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(54) Title: DRUG DELIVERY COMPOSITIONS (57) Abstract <p>Inclusion complexes comprising pharmaceutical, pesticidal, herbicidal, agricultural, cosmetic or personal care agents or pharmacologically active derivatives or metabolites thereof are disclosed. Methods for improving solubility of these agents in a neutral or acidic solution, improving the bioavailability of these agents and decreasing the gastroirritation of naproxen, by forming inclusion complexes comprising the agents and substituted or unsubstituted cyclodextrins are disclosed herein. Methods for treating mammals by orally or parenterally administering the foregoing pharmaceutical compositions are also provided.</p>		

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DRUG DELIVERY COMPOSITIONSFIELD OF THE INVENTION

This invention relates generally to inclusion complexes and pharmaceutical compositions comprising pharmaceutical compounds and substituted or unsubstituted cyclodextrins. This invention also relates to methods for treating a host mammal with such pharmaceutical compositions. More specifically, this invention relates to inclusion complexes and pharmaceutical compositions comprising Amiodarone, nitrogen mustard agents, Naproxen or pharmacologically active derivatives or metabolites thereof in specific substituted or unsubstituted cyclodextrins.

BACKGROUND OF THE INVENTION

Many of today's commonly prescribed drugs have undesirable properties or delivery profiles which detract from their efficacy and/or beneficial nature. For example, some drugs may exhibit a poor or unpredictable bioavailability profile, which may be due, in part, to the drug's poor solubility characteristics. Amiodarone, which is a potent antiarrhythmic (i.e., it works to restore a regular heartbeat), is one example of such a drug. Other examples of such drugs include melphalan, a potent anti-cancer compound, and other drugs which have similar nitrogen mustard structures. The poor bioavailability of compounds such as Amiodarone and melphalan may also be due to factors other than solubility. For example, melphalan contains a mustard group which can be hydrolyzed by stomach acid, thereby lessening the available amount of active drug.

Other drugs may be undesirable because they can cause harmful irritation to the gastrointestinal lining of some patients, thereby causing pain, discomfort or bleeding. One example of such a drug is Naproxen, which is a nonsteroidal anti-inflammatory drug (NSAID) useful in treating arthritis and other conditions involving inflammation.

Many patients who take drugs such as Naproxen must either do so on a full stomach, or take the Naproxen simultaneously with a second agent that coats or protects the stomach lining. Unfortunately, such measures do not work for some patients who must discontinue the medication or rely upon a less desirable substitute.

Accordingly, there is a continuing need for new drug delivery systems for Amiodarone, melphalan or other nitrogen mustard agents, Naproxen, and pharmacologically active derivatives or metabolites thereof.

SUMMARY OF THE INVENTION

It is an object of this invention to provide inclusion complexes and pharmaceutical compositions comprising Amiodarone, nitrogen mustard agents, or Naproxen with substituted or unsubstituted cyclodextrins.

It is another object of this invention to provide methods for increasing the solubility and/or bioavailability of Amiodarone, nitrogen mustard agents, and to decrease the gastroirritation of Naproxen.

It is yet another object of this invention to provide methods for treating mammals in need of such treatment with therapeutically effective amounts of the foregoing pharmaceutical compositions.

Accordingly, embodiments of this invention provide inclusion complexes and pharmaceutical compositions comprising Amiodarone or a pharmacologically active derivative or metabolite thereof included in a substituted or unsubstituted cyclodextrin or salt thereof selected from the group consisting of α -, β -, γ -, δ -, dimethyl β -, and amino cyclodextrin.

Another embodiment provides methods for increasing the solubility of Amiodarone or a derivative or metabolite thereof in

a neutral or acidic aqueous solution, comprising the step of forming one of the above-described inclusion complexes.

Another embodiment of this invention provides a method for improving the bioavailability of Amiodarone or a derivative or metabolite thereof in a host mammal comprising the step of forming one of the above-described inclusion complexes.

Another embodiment provides a method for treating a host mammal in need of such treatment, comprising orally or parenterally administering to said mammal a therapeutically effective amount of the aforementioned pharmaceutical compositions.

Other groups of embodiments provide inclusion complexes, pharmaceutical compositions, methods for improving the solubility and bioavailability, for decreasing gastroirritation, and for treating host mammals similar to those described above for a compound containing a nitrogen mustard agent, Naproxen, or pharmacologically active derivatives and metabolites thereof.

Additional objects and advantages of the invention will be set forth in part in the description that follows, and in part will be obvious from the description, or may be learned by practice of the invention. The objects and the advantages of this invention may be realized and obtained by means of the compositions of matter and methods particularly pointed out in the appended claims.

BRIEF DESCRIPTION OF THE DRAWINGS

Figure 1 is a graph illustrating the mean plasma concentrations of Amiodarone determined after oral administration of the drug alone or in combination with α -, β - and dimethyl β -cyclodextrin;

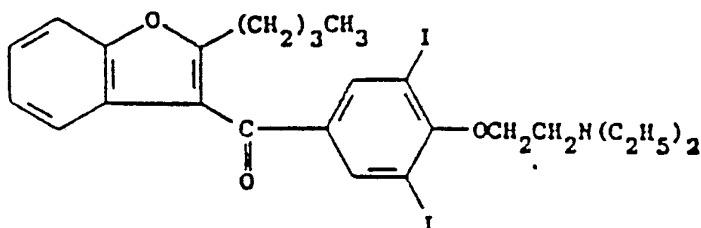
Figure 2 is a graph illustrating the mean plasma concentrations of melphalan determined after oral administration of the drug alone or in combination with dimethyl β -cyclodextrin; and

Figure 3 is a graph illustrating the mean plasma concentrations of Naproxen determined after oral administration of the drug alone or in combination with dimethyl β -cyclodextrin.

DESCRIPTION OF THE PREFERRED EMBODIMENTS**A. Amiodarone Compositions**

The first group of embodiments of this invention relates to Amiodarone compositions for oral or parenteral administration, and especially to compositions having improved water solubility and absorption in the gut.

Amiodarone, which can be described chemically as (2-Butyl-3-benzofuranyl)[4-[2-(diethylamino)ethoxyl]-3,5-diiodophenyl]methanone; 2-butyl-3-benzofuranyl 4-[2-(diethylamino)ethoxyl-3,5-diiodophenyl ketone; or 2-butyl-3-[3,5-diiodo-4-(beta-diethylaminoethoxy)-benzoyl]benzofuran) is an iodinated benzofuran derivative which has potent class III antiarrhythmic activity, and is active on oral administration. It has the following formula:



In vitro studies have shown that Amiodarone prolongs action potential duration and hence the refractory period ventricular, atrial and nodal tissues. Clinically, the drug is effective in treating junctional, ventricular and supraventricular arrhythmias. However, optimal therapy with Amiodarone is compromised by its unreliable absorption following oral administration. For example, the time for detectable concentrations of the drug to appear in plasma can be from less than about 30 minutes to about 3 hours, while the time to reach maximum plasma concentration can vary from 2 to 12 hours. The average Amiodarone bioavailability reported in previously published studies is about 40%, with individual values ranging from 22% to 86% for an orally administered 400 mg dose. It is possible that a considerable amount of the variation in Amiodarone bioavailability is due to dissolution rate-limited absorption, a result of its very poor aqueous solubility.

It is thought that active metabolites of Amiodarone may be involved in its action, particularly since it is slowly metabolized and eliminated. The desethyl derivative is known to accumulate in the plasma during chronic therapy.

It has recently been suggested that cyclodextrins may be useful in the stabilization and solubilization of pharmaceutical agents. Unfortunately, however, the cyclodextrin having the most appropriately-sized annulus to form inclusion complexes with many drugs, namely beta cyclodextrin, is the least soluble in water. Furthermore, most cyclodextrin-drug inclusion complexes have low stability constants (which measure the drug's affinity to remain included), which diminishes their potential for use as drug delivery systems.

It has now surprisingly been found that Amiodarone is more extensively absorbed following oral administration when it is administered in combination with the naturally occurring cyclodextrins, i.e., alpha or beta cyclodextrin, or with a cyclodextrin derivative having improved solubility in neutral or acidic aqueous solutions. Thus, one embodiment of this invention provides inclusion complexes comprising Amiodarone or a pharmacologically active derivative or metabolite thereof, together with a substituted or unsubstituted cyclodextrin or pharmacologically acceptable salt thereof.

Preferably the cyclodextrin is alpha-cyclodextrin, beta-cyclodextrin, gamma-cyclodextrin, or a derivative thereof selected from the group consisting of dimethyl beta-cyclodextrin (DMBCD), or an amino cyclodextrin in which at least one C2, C3 or C6 cyclodextrin hydroxyl is substituted with $-NH_2$, or a salt or hydrate thereof. Delta-cyclodextrins, which are currently being developed, may also be useful. In the amino cyclodextrin, one or both of the amino hydrogens may be replaced with suitable substituents. Where an amino cyclodextrin is used, the amino substitution is preferably at the C6 position, and beta cyclodextrins are preferred.

Suitable amino cyclodextrin derivatives and salts and hydrates thereof for use in the invention are disclosed in PCT application AU89/00359, published March 8, 1990 as WO 90/02141 and entitled "Compositions and Methods for Drug Delivery and

Chromatography", the text of which is herein incorporated by reference.

Preferably the molar ratio of Amiodarone to cyclodextrin is from about 1:1 to about 10:1.

Another embodiment of this invention provides pharmaceutical compositions comprising one of the aforementioned inclusion complexes together with one or more pharmaceutically acceptable carriers. Such carriers are well known to those skilled in this art, and are adequately discussed in published application WO 90/02141. Therapeutically effective amounts of such compositions can be determined by physicians having skill in this art.

