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(19)

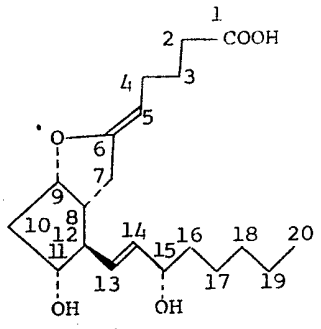
(54) COMPOSITIONS CONTAINING PROSTAGLANDIN ANALOGUES

(71) We, ONO PHARMACEUTICAL CO. LTD., a Japanese Body Corporate, of 14 Doshomachi 2-Chome, Higashiku, Osaka 541, Japan,

do hereby declare the invention, for which we pray that a patent may be granted to us, and the method by which it is to be performed, to be particularly described in and by the following statement:—

This invention relates to cyclodextrin clathrates of prostaglandin I_2 (PGI_2) analogues.

PGI_2 is a physiologically active substance having the following formula:



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and its chemical name is (5*Z*,13*E*)-(9α,11α,15*S*)-6,9-epoxy-11,15-dihydroxyprosta-5,13-dienoic acid [Nature, *263*, 663 (1976), Prostaglandins, *12*, 685 (1976), *ibid*, *12*, 915 (1976), *ibid*, *13*, 3 (1977), *ibid*, *13*, 375 (1977) and Chemical and Engineering News, Dec. 20, 17 (1976)].

It is well known that PGI_2 can be prepared by incubation of prostaglandin G_2 (PGG_2) or prostaglandin H_2 (PGH_2) with microsomal fraction prepared from thoracic aorta of swine, mesenteric artery of swine, rabbit aorta or the stomach fundus of rats. PGI_2 has a relaxing activity on the artery, which is peculiar to the artery and which does not operate on other smooth muscle. Furthermore, PGI_2 strongly inhibits blood platelet aggregation and has hypotensive activity.

Taking into consideration that thromboxane A_2 prepared by incubation of PGG_2 or PGH_2 with blood platelet microsome, has a contracting activity on the artery and an aggregating activity on blood platelets, the properties of PGI_2 heretofore mentioned show that PGI_2 fulfils a very important physiological part in a living body. Therefore, PGI_2 may be useful in the treatment of arteriosclerosis, cardiac failure or thrombosis.

PGI_2 is biosynthesized from PGG_2 or PGH_2 using the specific tissue microsomes mentioned above, and its chemical structure has been identified.

In view of its properties mentioned above, PGI_2 is expected to be applied for

medicinal use. However, it is considered that there are the following three disadvantages to its application as a pharmaceutical:—

i) PGI_2 has various physiological properties as heretofore mentioned. Therefore, if one property is to be used for a pharmacological purpose, the other properties cause side-effects.
ii) In the living body, PGI_2 easily loses its activities by being metabolized by PG-lytic enzymes, and its effects are transitory.
iii) As PGI_2 is extremely unstable especially in thermostability, it is difficult to prepare stable pharmaceutical formulations.

Because of the aforementioned defects of PGI_2, widespread investigations have been carried out in order to synthesize new analogues of PGI_2 having a different and narrower spectrum of activities and substantially longer duration of biological activities than PGI_2 and we have succeeded in synthesizing better compounds than PGI_2 in respect of points (i) and (ii).

However, the PGI_2 analogues obtained, like PGI_2, are also unstable to heat. The cause of the instability lies in the facts that they have double bond(s) or hydroxy group(s) in their structure and that the 5, 6 and 9 positions are in an extremely unstable enol ether form. For this reason, they are significantly more unstable than other pharmaceuticals.

Further extensive research and experimentation have been carried out in order to overcome this disadvantage and to obtain stabilized preparations of PGI_2 analogues. As a consequence of the present investigations, it has been found that the stability is considerably improved if PGI_2 analogues are converted into clathrate compounds with α-, β- or γ-cyclodextrin. The clathrates of the present invention stabilise the PGI_2 analogues against conversion by hydrolysis into 6-keto-$PGF_{1\alpha}$ compounds.

