearate (HLB=10.8, n=10) 7.0% Disodium sulbenicillin 30.0%	105.6	82.3	30.2	8.5	2.6	1.0	37.3
		6	Corn oil 79.2% POE.lauryl ether (HLB=13.0, n=12) 0.8% Disodium sulbenicillin 20.0%	360.0	231.0	69.7	8.1	2.3	1.0	69.8
Penicillin compounds of this invention	Pharmaceutical preparations for rectal use of this invention	7	Witepsol® 72.5% POE.cetyl ether (HLB=12.8, n=15) 12.5% Disodium sulbenicillin 25.0%	316.3	281.0	139.0	25.7	6.7	1.8	66.5
		8	Witepsol® 64.0% POE.sorbitan monolaurate (HLB=13.3, n=4) 19.3% Disodium sulbenicillin 16.7%	78.0	47.0	38.7	24.7	11.2	3.1	43.8
		9	Isocacao MO-5® 60 % POE.monostearate (HLB=13.0, n=13) 5 % Disodium carbenicillin 35 %	96.8	71.0	45.6	13.4	3.1	1.3	31.1
		10	Corn oil 54 % POE.monolaurate (HLB=10.8, n=10) 6 % Disodium carbenicillin 40 %	126.3	85.1	21.2	10.6	5.1	1.8	37.7
		11	Witepsol® 62.5% POE.monostearate (HLB=15.2, n=25) 12.5% Disodium carbenicillin 25.0%	143.1	59.0	11.3	4.5	1.6	0.8	50.8
		12	Witepsol® 54.5% POE.oleyl ether (HLB=10.0, n=10) 5.5% Disodium carbenicillin 40.0%	340.0	455.1	316.5	100.0	28.8	11.3	71.3
Penicillin compounds of this invention	Control	13	Polyethylene glycol 4000 7 % Polyethylene glycol 1000 56 % POE.monostearate (HLB=13.0, n=13) 7 % Disodium sulbenicillin 30 %	11.6	12.8	10.1	3.5	1.9	0.8	7.3
		14	Distilled water 57 % POE.monostearate (HLB=13.0, n=13) 3 % Disodium sulbenicillin 40 %	1.9	4.9	3.4	1.8	0.5	0.2	6.7
		15	Distilled water 57 % POE.monostearate (HLB=13.0, n=13) 3 % Disodium carbenicillin 40 %	1.5	4.0	3.2	1.2	0.7	0.2	5.1
		16	Corn oil 80 % Disodium sulbenicillin 20 %	16.3	12.8	6.7	1.2	0	0	-

Table 1 (Continued)

The blood concentrations(mcg./ml.) and urinary recoveries(%) of penicillin compounds [I]

(dosage: 400mg./rabbit)

		Test No.	Formulation		Blood concentration(mcg./ml.) 1/4hr.	1/2	1	2	4	6	% Recoveries in urine
Other penicillins	Control	17	Isocacao MO-5®	66.5%	0.4	0.4	1.6	2.2	1.1	0.2	3.3
			POE.monostearate (HLB=13.0, n=13)	3.5%							
			Ampicillin anhydrate	30.0%							
		18	Isocacao MO-5®	64 %	4.0	9.9	14.5	3.9	2.9	0.9	4.4
			POE.monostearate (HLB=13.0, n=13)	6 %							
			Dicloxacillin magnesium salt	30 %							
i.m.	Control	19	Disodium sulbenicillin	40 %	138.0	209.0	194.0	94.0	28.0	14.0	46.8
			Distilled water	60 %							

It is apparant from Table 1 that compared with the cases (Test No. 13 to 16) in which bases other than the oily or fatty base of this invention were employed, or the cases (Test No. 17 and 18) in which penicillin compounds other than the penicillin compounds [I] of this invention were employed, the use of the pharmaceutical preparations of the penicillin compounds for rectal use (Test No. 1 to 12) comprising the penicillin compounds [I], the oily or fatty base and the specific nonionic surfactant in specified proportions achieve extremely high concentrations of the penicillins in blood, at levels which are comparable to those attainable by the intramuscular route (Test No. 19).

EXAMPLE 1

To 47 g. of olive oil is added 8g. of POE.laurylether(HLB=11.5, n=9), and the mixture is stirred. In the resultant solution is dispersed 45 g. of fine-powdered disodium sulbenicillin, and 2.5 g. aliquots of the dispersion are dispensed into 3 ml. plastics containers tubes for rectal application.

EXAMPLE 2

To 50 g. of Isocacao MO-5 is added 20 g. of POE.-monostearate(HLB=13.0, n=13), and the mixture is melted at 45°C. In this melt is dispersed 30 g. of fine-powdered disodium sulbenicillin, and 1.33 g. aliquots of the dispersion are poured into plastic containers for suppositories, then solidified with ice-water. The procedure yields suppositories.

EXAMPLE 3

To 75 g. of cocoa butter is added a mixture of 6 g. of POE.monostearate(HLB=13.7, n=15) and 4 g. of POE.cetylether(HLB=8.8, n=7), which is melted at 45°C. In this melt is dispersed 15 g. of fine-powdered disodium carbenicillin, and 3 g. aliquots of the dispersion are poured into plastic containers for suppositories, then solidified with ice-water. The procedure yields suppositories.