Another embodiment of this invention provides a method for improving the solubility of Amiodarone or a pharmacologically active derivative or metabolite thereof in a neutral or acidic aqueous solution, comprising the step of forming an inclusion complex comprising said Amiodarone, derivative or metabolite thereof and one of the aforementioned cyclodextrins or derivatives thereof.

Another embodiment of this invention provides a method for improving the bioavailability of Amiodarone, derivative or metabolite thereof comprising the step of forming an inclusion complex comprising said Amiodarone, derivative or metabolite thereof and one of the aforementioned cyclodextrins or derivatives thereof.

Another embodiment of this invention provides a method for treating a mammal in need of such treatment (e.g., one that is suffering from a cardiac arrhythmia), comprising the step of orally or parenterally administering to said mammal a therapeutically effective amount of one of the pharmaceutical compositions. Where DMBCD is used, oral administration is preferred.

Example 1, infra, illustrates the preparation and oral administration of inclusion complexes and pharmaceutical compositions within the scope of this invention. It will be seen that such complexes can effect a "sustained release" of Amiodarone. That is, effective serum concentration levels of Amiodarone can be maintained over a longer period of time when

Amiodarone complexes in accordance with this invention are used. The beneficial effect is thus two-fold. First, the patient need not take the dosages as often, and thus convenience is served. More importantly, however, the total amount of Amiodarone which the patient must ingest can be decreased dramatically.

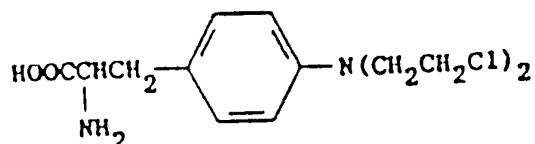
B. Compositions Containing Nitrogen Mustard Agents

A second group of embodiments of this invention relates to compositions containing nitrogen mustard agents and cyclodextrins, and particularly to such compositions of improved solubility, stability, and improved bioavailability upon oral or parenteral administration.

Alkylating agents, such as the nitrogen mustard compounds melphalan, uracil mustard, cyclophosphamide, mechlorethamine, and chlorambucil have been widely used in the therapy of cancer since 1942. Their cytotoxic effect results from alkylation of DNA. Unlike the mustard gases used in chemical warfare, nitrogen mustard compounds have no vesicant action.

Melphalan, which can be described chemically as (4-[Bis(2-chloroethyl)amino]-L-phenylalanine; p-di(2-chloroethyl)amino-L-phenylalanine; L-phenylalanine mustard; alanine nitrogen mustard; L-PAM; melphalan; L-sarcosine; NSC-8806; CB 3025; Alkeran; or Sarcoclorin, is an antineoplastic drug which is used chiefly for treating multiple myeloma and ovarian cancer.

The compound has the following formula:



The clinical use of melphalan presents a number of significant problems, including marked instability in solution. Furthermore, the absorption of melphalan from orally administered preparations is often low and variable, possibly due to its very poor water solubility. The half-life of melphalan in the plasma

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is about 90 minutes, and as much as 20-50% of the drug is recovered in the stools, while 10-15% is recovered unchanged in the urine.

Surprisingly, it has been found that compositions of a representative nitrogen mustard agent, melphalan, with dimethyl β -cyclodextrin show markedly improved absorption and bioavailability following oral administration. It is believed that amino substituted cyclodextrins and salts thereof also provide enhanced delivery.

Thus, according to one embodiment of this invention there is provided an inclusion complex comprising a compound containing a nitrogen mustard group and a cyclodextrin derivative or salt thereof. Preferably, the cyclodextrin derivative is dimethyl beta-cyclodextrin (DMBCD), or an amino cyclodextrin in which at least one C2 C3 or C6 cyclodextrin hydroxyl is substituted with -NH_2 , or a salt or hydrate thereof. As previously discussed, amino cyclodextrins in which one or both of the amino hydrogens are replaced with suitable substituents may also be used. Such amino cyclodextrin derivatives and salts and hydrates thereof for use in the invention are disclosed in the aforementioned PCT application WO 90/02141. Where an amino cyclodextrin is used, preferably the amino substitution is at the C6 position, particularly for beta-cyclodextrins.

Preferably the nitrogen mustard agent is selected from the group consisting of melphalan, chlorambucil, cyclophosphamide, uracil mustard and mechlorethamine.

Preferably the molar ratio of nitrogen mustard agent to cyclodextrin derivative is from about 1:1 to about 10:1.

Accordingly, other embodiments of this invention provide: pharmaceutical compositions comprising one of the aforementioned inclusion complexes and one or more pharmaceutically accepted carriers; a method for improving the solubility of a nitrogen mustard agent in a neutral or acidic aqueous solution by forming an inclusion complex with the agent and one of the recited cyclodextrin derivatives; a method for improving the bioavailability of a nitrogen mustard agent in a host mammal by forming said inclusion complexes; and a method for treating a mammal in need of such treatment (e.g., one suffering from a

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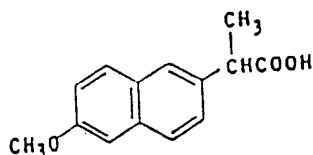
neoplastic disease) by orally or parenterally administering a therapeutically effective amount of an above described pharmaceutical composition. Determining suitable dosages is within the ordinary skill of physicians in this art. Where DMBCD is used, oral administration is preferred.

Example 2, *infra*, illustrates the preparation and oral administration of an inclusion complex and pharmaceutical composition within the scope of this invention. It will be seen that orally administering the inclusion complex of melphalan and DMBCD can rapidly achieve very high serum levels of melphalan. Such levels are almost twice as great as those achieved using melphalan alone. The obvious benefit is that either much higher serum levels can be achieved with the same amount of melphalan, or similar levels can be achieved with much smaller dosages. Example 3 illustrates that some inclusion complexes which are outside the scope of the claims do not exhibit the same beneficial effects.

C. Naproxen Compositions

A third group of embodiments of this invention relates to compositions of Naproxen or its pharmacologically active derivatives or metabolites with cyclodextrin derivatives or salts thereof.

Naproxen (6-methoxy- α -methyl-2-naphthalene acetic acid) is a nonsteroidal anti-inflammatory drug (NSAID) with analgesic and antipyretic properties. It is a derivative of naphthylpropionic acid and has the following formula:



Following oral administration, Naproxen is rapidly and completely absorbed from the gastrointestinal tract. Peak plasma levels of Naproxen are attained in 2 to 4 hours, with steady-state conditions normally achieved after 4-5 doses. The mean biological half-life of Naproxen in humans is approximately 13

hours, and at therapeutic levels it is greater than 99% bound. Approximately 95% of the dose is excreted in the urine, primarily as Naproxen, 6-O-desmethyl Naproxen or their conjugates.

Similar to other nonsteroidal anti-inflammatory drugs (NSAIDs), Naproxen can cause gastrointestinal bleeding, though less frequently than some of the other drugs of its type. However, when bleeding occurs, it can be very severe.

Surprisingly, it has been found that the oral absorption of Naproxen is sustained with no compromise on total bioavailability when it is administered in combination with dimethyl beta-cyclodextrin. It is believed that amino substituted cyclodextrins also provide enhanced delivery.

Thus, according to one embodiment of this invention there is provided an inclusion complex comprising Naproxen or a pharmacologically active derivative or metabolite thereof, together with a cyclodextrin derivative or salt thereof.

As before, the cyclodextrin derivative is preferably dimethyl beta-cyclodextrin (DMBCD) or amino cyclodextrins. Where amino cyclodextrins are used, C6 substituted β -cyclodextrins are preferred. The amino may be substituted with one or more substituents as described in WO 90/02141. The molar ratio of Naproxen to water-soluble cyclodextrin is preferably from about 1:1 to about 10:1.

Accordingly, other embodiments of this invention provide: pharmaceutical compositions comprising one of the aforementioned inclusion complexes and one or more pharmaceutically accepted carriers; a method for improving the solubility of Naproxen or a derivative or metabolite thereof in a neutral or acidic aqueous solution by forming an inclusion complex with the recited cyclodextrin derivatives; a method for decreasing the gastroirritation of Naproxen or a derivative or metabolite thereof in a host mammal by forming said inclusion complexes; and a method for treating a mammal in need of such treatment (e.g., one suffering from arthritic inflammation) by administering a therapeutically effective amount of an above described pharmaceutical composition. Determining such amounts will be within the ordinary skill of physicians in this art. Where DMBCD is used, oral administration is preferred.

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Example 4, *infra*, illustrates the preparation and oral administration of an inclusion complex and pharmaceutical composition within the scope of this invention. It will be seen that administering the inclusion complex of Naproxen and DMBCD appears to delay and prolong the absorption of Naproxen with no compromise on the total bioavailability of the drug.

The following examples are provided only to illustrate various embodiments of this invention, and do not in any way limit the scope of this invention.

EXAMPLE 1

Amiodarone (Sigma Chemical Co., St. Louis, MO) was triturated with the appropriate cyclodextrin (Nihon Shokuhin Kako Co Ltd., Chiyoda-Ku, Tokyo, Japan) in a 2:1 molar ratio and filled without compaction into size 00 hard gelatin capsules (DFC Thompson, Sydney, Australia). The dose of Amiodarone administered to pigs in each of the final formulations was 1500 mg. No formulation problems were experienced.