The present invention accordingly provides cyclodextrin clathrates of a PGI_2 analogue. By the term "PGI_2 analogue" as used in this specification and the accompanying claims is meant, for example, compounds in which the carboxy group of PGI_2 is esterified or replaced by an alcohol group (—CH_2OH), compounds which possess carbon skeletons similar to that of PGI_2 with a corresponding carboxy group but in which the side chains attached to the 6- and 12-positions may be longer or shorter than those of PGI_2, and in which the side chain attached to the 6-position may carry an alkyl substituent and the side chain attached to the 12-position may carry an alkyl, hydroxy, chloro, cycloalkyl, phenyl or phenoxy substituent, and such compounds in which the carboxy group is esterified or replaced by an alcohol group, and corresponding 5(*E*)—PGI_2 compounds, corresponding 11-deoxy-PGI_2 compounds, corresponding 13,14-dihydro-PGI_2 compounds and corresponding *trans*-Δ^2-PGI_2 compounds.

Preferred cyclodextrin clathrates of the invention are those containing esters or alcohol derivatives of PGI_2, 2a-homo-PGI_2, 7a-homo-PGI_2, 2-nor-PGI_2, 2-methyl-PGI_2, 3-methyl-PGI_2, 5-methyl-PGI_2, 7-methyl-PGI_2, 15-methyl-PGI_2, 16-methyl-PGI_2, 17-methyl-PGI_2, 16,16-dimethyl-PGI_2, 17,20-dimethyl-PGI_2, 17-ethyl-PGI_2, 20-hydroxy-PGI_2, 16-chloro-PGI_2, 15-cyclopentyl-16,17,18,19,20-pentanor-PGI_2, 15-(2-ethyl)cyclopentyl-16,17,18,19,20-pentanor-PGI_2, 15-(3-ethyl)cyclohexyl-16,17,18,19,20-pentanor-PGI_2, 16-phenyl-17,18,19,20-tetranor-PGI_2, 16-phenoxy-17,18,19,20-tetranor-PGI_2, 16-(4-chlorophenoxy)-17,18,19,20-tetranor-PGI_2, 16-(3-trifluoromethylphenoxy)-17,18,19,20-tetranor-PGI_2 and the corresponding (5*E*)—PGI_2 analogues, corresponding 11-deoxy-PGI_2 analogues, corresponding 13,14-dihydro-PGI_2 analogues and corresponding *trans*-Δ^2-PGI_2 analogues. Preferred esters of the foregoing PGI_2 analogues are straight- or branched-chain alkyl esters containing from 1 to 12, and preferably from 1 to 4, carbon atoms in the esterifying alkyl moiety, e.g. methyl, ethyl, propyl, n-butyl, isobutyl, n-hexyl, n-heptyl, n-octyl and n-decyl esters, aralkyl esters containing from 7 to 12 carbon atoms, e.g. benzyl, 1-phenylethyl, 2-phenylethyl, 3-phenylbutyl, 4-phenylbutyl, 1-(2-naphthylethyl) and 2-(1-naphthylethyl) esters, cycloalkyl esters containing from 4 to 7 carbon atoms in the ring, which may be unsubstituted or substituted pentyl, cyclohexyl and 3-ethylcyclohexyl esters, and phenyl esters in which the phenyl group is unsubstituted or carries at least one substituent selected from chlorine atoms, trifluoromethyl groups, straight- or branched-chain alkyl groups containing from 1 to 4 carbon atoms and phenyl groups, e.g. phenyl, 2-chlorophenyl, 2,4-dichlorophenyl, 2-tolyl, 4-ethylphenyl and 3-trifluoromethylphenyl esters.

Other preferred esters are esters of 2a-homo-PGI_2, 7a-homo-PGI_2, 2-nor-PGI_2,

2-methyl-PGI_2, 3-methyl-PGI_2, 5-methyl-PGI_2, 7-methyl-PGI_2, 20-hydroxy-PGI_2, 16-chloro-PGI_2 or of the corresponding (*5E*)—PGI_2 analogues, corresponding 11-deoxy-PGI_2 analogues, corresponding 13,14-dihydroxy-PGI_2 analogues and corresponding *trans*-Δ^2-PGI_2 analogues in which the esterifying moiety is a carboalkoxyalkyl moiety of the general formula $—C_nH_{2n}COOR^1$, wherein n represents an integer of from 1 to 12 and R^1 represents a straight- or branched-chain alkyl group containing from 1 to 4 carbon atoms, e.g., carboethoxymethyl, 8-carboethoxyoctyl, 9-carboethoxynonyl and 11-carboethoxyundecyl esters, a hydroxy- or alkoxy-alkyl moiety of the general formula $—C_mH_{2m}OR^2$, wherein m represents an integer from 2 to 12, and R^2 represents a hydrogen atom or a straight- or branched-chain alkyl group containing from 1 to 4 carbon atoms, e.g. 2-hydroxyethyl, 4-hydroxybutyl, 5-hydroxypentyl, 6-hydroxyhexyl, 8-hydroxyoctyl and 2-propoxyethyl esters, or an aminoalkyl moiety of the general formula