EXAMPLE 4

To 77 g. of squalene is added 3 g. of POE.lauryl ether(HLB=8.6, n=5), and the mixture is stirred. In this mixture is dispersed 20 g. of fine-powdered disodium sulbenicillin, and 2.5 g. aliquots of the resulting dispersion are poured into 3 ml. plastic container tubes for rectal application.

EXAMPLE 5

To 66.5 g. of Witepsol is added 3.5 g. of POE.monostearate(HLB=13.9, n=20), and the mixture is fused at 45°C. In this melt is dispersed 30 g. of fine-powdered disodium sulbenicillin, and 1.33 g. aliquots of the dispersion are poured into plastic containers, then solidified with cold water to obtain suppositories.

EXAMPLE 6

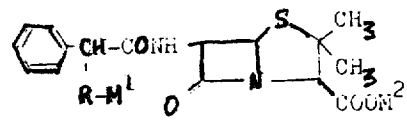
At 45°C, 26.7 g. of corn oil and 33.3 g. of Isocacao MO-5 are stirred together to obtain a solution. The solution is admixed with 6.7 g. of POE.sorbitan monolaurate(HLB=16.7, n=20) under stirring. Then, 33.3 g. of fine-powdered dipotassium sulbenicillin is dispensed therein, and 1.33 g. aliquots of the dispersion are poured into 2 ml. plastic containers tubes for rectal application, case being used to prevent settling.

EXAMPLE 7

To 50 g. of Witepsol are added 3 g. of POE.lauryl ether(HLB=13.0, n=12) and 2 g. of POE.sorbitan monolaurate(HLB=16.7, n=20), and the mixture is melted at 40°C. In this melt is dispersed 45 g. of fine-powdered disodium carbenicillin, and 2.3 g. aliquots of the dispersion are poured into plastic containers, care being used to prevent settling. The filled containers are solidified with ice-water to obtain suppositories.

What is claimed is:

1. A pharmaceutical composition for rectal use which comprises (1) a penicillin compound of the formula



wherein R is $-SO_2-O-$ or $-CO-O-$ and M^1 and M^2 are the same or different and each represents an alkali metal, (2) an oily or fatty suppository base in an amount of 0.5 to 15 times the weight relative to the

weight of the penicillin compound and (3) at least one nonionic surfactant selected from the group consisting of (a) polyoxyethylene higher alcohol ethers, wherein the average number of polyoxyethylene units is 5–30 and the higher alcohol has 8–18 carbon atoms, (b) polyoxyethylene fatty acid esters, wherein the average number of polyoxyethylene units is 5–30 and the fatty acid has 12–18 carbon atoms and (c) polyoxyethylene sorbitan fatty acid esters, wherein the average number of polyoxyethylene units is 4,5 or 20 and the fatty acid has 12–18 carbon atoms, in an amount of 0.01 to 0.5 time the weight relative to the weight of the oily or fatty base, the HLB value of the nonionic surfactant being within the range of 7 to 18.

2. A pharmaceutical composition as claimed in claim 1 wherein both of M^1 and M^2 are sodium.

3. A pharmaceutical composition as claimed in claim 1 wherein the nonionic surfactant is a polyoxyethylene higher alcohol ether.

4. A pharmaceutical composition as claimed in claim 3 wherein the nonionic surfactant is a polyoxyethylene higher alcohol ether having an HLB value of from 9 to 14.

5. A pharmaceutical composition as claimed in claim 1 wherein the nonionic surfactant is a mixture of a polyoxyethylene higher alcohol ether and a polyoxyethylene fatty acid ester.

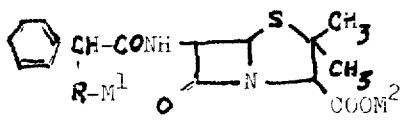
6. A pharmaceutical composition as claimed in claim 4 wherein the polyoxyethylene higher alcohol ether is polyoxyethylene lauryl ether having an HLB value of about 11.5.

7. A pharmaceutical composition as claimed in claim 4 wherein the polyoxyethylene higher alcohol ether is polyoxyethylene lauryl ether having an HLB value of about 13.0.

8. A pharmaceutical composition as claimed in claim 4 wherein the polyoxyethylene higher alcohol ether is polyoxyethylene cetyl ether having an HLB value of about 12.8.

9. A pharmaceutical composition as claimed in claim 4 wherein the polyoxyethylene higher alcohol ether is polyoxyethylene oleyl ether having an HLB value of about 10.

10. A method of treating a disease subject to treatment with sulbenicillin or carbenicillin which comprises administering through the rectal tract of a patient afflicted with the disease a composition containing (1) a penicillin compound of the formula



wherein R is $-SO_2-O-$ or $-CO-O-$ and M^1 and M^2 are the same or different and each represents an alkali metal, (2) an oily or fatty suppository base in an amount of 0.5 to 15 times the weight relative to the weight of the penicillin compound and (3) at least one nonionic surfactant selected from the group consisting of (a) polyoxyethylene higher alcohol ethers, wherein the average number of polyoxyethylene units is 5–30 and the higher alcohol has 8–18 carbon atoms, (b) polyoxyethylene fatty acid esters, wherein the average number of polyoxyethylene units is 5–30 and the fatty acid has 12–18 carbon atoms and (c) polyoxyethylene sorbitan fatty acid esters, wherein the average number of polyoxyethylene units is 4, 5 or 20 and the fatty acid has 12–18 carbon atoms, in an amount of 0.01 to 0.5 time the weight relative to the weight of the oily or fatty base, the HLB value of the nonionic surfactant being within the range of 7 to 18.

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