Eighteen healthy domestic pigs (Large White-Landrace cross) aged approximately 24 weeks and weighing 125 to 145 kg (mean 132.5; SE 1.1) were randomly allocated to four groups. Each of two groups of four pigs received Amiodarone and Amiodarone plus dimethyl β -cyclodextrin, respectively, while two groups of five pigs were given either Amiodarone plus alpha-cyclodextrin or Amiodarone plus beta-cyclodextrin.

An indwelling cannula was implanted into an internal jugular vein using a surgical technique similar to that reported previously. (Niiyama et al., H. Jpn. J. Vet. Res., Vol. 33, pp. 109 (1985)). Cannulae were kept clear between samplings with a heparin lock, which, together with the sampling line, was kept protected inside a small zippered pouch fixed dorsally to the neck with a collar. The entry point of the cannula tubing was sprayed routinely with an iodine-based antiseptic solution to prevent infection.

Animals were fasted for eighteen hours before drug administration, although free access to tap water was provided due to the propensity for pigs to suffer dehydration stress. Capsules were deposited at the back of the throat using a hollow

perspex tube with an internal plunger. Animals were observed closely for at least thirty minutes afterwards to ensure that the entire dose was ingested. Blood samples (5 ml) were withdrawn hourly during the first 6 hours after drug administration and then every two hours up to 12 hours. Further samples were taken at 24 hours, then daily for 7 days. Blood specimens were centrifuged (2500 g, 2 minutes) and the plasma removed and stored at -70°C until submitted for analysis. Amiodarone is stable under these storage conditions for several months. Plasma concentrations of Amiodarone were assayed within three weeks of blood collection by high performance liquid chromatography. (Muir et al., *J. Chromatogr.*, Vol. 374, pp. 394-9 (1986)).

Figure 1 shows the mean plasma concentrations of Amiodarone measured after oral administration of the drug alone or in combination with cyclodextrins. In most cases, measurable plasma concentrations of Amiodarone were present up to 12 hours, but never at 24 hours or later. The appearance of Amiodarone concentrations was delayed when the drug was administered in combination with the cyclodextrins. Surprisingly, drug released from the beta-cyclodextrin formulation peaked initially at 3 hours but gave a second, higher peak several hours later. Table 1 presents a summary of bioavailability parameters derived from the plotted data.

TABLE 1
Mean (SE) Bioavailability Parameters of
Amiodarone following Oral Administration
of Amiodarone (1500 mg) Alone and in
Combination with Cyclodextrins (1:2 molar ratio)
to 18 Pigs.

Treatment	N	Cmax [ng/ml]	Tmax [h]	AUC [0-24h] [ng/ml.h]
Amiodarone	4	285 (76)	3.25 (0.48)	1212 (345)
Amiodarone plus alpha-cyclodextrin	5	342 (50)	7.22 (1.65)	2034 (585)

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Amiodarone plus	5	250 (33)	4.80 (0.20)	1797 (360)
beta-cyclodextrin				
Amiodarone plus	4	333 (36)	5.22 (1.03)	1951 (331)
DMBCD				

Areas under the Amiodarone plasma concentration-time curve (AUC) were calculated using the trapezoidal rule routine in the MKMODEL pharmacokinetic package (MKMODEL. An Extended Least Squares Modelling System. Elsevier-Biosoft: London, 1987). AUCs from 0 to 24 hours were reported since, in most cases, insufficient data in the terminal decay phase precluded an accurate extrapolation of areas to infinite time. AUCs determined after administration of the beta- dimethyl beta- and alpha-cyclodextrin formulations gave mean, rank-order increases of 41%, 61% and 68%, when compared with the area obtained after administration of Amiodarone alone.

The pharmacokinetics of Amiodarone are complex. For example, in man, the long biological half-life of the drug is increased further on repeated dosing, supposedly because of tissue saturation effects. It was decided, therefore, to adopt a parallel trial design in which each animal received only one Amiodarone formulation during the entire study period. It is evident that the three cyclodextrins presently tested facilitated an improvement in the extent of oral Amiodarone absorption. Of interest is an apparent prolonged absorption of Amiodarone from the cyclodextrin formulations, without any marked compromise in the magnitude of peak Amiodarone concentrations.

Without wishing to be bound by any proposed mechanism for the observed beneficial effect, it is possible that a "sustained release" effect prevails, perhaps due to binding of Amiodarone to the internal, hydrophobic environment of the hollow cyclodextrin annulus.

EXAMPLE 2

Melphalan (Sigma Chemical Co., St. Louis, MO) was triturated with dimethyl beta-cyclodextrin, DMBCD (Nihon Shokuhin Kako Co. Ltd., Chiyoda-Ku, Tokyo, Japan) in a 2:1 molar ratio and filled without compaction into size 00 hard gelatin capsules (DFC

Thompson, Sydney, Australia). The dose of melphalan administered was 40 mg. No formulation difficulties were experienced.

Five healthy domestic pigs (Large White-Landrace hybrid) aged approximately 24 weeks and weighing 127-154 kg (mean 143; SE 7.9 kg) were selected for the study. An indwelling cannula was implanted into an internal jugular vein as described in Example 1.

On the first occasion, each animal received melphalan without DMBCD, followed one week later by the melphalan-DMBCD formulation. Animals were fasted for eighteen hours before drug administration, although free access to tap water was provided due to the propensity for pigs to suffer dehydration stress. Capsules were deposited at the back of the throat using a hollow perspex tube with an internal plunger. Animals were observed closely for at least thirty minutes to ensure that the entire dose was ingested.

Blood samples (10 ml) were withdrawn at 15, 30, 45, 60, 90, 120, 150 and 180 minutes after drug administration. Further samples were taken at 4, 5, 6, 8, 10, 12 and 24 hours. A pre-dose control was taken routinely just prior to drug administration.

Blood specimens were immediately centrifuged (ca. 2500 g, 2 minutes) and the plasma quickly removed and stored at -70°C until submitted for analysis. It was confirmed that melphalan is stable under these storage conditions for several weeks (Bosanquet & Gilby, 1982). Plasma concentrations of melphalan were assayed within three weeks of blood collection using a modified HPLC procedure (Adair et al., 1985).

Figure 2 shows the mean plasma concentrations of melphalan determined after oral administration of the drug alone or in combination with DMBCD. Melphalan was more rapidly absorbed from the cyclodextrin formulation; the mean half life of absorption from Figure 2 was approximately 30 minutes compared with about 60 minutes when melphalan alone was administered. The terminal half-life of melphalan in the pig was approximately 90 minutes, which compares favorably with that reported for the drug in man (Alberts et al., 1979). Surprisingly, the disappearance of melphalan from plasma appeared to be more rapid when the

cyclodextrin formulation was given. Area under the melphalan plasma concentration-time curve (AUC), peak melphalan plasma concentration (C_{max}) and time to reach peak concentration (T_{max}) were used to assess the comparative oral bioavailability of melphalan. AUCs were calculated using the trapezoidal rule. Areas from 0 to 12 hours were reported since, in some cases, insufficient data in the terminal decay phase precluded an accurate extrapolation of areas to infinite time. The bioavailability parameters are summarized in Table 2.

TABLE 2

Means (s.e. mean) bioavailability parameters of melphalan following oral administration of melphalan (40 mg) alone and in combination with DMBCD to 4 pigs

Treatment	C _{max} (ng ml ⁻¹)	T _{max} (h)	AUC (ng ml ⁻¹ h)
Melphalan	114 (47)	2.0 (0.3)	222 (97)
Melphalan + DMBCD	224 (36)	1.9 (0.4)	426 (99)

Unfortunately, specimens from one animal given melphalan were lost due to equipment malfunction, while data from a second animal given melphalan plus DMBCD could not be analyzed due to unexplained chromatographic interference.

The results indicate that the oral absorption of melphalan is markedly improved when the drug is administered with excess DMBCD. There was nearly a two-fold increase in both the peak melphalan concentration and area under the curve when the physical mixture of DMBCD and melphalan was given.

In animal, melphalan was undetectable in plasma over the entire sampling period, but was readily measurable (C_{max}, 131 ng ml⁻¹) when the drug was given with DMBCD. Besides improving melphalan absorption, it is also significant that the administration of the DMBCD formulation reduced the variability in the AUC and C_{max} by a factor of one half (see Table 2).

EXAMPLE 3

Administration of melphalan together with either alpha-cyclodextrin or beta-cyclodextrin caused a decrease in AUC and Cmax values of nearly 50%. No significant difference in Tmax was observed. Formulations were prepared and administered as in Example 2.

Without wishing to be bound by an proposed mechanism for the observed beneficial effects, it appears that the difference in effect between the naturally occurring cyclodextrins and DMBCD is due to the much greater solubility in water of the latter compound (Uekama and Otagiri, 1987). It is likely that an important factor in the improved absorption of melphalan is an increased rate of drug dissolution in vivo. It is also possible that DMBCD plays a part in protecting melphalan from hydrolysis during its transit through the gastro-intestinal tract.

EXAMPLE 4

Naproxen (Sigma Chemical Co., St Louis, Mo) was triturated with dimethyl beta-cyclodextrin, DMBCD (Nihon Shokuhin Kako Co. Ltd. Chihoda-Ku, Tokyo, Japan) in a 2:1 molar ratio and filled without compaction into size 00 hard gelatin capsules (DFC Thompson, Sydney, Australia). The dose of Naproxen administered was 500 mg. No formulation difficulties were experienced.

Seventeen healthy domestic pigs (Large White-Landrace cross) aged approximately 24 weeks and weighing 124 to 160 kg were randomly allocated to two groups (Table 3). A group of 12 pigs received Naproxen alone (500 mg) and another group of 5 pigs received Naproxen plus dimethyl beta-cyclodextrin, respectively.