$$—C_mH_{2m}N<^{R^3}_{R^4},$$

wherein R^3 and R^4, which may be the same or different, each represents a hydrogen atom or a straight- or branched-chain alkyl group containing from 1 to 4 carbon atoms and m is as hereinbefore defined, e.g. 2-methylaminoethyl and 2-dimethylaminoethyl esters.

Other preferred esters are esters of 15-cyclohexyl-16,17,18,19,20-pentanor-PGI_2, 15 - (1 - butyl) - cyclobutyl - 16,17,18,19,20 - pentanor - PGI_2, 15 - (3 - ethyl)-cyclopentyl - 16,17,18,19,20 - pentanor - PGI_2, 15 - (3 - propyl) - cyclopentyl-16,17,18,19,20 - pentanor - PGI_2, 15 - (4 - ethyl) - cyclohexyl - 16,17,18,19,20-pentanor - PGI_2, 16 - cyclohexyl - 17,18,19,20 - tetranor - PGI_2, 16 - cyclopentyl-18,19,20 - trinor - PGI_2, 17 - cyclohexyl - 18,19,20 - trinor - PGI_2, 17 - cyclohexyl - 19,20 - dinor - PGI_2, 16 - methyl - 17 - cyclohexyl - 18,19,20 - trinor-PGI_2 or 19-cyclohexyl-20-nor-PGI_2, or of a corresponding (*5E*)—PGI_2 analogue, corresponding 11-deoxy-PGI_2 analogue, corresponding 13,14-dihydro-PGI_2 analogue or corresponding *trans*-Δ^2-PGI_2 analogue in which the ester is an aralkyl ester containing from 7 to 12 carbon atoms, a cycloalkyl ester containing from 4 to 7 carbon atoms in the ring, which may be unsubstituted or substituted by at least one alkyl group containing from 1 to 4 carbon atoms, or a phenyl ester in which the phenyl group is unsubstituted or carries at least one substituent selected from chlorine atoms, trifluoromethyl groups, straight- or branched-chain alkyl groups containing from 1 to 4 carbon atoms and phenyl groups.

The cyclodextrin clathrates of the PGI_2 analogues may be prepared by dissolving the cyclodextrin in water or an organic solvent which is miscible with water in the presence of triethylamine and adding to the solution the PGI_2 analogue in a water-miscible organic solvent, preferably ethanol. The mixture is stirred vigorously and then the desired cyclodextrin clathrate product is isolated by concentrating the mixture under reduced pressure, or by cooling and separating the product by filtration or decantation. The ratio of organic solvent to water may be varied according to the solubilities of the starting materials and products. The temperature of the reaction mixture should not be allowed to exceed 40°C, and is preferably kept at room temperature, during the preparation of the cyclodextrin clathrates. α-, β- or γ-Cyclodextrins or mixtures thereof may be used in the preparation of the cyclodextrin clathrates.

In the production of cyclodextrin clathrates of PGI_2 analogues, the molar ratio of cyclodextrin to PGI_2 analogue is generally from 1 to 25:1 and preferably from 3 to 15:1.

The cyclodextrin clathrates according to the invention may, where appropriate, be used as such in various pharmaceutical formulations or may be used to prepare pharmaceutical formulations by any method known *per se*. In clinical practice the compositions will normally be administered parenterally, vaginally or rectally.

Pharmaceutical compositions which comprise, as active ingredient, a cyclodextrin clathrate of a PGI_2 analogue in association with a pharmaceutically acceptable carrier, constitute a further feature of the present invention.

By the expression "method known *per se*" as used in this specification is meant any method heretofore used or described in the literature.

The following Examples illustrate the present invention. In the Examples "TLC" represents "thin layer chromatography".

EXAMPLE 1.

A solution of 5.59 mg of PGI_2 methyl ester in 1.5 ml of ethanol was added to a solution of 71.69 mg of β-cyclodextrin in 3 ml of distilled water containing 1% v/v triethylamine at room temperature. The reaction mixture was stirred for about 1 minute and then concentrated under reduced pressure at below 35°C to give 72.85 mg of β-cyclodextrin clathrate of PGI_2 methyl ester. The content of PGI_2 methyl ester in the product was 7.7% by weight.

By proceeding as described above, 175.58 mg of α-cyclodextrin clathrate of PGI_2 methyl ester was prepared from 5.58 mg of PGI_2 methyl ester and 184.00 mg of α-cyclodextrin. The content of PGI_2 methyl ester in the product was 3.2% by weight.

The stabilizing effect on PGI_2 methyl ester of cyclodextrin clathrate formation was confirmed by a stability test carried out at 60°C. The results were evaluated with respect to the percentage of residual PGI_2 methyl ester after heating the cyclodextrin clathrate and PGI_2 methyl ester itself for definite periods of time, the residual percentage being estimated by comparison of the size and intensity of colour of the spots of PGI_2 methyl ester and of its degradation products in TLC.

The TLC was carried out with a 0.25 mm plate of Kieselgel F_{254} (Merck) pretreated with a 5% v/v solution of triethylamine in diethyl ether, using as developing solvent a mixture of diethyl ether and acetone (3:1) containing 0.1% v/v triethylamine, and a cupric acetate solution [prepared by dissolving 3 g of copper (II) acetate in 100 ml of a 20% v/v aqueous solution of phosphoric acid] as colour developer. After heating at 60°C, about 1.3 mg of the β-cyclodextrin clathrate or about 3.1 mg of the α-cyclodextrin clathrate of PGI_2 methyl ester was dissolved in distilled water containing 1% v/v triethylamine and the mixture was extracted with diethyl ether containing 0.1% v/v triethylamine. The extract was concentrated under reduced pressure and the residue obtained was tested by TLC as described above. About 100μg of PGI_2 methyl ester, which had also been heated at 60°C was also tested by TLC.

The results of the test are given in Table I which follows.

EXAMPLE 2.

71 mg of α-cyclodextrin clathrate containing 3.1% w/w of PGI_2 methyl ester and 63 mg of α-cyclodextrin clathrate containing 3.1% w/w of 17(S), 20-dimethyl-PGI_2 methyl ester were prepared in the same manner as described in Example 1.

The stabilizing effect of α-cyclodextrin clathrate formation on the PGI_2 analogues was confirmed in a similar manner to that described in Example 1 but the stability test was carried out at 40°C.

The results of the test are given in Table II which follows.

EXAMPLE 3.

333 mg of α-cyclodextrin clathrate of PGI_2 methyl ester (containing 10 mg of PGI_2 methyl ester) were dissolved in distilled water containing 1% v/v triethylamine and the solution obtained, after being made up to 50 ml, was then sterilized by passage through a bacteria-retaining filter and placed in 0.5 ml portions in 5 ml ampoules. The solution was immediately lyophilized to give 100 μg of PGI_2 methyl ester per ampoule. The ampoules were sealed. The contents of an ampoule dissolved in a suitable volume, e.g. 1 ml of tris-HCl-buffer solution (pH 8.6), gave a solution ready for administration by injection.

EXAMPLE 4.

Another composition according to the invention was obtained by proceeding as described in Example 3, but replacing the PGI_2 methyl ester by 17(S),20-dimethyl-PGI_2 methyl ester.

TABLE I

Sample	Percentage of PGI_2 methyl ester remaining after heating (60°C)							
	(hours) 3	6	(days) 1	2	4	7	10	14
PGI_2 methyl ester	<5	<5						
α-cyclodextrin clathrate of PGI_2 methyl ester	100	100	100	97–95	97–95	97–95	97–95	95–90
β-cyclodextrin clathrate of PGI_2 methyl ester	100	95–90	90–80	80–67	80–67	80–67	67–50	50

TABLE II

Sample	Percentage of PGI_2 analogues remaining after heating (40°C)							
	(hours) 3	6	(days) 1	2	4	7	10	14
A	67–50	<25	<10	0				
α-cyclodextrin clathrate of A	100	100	100	98–97	97–95	95	97–95	95–90
B	50–34	<25	<10	0				
α-cyclodextrin clathrate of B	100	100	100	97–95	97–95	95–90	95–90	95–90

A: PGI_2 methyl ester

B: 17(*S*), 20-dimethyl-PGI_2 methyl ester.