TABLE 3

Weights of pigs treated with Naproxen alone and Naproxen plus dimethyl beta cyclodextrin (DMBCD)

Treatment	Weights of Pigs	Mean (SD)
Naproxen alone	153 160 151 158 155 130 132 135 137 157 137 134 145 (12)	
Naproxen 132 142 147 124 152 and DMBCD		139 (13)

* No significant difference (at 10% level) in weights was found in between these two groups of pigs

An indwelling cannula was implanted into an internal jugular vein using the surgical technique described in Example 1.

Animals were fasted for eighteen hours before drug administration, although free access to tap water was provided due to the propensity for pigs to suffer dehydration stress. Capsules were deposited at the back of the throat using a hollow perspex tube with an internal plunger. Animals were observed closely for at least thirty minutes afterwards to ensure that the entire dose was ingested. Blood samples (5 mls) were withdrawn at 15, 30, 45, 60, 90, 120, 150 and 180 minutes after drug administration. Further samples were taken at 4, 5, 6, 8, 10, 12, 17, 24, 35 and 48 hours. A pre-dose control was taken routinely just prior to drug administration.

Blood specimens were immediately centrifuged (ca. 2500g, 2 minutes) and the plasma quickly removed and stored at -70°C until submitted for analysis. Naproxen is stable under these storage conditions for several months. Plasma concentrations of Naproxen were assayed within three weeks of blood collection by gas chromatography.

Figure 3 shows the mean plasma concentrations of Naproxen determined after oral administration of the drug alone or in combination with DMBCD.

The mean bioavailability parameters are summarized in Table 4.

TABLE 4

Mean (SD) bioavailability parameters of Naproxen oral administration of Naproxen (500mg) alone and in combination with DMBCD to 17 pigs.

Treatment	N	Cmax mg/l	Tmax hr	AUC (0-48 hr) mg/l.hr	AUC (0-∞) mg/l.hr	t1/2 hr
Naproxen alone	12	38.9 (11.5)	2.21 (1.39)	482 (259)	552 (334)	12.7 (5.65)
Naproxen DMBCD	5	20.8 (10.9)	8.80 (3.60)	477 (113)	641 (203)	22.3 (14.7)
F value		9.03	31.1	0.0	0.3	4.06
level of significance		<0.01	<0.001	N.S.	N.S.	<0.1

The Cmax, Tmax and the terminal half-life of Naproxen in the pigs receiving Naproxen alone were 38.9 mg/l, 2.21 hours and 12.7 hours, respectively, which compared favorably with that reported for the drug in man. However, the parameters such as Cmax and Tmax were found to be significantly lower in pigs receiving Naproxen plus DMBCD. Despite the differences in these parameters, there is no significant difference in area under the Naproxen plasma concentrations time curve (AUC) in between these two groups of pigs. Therefore, DMBCD appeared to delay and prolong the absorption of Naproxen with no compromise on the total bioavailability of the drug. This suggestion was further supported by the finding that the elimination half-life was longer in pigs receiving the cyclodextrin formulation since elimination half-life is determined by the volume of distribution and the clearance of the individual. These two groups of pigs were physiologically and anatomically (i.e. weight) similar and no difference in elimination half-life in these two groups would be expected. The apparent extended half-life observed in pigs

receiving the cyclodextrin formulation was then caused by the continuous absorption during the elimination phase of the drug.

It is evident that the dimethyl beta-cyclodextrin presently tested prolonged absorption of Naproxen from the cyclodextrin formulation, without any compromise in the total bioavailability.

Examples 5-10, illustrate the association constants between Naproxen and α -, β -, γ -, dimethyl β -, and amino cyclodextrins.

EXAMPLE 5

Measurement of association constant between α -CD and Naproxen

A stock solution of $8.27 \times 10^{-4} \text{M}$ Naproxen and a stock solution of $1.34 \times 10^{-1} \text{M}$ α -CD were made up in phosphate buffer at pH 6.9. A total of 17 spectra were run, both sample and reference solutions being made up by weight dilutions of the stocks.

sample [α -CD] = 6.43, 6.22, 5.92, ..., 0.581, $0.311 \times 10^{-2} \text{M}$
reference [α -CD] = 12.8, 12.4, 11.9, ..., 1.16, $0.623 \times 10^{-2} \text{M}$
sample [Naproxen] = $(4.135 \pm 0.005) \times 10^{-4} \text{M}$
reference [Naproxen] = $8.27 \times 10^{-4} \text{M}$

The spectrum of each sample/reference solution pair was recorded in 2.000 cm pathlength cells over 340-280 nm, sampling at 1.0 nm intervals, using an integration time of 6.4 seconds per wavelength and a band width of 1.0 nm. Fitted values in the region 340-333 nm and 294-288 nm were averaged to give an association constant of 16 ± 1 .

EXAMPLE 6

Measurement of association constant between β -CD and Naproxen

A stock solution of $8.92 \times 10^{-4} \text{M}$ Naproxen and a stock solution of $1.58 \times 10^{-2} \text{M}$ β -CD were made up in phosphate buffer at pH 6.9. A total of 16 spectra were run, both sample and reference solutions being made up by weight dilutions of the stocks.

sample [β -CD] = 7.71, 7.04, 6.44, ..., 0.643, $0.331 \times 10^{-3} \text{M}$
reference [β -CD] = 15.4, 14.1, 12.9, ..., 1.29, $0.662 \times 10^{-3} \text{M}$
sample [Naproxen] = $(4.455 \pm 0.005) \times 10^{-4} \text{M}$
reference [Naproxen] = $8.92 \times 10^{-4} \text{M}$

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The spectrum of each sample/reference solution pair was recorded in 2.000 cm pathlength cells over 340-280 nm, sampling at 1.0 nm intervals, using an integration time of 6.4 seconds per wavelength and a band width of 1.0 nm. Fitted values in the region 339-334 nm and 293-289 nm were averaged to give an association constant of 670 ± 40 .

EXAMPLE 7

Measurement of association constant between γ -CD and Naproxen

A stock solution of 7.99×10^{-4} M Naproxen and a stock solution of 1.2×10^{-2} M γ -CD were made up in phosphate buffer at pH 6.9. A total of 23 spectra were run, both sample and reference solutions being made up by weight dilutions of the stocks.

sample [γ -CD]=5.75, 5.50, 5.17, ..., 0.487, 0.242×10^{-3} M
reference [γ -CD]=11.4, 10.9, 10.3, ..., 0.970, 0.484×10^{-3} M
sample [Naproxen]= $(3.95 \pm 0.05) \times 10^{-4}$ M
reference [Naproxen]= 7.99×10^{-4} M

The spectrum of each sample/reference solution pair was recorded in 2.000 cm pathlength cells over 350-280 nm, sampling at 1.0 nm intervals, using an integration time of 6.4 seconds per wavelength and a band width of 1.0 nm. Fitted values in the region 340-334 nm and 293-288 nm were averaged to give an association constant of 120 ± 10 .

EXAMPLE 8

Measurement of association constant between dimethyl- β -cyclodextrin (DIMEB) and Naproxen

A stock solution of 7.68×10^{-4} M Naproxen and two stock solutions of 1.44×10^{-1} M and 2.88×10^{-2} M DIMEB were made up in phosphate buffer at pH 6.9. A total of 20 spectra were run, both sample and reference solutions being made up by weight dilutions of the stocks.

sample [DIMEB]=6.69, 5.82, 4.80, ..., 0.219, 0.102×10^{-2} M
reference [DIMEB]=13.4, 11.6, 9.61, ..., 0.439, 0.204×10^{-2} M
Sample [Naproxen]= 3.84×10^{-4} M
reference [Naproxen]= 7.68×10^{-4} M

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The spectrum of each sample/reference solution pair was recorded in 0.8750 cm pathlength cells over 340-280 nm, sampling at 1.0 nm intervals, using an integration time of 1.6 seconds per wavelength and a slit width of 0.4 nm. Fitted values in the region 340-331 nm, 325-321 nm and 289-285 nm were averaged to give an association constant of 510 ± 80 .

EXAMPLE 9

Measurement of association constant between

β -CDNH₂ and Naproxen

A stock solution of 7.68×10^{-4} M Naproxen and a stock solution of 2.03×10^{-2} M β -CDNH₂ were made up in phosphate buffer at pH 6.9. A total of 14 spectra were run, both sample and reference solutions being made up by weight dilutions of the stocks.

sample [β -CDNH₂]=9.45, 8.50, 7.51, ..., 2.15, 1.66×10^{-3} M

reference [β -CDNH₂]=18.9, 17.0, 15.0, ..., 4.29, 3.32×10^{-3} M

sample [Naproxen]= 3.84×10^{-4} M

reference [Naproxen]= 7.68×10^{-4} M

The spectrum of each sample/reference solution pair was recorded in 0.8750 cm pathlength cells over 340-280 nm, sampling at 1.0 nm intervals, using an integration time of 1.6 seconds per wavelength and a slit width of 0.6 nm. Fitted values in the region 340-331 nm, 319 nm and 291-285 nm were averaged to give an association constant of 640 ± 100 .