REFERENCE EXAMPLE 1.

Following the procedure of Example 2 the stabilising effect of cyclodextrin clathrate formation was demonstrated on other PGI_2 analogues.

58 mg of α-cyclodextrin clathrate containing 3.2% w/w of 15-(3-propyl)cyclopentyl-16,17,18,19,20-pentanor-PGI_2 methyl ester, 67 mg of α-cyclodextrin clathrate containing 3.1% w/w of 16ξ-cyclopentyl-18,19,20-trinor-PGI_2 methyl ester, 67 mg of α-cyclodextrin clathrate containing 3.1% w/w of 16ξ-methyl-20-chloro-PGI_2 methyl ester and 69 mg of α-cyclodextrin clathrate of PGI_2 N,N-dimethylaminoethyl ester were prepared in the same manner as described in Example 1.

The results of the stability test carried out at 40°C are given in Table III which follows.

TABLE III

Sample	Percentage of PGI_2 analogues remaining after heating (40°C)							
	(hours)		(days)					
	3	6	1	2	4	7	10	14
C	80–67	<25	<10	0				
α-cyclodextrin clathrate of C	100	100	100	97–95	95–90		95–90	95–90
D	50	<25	<10	0				
α-cyclodextrin clathrate of D	100	100	100	90	90–80	95–90	90–80	80–67
E	50–34	<25	<10	0				
α-cyclodextrin clathrate of E	100	100	100	95–90	90–80	90–80	90–80	80–67
F	100	100	67	<50	<10	0		
α-cyclodextrin clathrate of F	100	100	90–80	90–80	90–80	90–80	80–67	80–67

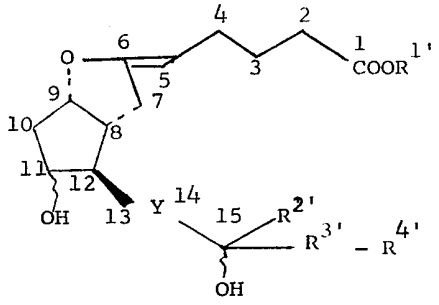
C: 15-(3-propyl)cyclopentyl-16,17,18,19,20-pentanor-PGI_2 methyl ester

D: 16ξ-cyclopentyl-18,19,20-trinor-PGI_2 methyl ester

E: 16ξ-methyl-20-chloro-PGI_2 methyl ester

F: PGI_2 N,N-dimethylaminoethyl ester

Cyclodextrin clathrates of prostaglandin analogues of the general formula:—



[wherein Y represents ethylene or *trans*-vinylene, $R^{1'}$ represents a group

$$-C_pH_{2p}COOR^{5'}, \quad -C_qH_{2q}OR^{6'} \quad \text{or} \quad -C_qH_{2q}N<\begin{matrix}R^{7'}\\R^{8'}\end{matrix}$$

(wherein $R^{5'}$ represents a straight- or branched-chain alkyl group containing from 1 to 4 carbon atoms, $R^{6'}$ represents a hydrogen atom or a straight- or branched-chain alkyl group containing from 1 to 4 carbon atoms, $R^{7'}$ and $R^{8'}$, which may be the same or different, each represents a straight- or branched-chain alkyl group containing from 1 to 4 carbon atoms, p represents an integer of from 1 to 12 and q represents an integer of from 2 to 12), $R^{2'}$ represents a hydrogen atom or a methyl or ethyl group, $R^{3'}$ represents a single bond or a straight- or branched chain alkylene group containing from 1 to 4 carbon atoms, $R^{4'}$ represents a hydrogen atom, a straight- or branched-chain alkyl group containing from 1 to 8 carbon atoms, a cycloalkyl group containing from 4 to 7 carbon atoms in the ring, which may be unsubstituted or substituted by at least one straight- or branched-chain alkyl group containing from 1 to 8 carbon atoms, or represents a phenyl or phenoxy group which may be unsubstituted or substituted by at least one chlorine atom, trifluoromethyl group or alkyl group containing from 1 to 3 carbon atoms, the wavy line ~ attached to the carbon atoms in positions 11 and 15 represents α- or β-configuration or mixtures thereof, and the double bond between C_5—C_6 is *Z*] are described and claimed in our published Patent Application Serial No. 2,006,754 and we make no claim to those cyclodextrin clathrates in the following claims.