EXAMPLE 10

Measurement of association constant between β -CDN4N and Naproxen

A stock solution of 7.80×10^{-4} M Naproxen and a stock solution of 4.23×10^{-2} M β -CDN4N were made up in tris buffer at pH 8.6. A total of 15 spectra were run, both sample and reference solutions being made up by weight dilutions of the stocks.

sample [β -CDN4N]=19.6, 17.9, 1.58, ..., 3.73, 2.78×10^{-3} M

reference [β -CDN4N]=39.2, 35.8, 31.6, ..., 7.47, 5.55×10^{-3} M

sample [Naproxen]= 3.90×10^{-4} M

reference [Naproxen]= 7.80×10^{-4} M

The spectrum of each sample/reference solution pair was recorded in 0.8750 cm pathlength cells over 340-270 nm, sampling at 1.0 nm intervals, using an integration time of 1.6 seconds per wavelength and a slit width of 1.0 nm. Fitted values in the region 340-332 nm, 323 nm and 290-287 nm were averaged to give an association constant of 150 ± 30 .

Examples 11-13 illustrate the preparation of inclusion complexes with varying ratios of Naproxen and cyclodextrin derivative in solution. It has been found that, in some instances, greater concentrations of cyclodextrin derivative can more quickly include a given quantity of drug.

EXAMPLE 11

Naproxen with 6^A-amino-6^A-deoxy- β -cyclodextrin 1:2 complex

To a solution of β -CDNH₂ (250 mg, 0.22 mmol) in Milli-Q® water (10 ml) was added solid Naproxen (25 mg, 0.11 mmol) and the resulting suspension was stirred at room temperature for 2 hours during which time a clear colorless solution was obtained. Filtration and evaporation to dryness in vacuo over phosphorus pentoxide gave a yellow powder (250 mg) which was the Naproxen modified cyclodextrin formulation.

EXAMPLE 12

Naproxen with 6^A-amino-6^A-deoxy- β -cyclodextrin 1:4 complex

To a solution of β -CDNH₂ (500 mg, 0.44 mmol) in Milli-Q® water (20 ml) was added solid Naproxen (25 mg, 0.11 mmol) and the resulting suspension was stirred at room temperature for 2 hours during which time a clear colorless solution was obtained. Filtration and evaporation to dryness in vacuo over phosphorus pentoxide gave a yellow powder (515 mg) which was the Naproxen modified cyclodextrin formulation.

EXAMPLE 13**Naproxen with 6^A-amino-6^A-deoxy- β -cyclodextrin 1:1 complex**

To a solution of β -CDNH₂ (250 mg, 0.22 mmol) in Milli-Q® water (10 ml) was added solid Naproxen (50 mg, 0.22 mmol) and the resulting suspension was stirred at room temperature for 4 hours during which time a clear colorless solution was obtained. filtration and evaporation to dryness in vacuo resulted in the isolation of a glassy material. Drying to constant weight in vacuo over phosphorus pentoxide gave a yellow powder (268 mg) which was the Naproxen modified cyclodextrin formulation.

Example 14 illustrates the measurement of the solubility of Amiodarone HCl in pure water.

EXAMPLE 14**Solubility of AmiodaroneHCl in pure water**

The saturated solution of AmiodaroneHCl in pure water was prepared by adding an excess of AmiodaroneHCl (0.1 g) to 10 ml MILLI-Q water and shaking the sample bottle in a water bath thermostatted at 25.0°C for at least 3 days. The clear solution (0.4 g) was mixed with 1.6 g ethanol. The concentration of the solution was calculated from the measured absorbance at 242 nm and the known extinction coefficient, which led to the determination of the solubility of AmiodaroneHCl in pure water, 200 mg.l⁻¹. Same procedure was repeated 3 days after to assure the saturation of the solution.

It will be apparent to those skilled in the art that various modifications and variations can be made to the compositions of matter and methods of this invention. Thus, it is intended that the present invention cover the modifications and variations of this invention provided they come within the scope of the appended claims and their equivalents. All references in the claims to a composition of matter such as an inclusion complex, cyclodextrin derivative, and pharmaceutical composition expressly includes the salts and hydrates thereof.

What is claimed is:

1. An inclusion complex comprising Amiodarone or a pharmacologically active derivative or metabolite thereof included in a substituted or unsubstituted cyclodextrin or salt thereof selected from the group consisting of α -, β -, γ -, δ -, dimethyl β -, and amino cyclodextrin.
2. An inclusion complex according to claim 1, wherein the cyclodextrin is amino cyclodextrin.
3. An inclusion complex according to claim 2, wherein at least one C6 hydroxyl of said cyclodextrin is substituted with an amino group, and said amino group may be substituted with one or more substituents.
4. An inclusion complex according to claim 3, wherein the cyclodextrin is β -cyclodextrin.
5. An inclusion complex according to claim 1, wherein said substituted cyclodextrin is dimethyl β -cyclodextrin.
6. A method for improving the solubility of Amiodarone or a pharmacologically active derivative or metabolite thereof in a neutral or acidic aqueous solution, comprising the step of forming an inclusion complex comprising Amiodarone or said derivative or metabolite included in a substituted or unsubstituted cyclodextrin or salt thereof selected from the group consisting of α -, β -, γ -, δ -, dimethyl β -, and amino cyclodextrin.
7. A method according to claim 6, wherein the cyclodextrin is amino cyclodextrin.
8. A method according to claim 7, wherein at least one C6 hydroxyl of the cyclodextrin is substituted with an amino group, and said amino group may be substituted with one or more substituents.

9. A method according to claim 7, wherein the cyclodextrin is β -cyclodextrin.

10. A method according to claim 6, wherein said substituted cyclodextrin is dimethyl β -cyclodextrin.

11. A method for improving the bioavailability of Amiodarone or a pharmacologically active derivative or metabolite thereof in a host mammal, comprising the step of forming an inclusion complex comprising Amiodarone or said derivative or metabolite included in a substituted or unsubstituted cyclodextrin or salt thereof selected from the group consisting of α -, β -, γ -, δ -, dimethyl β -, and amino cyclodextrin.

12. A method according to claim 11, wherein the cyclodextrin is amino cyclodextrin.

13. A method according to claim 12, wherein at least one C6 hydroxyl of the cyclodextrin is substituted with an amino group, and said amino group may be substituted with one or more substituents.

14. A method according to claim 13, wherein the cyclodextrin is β -cyclodextrin.

15. A method according to claim 11, wherein said substituted cyclodextrin is dimethyl β -cyclodextrin.

16. A pharmaceutical composition comprising a pharmaceutically acceptable carrier and an inclusion complex according to any of claims 1-5.

17. A method for treating a mammal in need of such treatment, comprising orally or parenterally administering to said mammal a therapeutically effective amount of the pharmaceutical composition of claim 16.

18. An inclusion complex comprising a compound containing a nitrogen mustard group and a cyclodextrin derivative or salt thereof selected from the group consisting of dimethyl β -cyclodextrin and amino cyclodextrin.

19. An inclusion complex according to claim 18, wherein said compound containing a nitrogen mustard group is selected from the group consisting of melphalan, uracil mustard, cyclophosphamide, mechlorethamine and chlorambucil.

20. An inclusion complex according to claim 19, wherein said cyclodextrin derivative is an amino cyclodextrin.

21. An inclusion complex according to claim 20, wherein at least one C6 hydroxyl of the cyclodextrin is substituted with an amino group, and said cyclodextrin is a β -cyclodextrin.

22. An inclusion complex according to claim 21, wherein said amino group is substituted with one or more substituents.

23. An inclusion complex according to claim 19, wherein the cyclodextrin derivative is dimethyl β -cyclodextrin.

24. A pharmaceutical composition comprising a pharmaceutically acceptable carrier, and an inclusion complex according to any of claims 18-23.

25. A method for treating a mammal in need of such treatment, comprising orally or parenterally administering a therapeutically effective amount of a pharmaceutical composition according to claim 24.

26. A method for improving the solubility of a compound containing a nitrogen mustard group in a neutral or acidic aqueous solution, comprising the step of forming an inclusion complex comprising a compound containing a nitrogen mustard group included in a cyclodextrin derivative or salt thereof selected

from the group consisting of dimethyl β -cyclodextrin and amino cyclodextrin.

27. A method according to claim 26, wherein said compound containing a nitrogen mustard group is selected from the group consisting a melphalan, uracil mustard, cyclophosphamide, mechlorethamine and chlorambucil.

28. A method according to claim 27, wherein said cyclodextrin derivative is an amino cyclodextrin.

29. A method according to claim 28, wherein at least one C6 hydroxyl of the cyclodextrin is substituted with an amino group, and said cyclodextrin is a β -cyclodextrin.

30. A method according to claim 29, wherein said amino group is substituted with one or more substituents.

31. A method according to claim 27, wherein said cyclodextrin derivative is dimethyl β -cyclodextrin.

32. A method for improving the bioavailability of a compound containing a nitrogen mustard group in a host mammal, comprising the step of forming an inclusion complex comprising a compound containing a nitrogen mustard group included in a cyclodextrin derivative or salt thereof selected from the group consisting of dimethyl β -cyclodextrin and amino cyclodextrin.

33. A method according to claim 32, wherein said compound containing a nitrogen mustard group is selected from the group consisting a melphalan, uracil mustard, cyclophosphamide, mechlorethamine and chlorambucil.

34. A method according to claim 33, wherein said cyclodextrin is an amino cyclodextrin.

35. A method according to claim 34, wherein at least one C6 hydroxyl of the cyclodextrin is substituted with an amino group, and said cyclodextrin is a β -cyclodextrin.

36. A method according to claim 35, wherein said amino group is substituted with one or more substituents.

37. A method according to claim 33, wherein said cyclodextrin derivative is dimethyl β -cyclodextrin.

38. An inclusion complex comprising Naproxen or a pharmacologically active derivative or metabolite thereof included in a cyclodextrin derivative or salt thereof selected from the group consisting of dimethyl β -cyclodextrin and amino cyclodextrin.