Subject to the foregoing disclaimer, WHAT WE CLAIM IS:—

1. A cyclodextrin clathrate of a PGI_2 analogue.

2. A cyclodextrin clathrate of a PGI_2 analogue with α- or β-cyclodextrin.

3. A cyclodextrin clathrate according to claim 1 or 2 which contains an ester or alcohol derivative of PGI_2, 2a-homo-PGI_2, 7a-homo-PGI_2, 2-nor-PGI_2, 2-methyl-PGI_2, 3-methyl-PGI_2, 5-methyl-PGI_2, 7-methyl-PGI_2, 15-methyl-PGI_2, 16-methyl-PGI_2, 17-methyl-PGI_2, 16,16-dimethyl-PGI_2, 17,20-dimethyl-PGI_2, 17-ethyl-PGI_2, 20-hydroxy-PGI_2, 16-chloro-PGI_2, 15-cyclopentyl-16,17,18,19,20-pentanor-PGI_2, 15-(2 - ethyl)cyclopentyl - 16,17,18,19,20 - pentanor - PGI_2, 15 - (3 - ethyl)cyclohexyl - 16,17,18,19,20 - pentanor - PGI_2, 16 - phenyl - 17,18,19,20 - tetranor-PGI_2, 16 - phenoxy - 17,18,19,20 - tetranor - PGI_2, 16 - (4 - chlorophenoxy)-17,18,19,20 - tetranor - PGI_2, 1 6 -(3 - trifluoromethylphenoxy) - 17,18,19,20-tetranor-PGI_2 or of a corresponding (5*E*)-PGI_2 analogue, corresponding 11-deoxy-PGI_2 analogue, corresponding 13,14-dihydro-PGI_2 analogue or corresponding *trans*-Δ^2-PGI_2 analogue.

4. A cyclodextrin clathrate according to claim 1 or 2 which contains an alkyl ester of PGI_2, 15 - methyl - PGI_2, 16 - methyl - PGI_2, 17 - methyl - PGI_2, 16,16 - dmethyl - PGI_2, 17 - ethyl - PGI_2, 15 - cyclopentyl - 16,17,18,19.20-pentanor - PGI_2, 15 - (2 - ethyl)cyclopentyl - 16,17,18,19,20 - pentanor - PGI_2, 15 - (3 - ethyl)cyclohexyl - 16,17,18,19,20 - pentanor - PGI_2, 16 - phenyl-17,18,19.20 - tetranor - PGI_2, 16 - phenoxy - 17,18,19,20 - tetranor - PGI_2, 16-(4 - chlorophenoxy) - 17,18,19.20 - tetranor - PGI_2, 16 - (3 - trifluoromethyl-phenoxy)-17,18,19,20-tetranor-PGI_2, or of a corresponding 13,14-dihydro derivative thereof.

5. A cyclodextrin clathrate according to claim 1 or 2 containing an ester of a PGI_2 analogue specified in claim 3 in which the ester is a straight- or branched-chain alkyl ester containing from 1 to 12 carbon atoms in the esterifying alkyl moiety, an aralkyl ester containing from 7 to 12 carbon atoms, a cycloalkyl ester containing from 4 to 7 carbon atoms in the ring, which may be unsubstituted or substituted by at least one alkyl group containing from 1 to 4 carbon atoms, or a phenyl ester in which the phenyl group is unsubstituted or carries at least one substituent selected from chlorine atoms, trifluoromethyl groups, straight- or branched-chain alkyl groups containing from 1 to 4 carbon atoms and phenyl groups.