39. An inclusion complex according to claim 38, wherein the cyclodextrin derivative is amino cyclodextrin.

40. An inclusion complex according to claim 38, wherein at least one C6 hydroxyl of the cyclodextrin is substituted with an amino group, and said cyclodextrin is a β -cyclodextrin.

41. An inclusion complex according to claim 38, wherein said amino group is substituted with one or more substituents.

42. An inclusion complex according to claim 38, wherein said cyclodextrin derivative is dimethyl β -cyclodextrin.

43. A method for improving the solubility of Naproxen or a pharmacologically active derivative or metabolite thereof in a neutral or acidic aqueous solution, comprising the step of forming an inclusion complex comprising Naproxen or said derivative or metabolite included in a cyclodextrin derivative or salt thereof selected from the group consisting of dimethyl β -cyclodextrin and amino cyclodextrin.

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44. A method according to claim 43, wherein the cyclodextrin is amino cyclodextrin.

45. A method according to claim 43, wherein at least one C6 hydroxyl of the cyclodextrin is substituted with an amino group, and said cyclodextrin is a β -cyclodextrin.

46. A method according to claim 43, wherein said amino group is substituted with one or more substituents.

47. A method according to claim 43, wherein the cyclodextrin derivative is dimethyl β -cyclodextrin.

48. A method for decreasing the gastroirritation of Naproxen or a pharmacologically active derivative or metabolite thereof in a host mammal, comprising the step of forming an inclusion complex comprising Naproxen or said derivative or metabolite included in a cyclodextrin derivative or salt thereof selected from the group consisting of dimethyl β -cyclodextrin and amino cyclodextrin.

49. A method according to claim 48, wherein the cyclodextrin is amino cyclodextrin.

50. A method according to claim 48, wherein at least one C6 hydroxyl of the cyclodextrin is substituted with an amino group, and said cyclodextrin is a β -cyclodextrin.

51. A method according to claim 48, wherein said amino group is substituted with one or more substituents.

52. A method according to claim 48, wherein the cyclodextrin derivative is dimethyl β -cyclodextrin.

53. A pharmaceutical composition comprising a pharmaceutically acceptable carrier, and an inclusion complex according to any of claims 38-42.

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54. A method for treating a mammal in need of such treatment, comprising orally administering to said mammal a therapeutically effective amount of the pharmaceutical composition of claim 53.

55. An inclusion complex substantially as hereinbefore described with reference to the accompanying drawings and/or any one of the foregoing examples.

56. A method substantially as hereinbefore described with reference to the accompanying drawings and/or any one of the foregoing examples.

57. A pharmaceutical composition substantially as hereinbefore described with reference to the accompanying drawings and/or any one of the foregoing examples.

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58. An inclusion complex comprising at least one pharmaceutical, pesticidal, herbicidal, agricultural, cosmetic or personal care agent or a pharmacologically active derivative or metabolite thereof included in a substituted or unsubstituted cyclodextrin or salt thereof.

59. An inclusion complex according to Claim 58, wherein the cyclodextrin is an α - or a γ -cyclodextrin.

60. An inclusion complex according to Claim 58, wherein the cyclodextrin is a β -cyclodextrin.

61. An inclusion complex according to Claim 58, wherein the cyclodextrin is hydroxypropyl- α -cyclodextrin or hydroxypropyl- γ -cyclodextrin.

62. An inclusion complex according to Claim 58, wherein the cyclodextrin is hydroxypropyl- β -cyclodextrin.

63. An inclusion complex according to Claim 58, wherein said substituted or unsubstituted cyclodextrin is dimethyl- β -cyclodextrin.

64. An inclusion complex according to Claim 58, wherein said substituted or unsubstituted cyclodextrin is dimethyl- α -cyclodextrin or dimethyl- γ -cyclodextrin.

65. An inclusion complex according to any one of Claims 58 to 64, wherein at least one C2, C3, C6 hydroxyl of said cyclodextrin is substituted with a carboxylic acid group or with a substituent that contains a carboxylic acid group.

66. An inclusion complex according to Claim 65, wherein said substituent containing a carboxylic acid group

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comprises an ester, amide, amino, ether, thioether, alkyl, or aryl group.

67. An inclusion complex according to Claim 66, wherein said substituent containing a carboxylic acid group comprises an amide group.

68. An inclusion complex according to Claim 67, wherein the cyclodextrin is 6^A-amino-6^A-deoxy-6^A-N-(3-carboxypropanoyl) - β -cyclodextrin, 6^A-amino-6^A-deoxy-6^A-N-(3-carboxypropanoyl) - α -cyclodextrin or 6^A-amino-6^A-deoxy-6^A-N-(3-carboxypropanoyl) - γ -cyclodextrin.

69. An inclusion complex comprising at least one pharmaceutical, pesticidal, herbicidal, agricultural, cosmetic, or personal care agent included in a cyclodextrin derivative or salt thereof, said cyclodextrin derivative comprising a cyclodextrin having at least one substitution in which a C2, C3 or C6 hydroxyl is substituted with a substituent comprising an amino, ester, amido, ether, thioether, substituted or unsubstituted alkyl or aryl, or carboxylic acid group.

70. An inclusion complex according to Claim 69, wherein said cyclodextrin derivative is an α -cyclodextrin derivative or a γ -cyclodextrin derivative.

71. An inclusion complex according to Claim 69, wherein said cyclodextrin derivative is a β -cyclodextrin derivative.

72. An inclusion complex according to any one of Claims 69 to 71 wherein said substituent is a carboxylic acid group, or a group which contains a carboxylic acid group.

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73. An inclusion complex according to Claim 72, wherein said substituent containing a carboxylic acid group comprises an amide group.

74. An inclusion complex according to any one of Claims 69 to 73 wherein a C6 hydroxyl is substituted with said substituent.

75. An inclusion complex according to Claim 73, wherein said cyclodextrin derivative is 6^A-amino-6^A-deoxy-6^A-N- (3-carboxypropanoyl) - α -cyclodextrin, 6^A-amino-6^A-deoxy-6^A-N- (3-carboxypropanoyl) - γ -cyclodextrin or 6^A-amino-6^A-deoxy-6^A-N- (3-carboxypropanoyl) - β -cyclodextrin.

76. An inclusion complex comprising at least one pharmaceutical, pesticidal, herbicidal, agricultural, cosmetic, or personal care agent included in a cyclodextrin derivative or salt thereof, said cyclodextrin derivative comprising a cyclodextrin having at least one substitution in which a C2, C3 or C6 hydroxyl is substituted with a group which, in neutral aqueous solution, has a net negative charge.

77. An inclusion complex according to Claim 76 wherein said group comprises carboxyl (CO_2^-), phosphato (PO_4^{-3}) or sulfonato (SO_3^-).

78. A method for improving the solubility of at least one pharmaceutical, pesticidal, herbicidal, agricultural, cosmetic or personal care agent in an aqueous and/or acidic solution, comprising the step of forming an inclusion complex comprising the at least one pharmaceutical, pesticidal, herbicidal, agricultural, cosmetic or personal care agent included in a substituted or unsubstituted cyclodextrin or salt thereof.

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79. A method according to Claim 78, wherein said inclusion complex comprising the at least one pharmaceutical, pesticidal, herbicidal, agricultural, cosmetic or personal care agent included in a cyclodextrin derivative or salt thereof comprises a cyclodextrin having one or more substitutions, wherein at least one C2, C3 or C6 hydroxyl is substituted with a substituent which contains a carboxylic acid group.

80. A method according to Claims 78 or 79, wherein said substituent comprises ester, amide, amine, ether, thioether, or substituted or unsubstituted alkyl or aryl.

81. A method according to Claim 79, wherein a C6 hydroxyl is substituted with a carboxylic acid group, or an ester or amide containing a carboxylic acid group.

82. A method according to any one of Claims 78 to 81 wherein said cyclodextrin derivative comprises a cyclodextrin having one or more substitutions, wherein at least one C2, C3 or C6 hydroxyl is substituted with a group which, in neutral aqueous solution, has a net negative charge.

83. A method according to any one of Claims 78 to 82, wherein said group comprises carboxyl, phosphato or sulfonato.

84. A method according to any one of Claims 77 to 83, wherein said cyclodextrin is a β -cyclodextrin.

85. A method according to any one of Claims 77 to 83, wherein said cyclodextrin is a α -cyclodextrin or γ -cyclodextrin.

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86. A method according to any one of Claims 78 to 83 wherein said inclusion complex comprises the at least one pharmaceutical, pesticidal, herbicidal, agricultural, cosmetic or personal care agent and 6^A-amino-6^A-deoxy-6^A-N (3-carboxypropanoyl) -β-cyclodextrin.

87. A method according to any one of Claims 78 to 83 wherein said inclusion complex comprises the at least one pharmaceutical, pesticidal, herbicidal, agricultural, cosmetic or personal care agent and 6^A-amino-6^A-deoxy-6^A-N (3-carboxypropanoyl) -α-cyclodextrin or 6^A-amino-6^A-deoxy-6^A-N (3-carboxypropanoyl) γ-cyclodextrin.

88. A method for improving the bioavailability of at least one pharmaceutical, pesticidal, herbicidal, agricultural, cosmetic or personal care agent in a host mammal comprising the step of forming an inclusion complex comprising the at least one pharmaceutical, pesticidal, herbicidal, agricultural, cosmetic or personal care agent included in a substituted or unsubstituted cyclodextrin or salt thereof.

89. A method according to Claim 88, wherein said inclusion complex comprising the at least one pharmaceutical, pesticidal, herbicidal, agricultural, cosmetic or personal care agent included in a cyclodextrin derivative or salt thereof comprises a cyclodextrin having one or more substitutions, wherein at least one C2, C3 or C6 hydroxyl is substituted with a carboxylic acid group or a substituent which contains a carboxylic acid group.

90. A method according to Claim 88 or 89, wherein said substituent comprises ester, amide, amine, ether, thioether, or substituted or unsubstituted alkyl or aryl.

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91. A method according to any one of Claims 88 to 90, wherein a C6 hydroxyl is substituted with a carboxylic acid group, or an ester or amide containing a carboxylic acid group.

92. A method according to any one of Claims 88 to 91, wherein said cyclodextrin derivative comprises a cyclodextrin having one or more substitutions, wherein at least one C2, C3 or C6 hydroxyl is substituted with a group which, in neutral aqueous solution, has a net negative charge.

93. A method according to Claim 92, wherein said group comprises carboxyl, phosphato or sulfonato.

94. A method according to any one of Claims 88 to 93, wherein said cyclodextrin is a β -cyclodextrin.

95. A method according to any one of Claims 88 to 93, wherein said cyclodextrin is an α -cyclodextrin or γ -cyclodextrin.

96. A method according to any one of Claims 88 to 91 wherein said inclusion complex comprises the at least one pharmaceutical, pesticidal, herbicidal, agricultural, cosmetic or personal care agent and 6^A-amino-6^A-deoxy-6^A-N-(3-carboxypropanoyl) - β -cyclodextrin.

97. A method according to any one of Claims 88 to 91, wherein said inclusion complex comprises the at least one pharmaceutical, pesticidal, herbicidal, agricultural, cosmetic or personal care agent and 6^A-amino-6^A-deoxy-6^A-N-(3-carboxypropanoyl) - α -cyclodextrin or 6^A-amino-6^A-deoxy-6^A-N-(3-carboxypropanoyl) - γ -cyclodextrin.

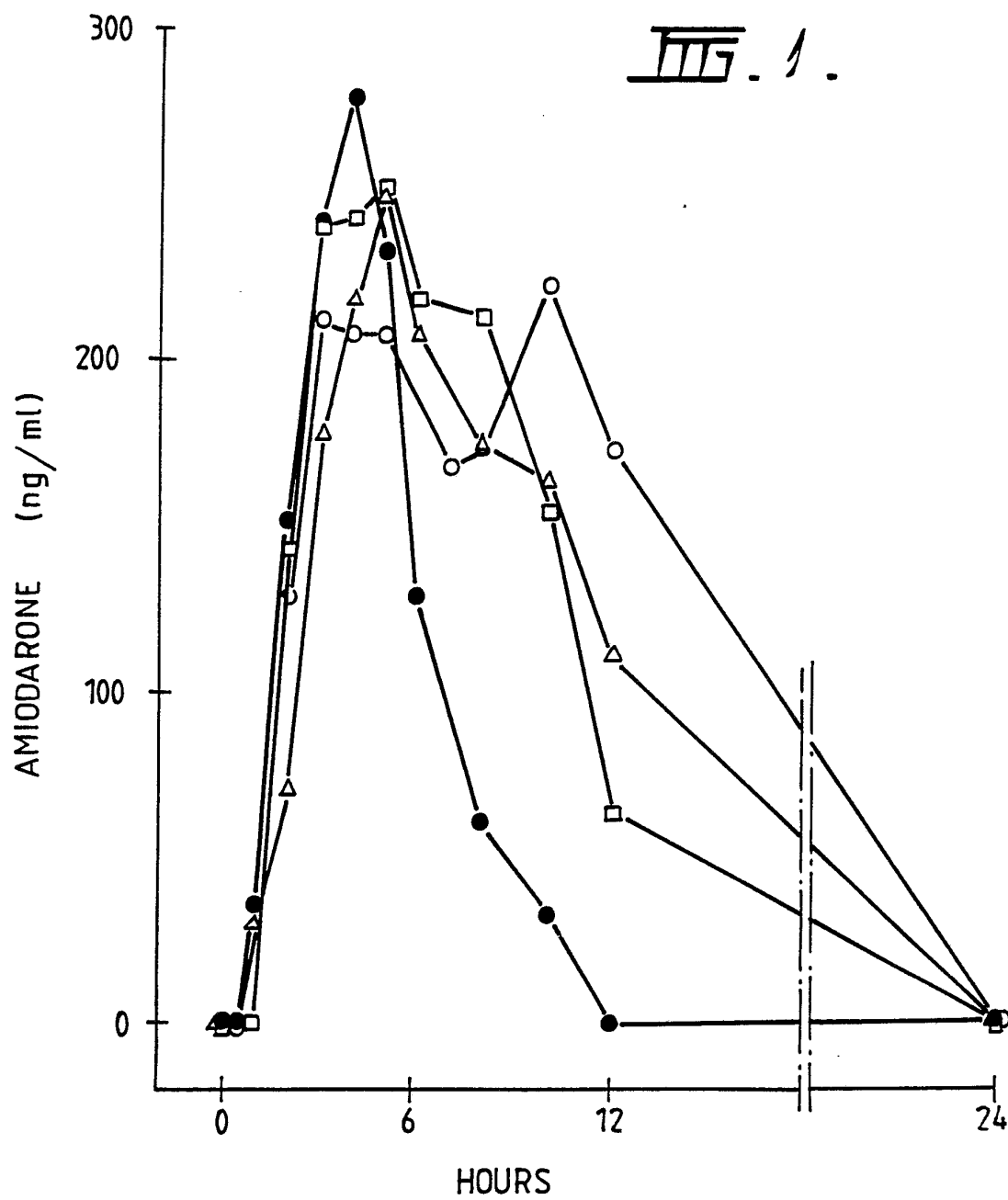
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98. A pharmaceutical composition comprising a pharmaceutically acceptable carrier and an inclusion complex according to any one of Claims 58 to 77.

99. A method for treating a mammal in need of such treatment, comprising orally or parenterally administering to said mammal a therapeutically effective amount of the pharmaceutical composition of Claim 98.

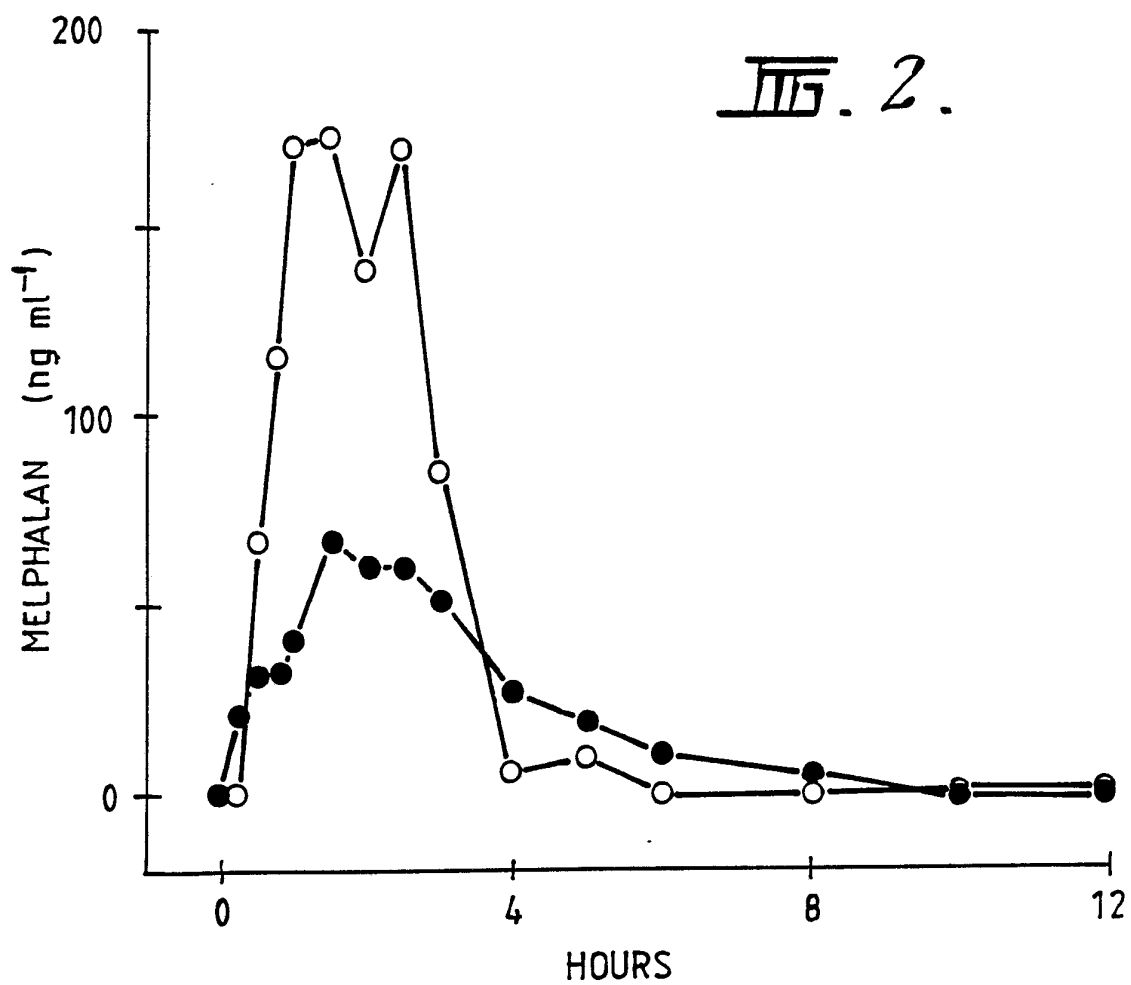
100. A method for treating a mammal in need of such treatment, comprising orally or parenterally administering to said mammal a therapeutically effective amount of the pharmaceutical composition of Claim 98.