6. A cyclodextrin clathrate according to claim 1 or 2 which contains an ester of 2a-homo-PGI_2, 7a-homo-PGI_2, 2-nor-PGI_2, 2-methyl-PGI_2, 3-methyl PGI_2, 5-methyl-PGI_2, 7-methyl-PGI_2, 20-hydroxy-PGI_2, or 16-chloro-PGI_2, or of a corresponding (*5E*)—PGI_2 analogue, corresponding 11-deoxy-PGI_2 analogue, corresponding 13,14-dihydro-PGI_2 analogue or corresponding *trans*-Δ^2-PGI_2 analogue, in which the esterifying moiety is a carboalkoxyalkyl moiety of the general formula $—C_nH_{2n}COOR^1$, wherein n represents an integer of from 1 to 12 and R^1 represents a straight- or branched-chain alkyl group containing from 1 to 4 carbon atoms, a hydroxy- or alkoxy-alkyl moiety of the general formula $—C_mH_{2m}OR^2$, wherein m represents an integer from 2 to 12 and R^2 represents a hydrogen atom or a straight- or branched-chain alkyl group containing from 1 to 4 carbon atoms, or an aminoalkyl moiety of the general formula

$$—C_mH_{2m}N<\begin{matrix}R^3\\R^4\end{matrix},$$

wherein R^3 and R^4, which may be the same or different, each represents a hydrogen atom or a straight- or branched-chain alkyl group containing from 1 to 4 carbon atoms and m is as hereinbefore defined.

7. A cyclodextrin clathrate according to claim 5 in which the ester is an alkyl ester containing from 1 to 4 carbon atoms in the esterifying alkyl moiety.

8. A cyclodextrin clathrate according to claim 1 or 2 wherein the PGI_2 analogue is an ester of 15 - cyclohexyl - 16,17,18,19,20 - pentanor - PGI_2, 15 - (1-butyl) - cyclobutyl - 16,17,18,19,20 - pentanor - PGI_2, 15 - (3 - ethyl) - cyclopentyl - 16,17,18,19,20 - pentanor - PGI_2, 15 - (3 - propyl) - cyclopentyl-16,17,18,19,20 - pentanor - PGI_2, 15 - (4 - ethyl) - cyclohexyl - 16,17,18,19,20-pentanor - PGI_2, 16 - cyclohexyl - 17,18,19,20 - tetranor - PGI_2, 16 - cyclopentyl-18,19,20 - trinor - PGI_2, 17 - cyclohexyl - 18,19,20 - trinor - PGI_2, 17 - cyclohexyl - 19,20 - dinor - PGI_2, 16 - methyl - 17 - cyclohexyl - 18,19,20 - trinor-PGI_2, or 19-cyclohexyl-20-nor-PGI_2, or of a corresponding (*5E*)—PGI_2 analogue, corresponding 11-deoxy-PGI_2 analogue, corresponding 13,14-dihydro-PGI_2 analogue or corresponding *trans*-Δ^2-PGI_2 analogue in which the ester is an aralkyl ester containing from 7 to 12 carbon atoms, a cycloalkyl ester containing from 4 to 7 carbon atoms in the ring, which may be unsubstituted or substituted by at least one alkyl group containing from 1 to 4 carbon atoms, or a phenyl ester in which the phenyl group is unsubstituted or carries at least one substituent selected from chlorine atoms, trifluoromethyl groups, straight- or branched-chain alkyl groups containing from 1 to 4 carbon atoms and phenyl groups.

9. A β-cyclodextrin clathrate of PGI_2 methyl ester.

10. An α-cyclodextrin clathrate of PGI_2 methyl ester.

11. An α-cyclodextrin clathrate of 17(*S*),20-dimethyl-PGI_2 methyl ester.

12. A cyclodextrin clathrate according to any one of the preceding claims in which the molar ratio of cyclodextrin to PGI_2 analogue is from 1 to 25:1.

13. A cyclodextrin clathrate according to claim 12 in which the molar ratio is from 3 to 15:1.

14. A cyclodextrin clathrate according to claim 12 or 13 of a PGI_2 analogue specified in any one of claims 3 to 8.

15. A cyclodextrin clathrate of a PGI_2 analogue substantially as hereinbefore described with especial reference to Example 1 or 2.

16. A process for the preparation of a cyclodextrin clathrate of a PGI_2 analogue substantially as hereinbefore described.

17. A process for the preparation of a cyclodextrin clathrate of a PGI_2 analogue substantially as hereinbefore described with especial reference to Example 1 or 2.

18. Pharmaceutical compositions which comprise, as active ingredient, a cyclodextrin clathrate as claimed in any one of claims 1 to 15 in association with a pharmaceutically acceptable carrier.

19. Pharmaceutical compositions according to claim 18 substantially as hereinbefore described with especial reference to Example 3 or 4.

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