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- — Amiodarone 1500 mg
- — Amiodarone plus α -cyclodextrin
- △ — Amiodarone plus β -cyclodextrin
- — Amiodarone plus dimethyl β -cyclodextrin

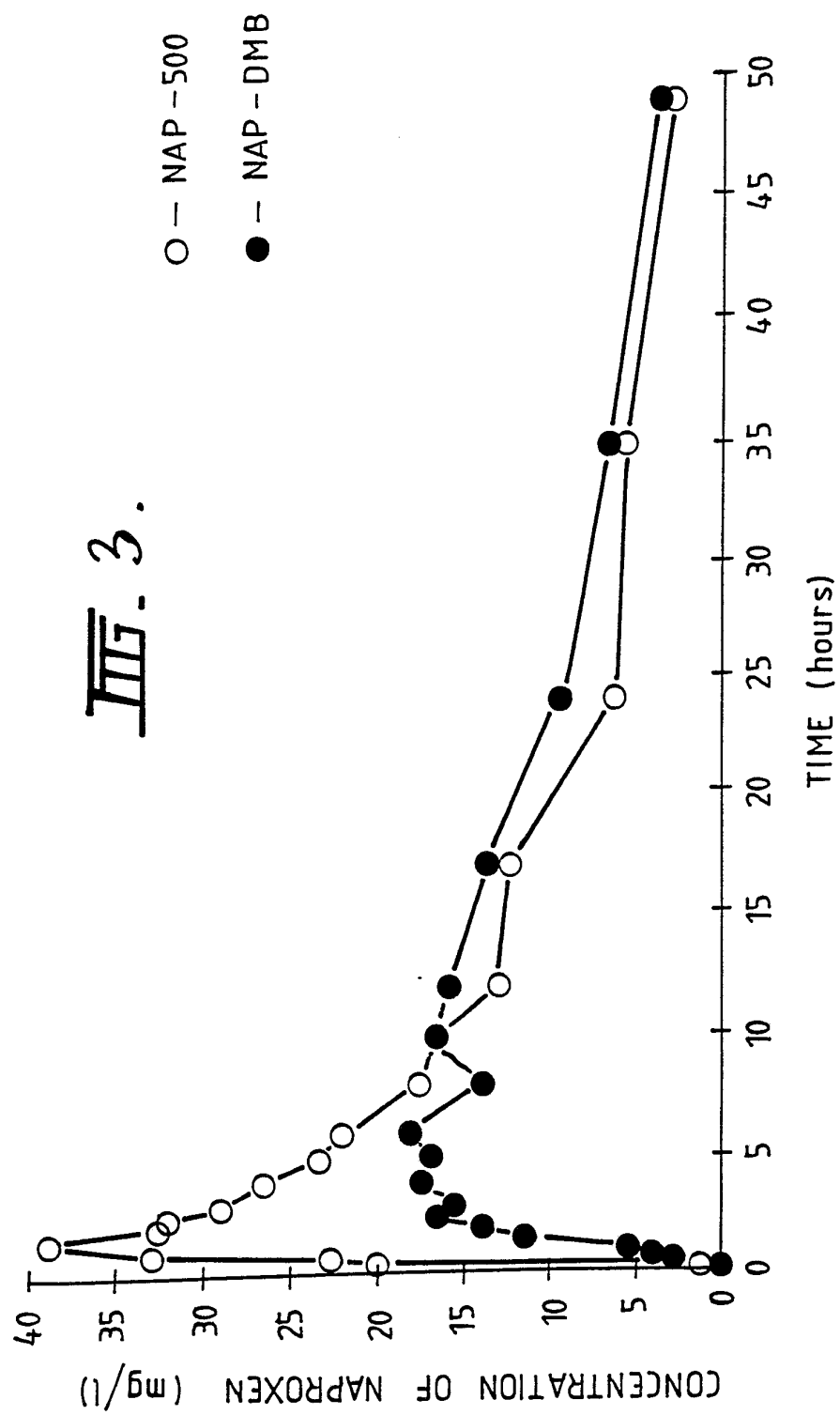
2/3



● — Melphalan

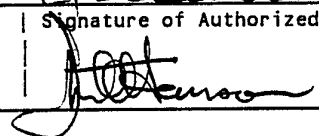
○ — Melphalan + DMB C D

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INTERNATIONAL SEARCH REPORT

International Application No. **PCT/AU 90/00418**

I. CLASSIFICATION OF SUBJECT MATTER (if several classification symbols apply, indicate all) 6		
According to International Patent Classification (IPC) or to both National Classification and IPC		
Int. Cl. ⁵ A61K 31/34, 31/19, 31/195, 31/505, 31/675, 47/40, 47/00, A01N 25/00		
II. FIELDS SEARCHED		
Minimum Documentation Searched 7		
Classification System	Classification Symbols	
IPC	A61K 47/40, 47/00, A01N 25/00	
Documentation Searched other than Minimum Documentation to the extent that such Documents are Included in the Fields Searched 8		
III. DOCUMENTS CONSIDERED TO BE RELEVANT 9		
Category*	Citation of Document, ¹¹ with indication, where appropriate, of the relevant passages 12	Relevant to Claim No 13
X,P	EP,A2, 0335545 (UNIVERSITY OF FLORIDA) 4 October 1989 (04.10.89) see claims 11 and 23	(18,19,23-27,31-33, 37,38,42,43,47,48, 52-54,58-64,69-71, 78,88,90,94,95, 98-100) (all other claims)
Y,P		
X,P	WO,A1, 90/02141 (AUSTRALIAN COMMERCIAL RESEARCH AND DEVELOPMENT LIMITED) 8 March 1990 (08.03.90)	(58-60,66,67,69-74, 76-85,88-95,98) (all other claims)
Y,P		
X	US,A, 3541077 (ARMBRUSTER, F.C.) 17 November 1970 (17.11.70)	(58,59,60)
Y	see column 1	(all other claims)
(continued)		
<p>* Special categories of cited documents: 10 "T" Later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention</p> <p>"A" document defining the general state of the art which is not considered to be of particular relevance "X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step</p> <p>"E" earlier document but published on or after the international filing date "Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.</p> <p>"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)</p> <p>"O" document referring to an oral disclosure, use, exhibition or other means "&" document member of the same patent family</p> <p>"P" document published prior to the international filing date but later than the priority date claimed</p>		
IV. CERTIFICATION		
Date of the Actual Completion of the International Search	Date of Mailing of this International Search Report	
	21 December 1990	
International Searching Authority	Signature of Authorized Officer	
Australian Patent Office	 (JOHN G. HANSON)	

III. DOCUMENTS CONSIDERED TO BE RELEVANT (CONTINUED FROM THE SECOND SHEET)

Category*	Citation of Document, with indication, where appropriate, of the relevant passages	Relevant to Claim No
X	US,A, 4826963 (STADLER NEE SZOKES et al) 2 May 1989 (02.05.89) see column 2	(58-60,63,64,69-71, 74,78,80,84,85, 88-90,94,95)
Y		(all other claims)
X	AU,B, 38352/85 (JANSSEN PHARMACEUTICA N.V.) 12 July 1985 (12.07.85) see page 2 lines 10-35, page 3 line 33 to page 4 line 5, page 5 lines 5 to 10	(58-64,69-71,74, 78,80,84,85,88,90, 94,95,98,99)
Y		(all other claims)
X	AU,A, 18352/88 (JANSSEN PHARMACEUTICA N.V.) 5 January 1989 (05.01.89) see pages 2-5	(58-66,69-72,74, 78-81,83-85,88-91, 93-95,98-100)
Y		(all other claims)
X	US,A, 4764604 (BEND W.W. MULLER) 16 August 1988 (16.08.88) see columns 1 and 2	(58- 6 6,69-71,74, 78,80,84,85,88, 90,94,95,98-100)
Y		(all other claims)
X	International Journal of Pharmaceutics, Volume 48(1-3) issued 1988, N. Erden and N. Celebi, "A Study of the Inclusion Complex of Naproxen with Cyclodextrin", see pages 83 to 88	(58,60,71,78,84, 88,98)
Y		(38-54) (all other claims)

ANNEX TO THE INTERNATIONAL SEARCH REPORT ON
INTERNATIONAL APPLICATION NO. PCT/AU 90/00418

This Annex lists the known "A" publication level patent family members relating to the patent documents cited in the above-mentioned international search report. The Australian Patent Office is in no way liable for these particulars which are merely given for the purpose of information.

Patent Document Cited in Search Report			Patent Family Members		
US	4764604	AU 54760/86 EP 197571 HU 42514 NO 860971 ZA 8601930	AU 583599 ES 552984 HU 198092 NZ 215350 US 4870060	DK 1214/86 FI 861064 JP 61275301 PT 82186	
EP	335545	AU 31762/89 EP 327766	EP 335545 JP 1294663	JP 2009825	
US	4826963	CN 1006889 FI 863652 JP 62103077	DD 254939 HU 41759 KR 9000542	EP 214647 HU 199444 PL 261349	
AU	38352/85	AU 565966 EP 149197 HU 200943 ZA 8410042	CA 1222697 FI 853198 NO 853070	DK 3595/85 HU 40561 WO 8502767	
AU	18352/88	DK 3609/88 HU 47433 NZ 225045 US 4956351	EP 300526 JP 1045319 PT 87880	FI 883136 NO 882926 ZA 8804747	
WO	9002141	AU 44290/89	CN 1040987	PT 91563	

END OF ANNEX