PCT WORLD INTELLECTUAL PROPERTY ORGANIZATION
International Bureau

INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 6 :
C08B 37/00, A61K 47/48, 31/135

A1

(11) International Publication Number: **WO 98/18827**

(43) International Publication Date: 7 May 1998 (07.05.98)

(21) International Application Number: PCT/GB97/02947

(22) International Filing Date: 27 October 1997 (27.10.97)

(30) Priority Data:
96/9049 28 October 1996 (28.10.96) ZA

(71) Applicant *(for all designated States except IS US)*: FARMARC NEDERLAND B.V. [NL/NL]; Citco Trust International Management (T.I.M.) B.V., World Trade Center, Tower B, 17th floor, Strawinskylaan 1725, NL–1007 JE Amsterdam (NL).

(71) Applicant *(for IS only)*: DYER, Alison, Margaret [GB/ZA]; 10 Veldtuin Place, Morningside, Sandton 2057 (ZA).

(72) Inventors; and
(75) Inventors/Applicants *(for US only)*: PENKLER, Lawrence, John [ZA/ZA]; 4 Verdun Road, Lorraine, Port Elizabeth 6070 (ZA). DE KOCK, Luéta–Ann [ZA/ZA]; The Barn, Kragga Kamma Road, Port Elizabeth 6055 (ZA).

(74) Agents: CURTIS, Philip, Anthony et al.; A.A. Thornton & Co., Northumberland House, 303–306 High Holborn, London WC1V 7LE (GB).

(81) Designated States: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, HU, ID, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW, ARIPO patent (GH, KE, LS, MW, SD, SZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG).

Published
With international search report.

(54) Title: INCLUSION COMPLEXES OF BETA–2–ANDRENERGICS FOR ORAL MUCOSAL DELIVERY

(57) Abstract

A pharmaceutical composition for oral mucosal delivery comprises an active ingredient, an inclusion complex of (a) a selective β_2–adrenergic agonist or a pharmaceutically acceptable salt thereof such as salbutamol, and (b) an unsubstituted or substituted beta– or gamma–cyclodextrin, and a pharmaceutically acceptable carrier for oral mucosal delivery. The pharmaceutical composition is of use in the treatment of reversible obstructive airways diseases such as asthma.

FOR THE PURPOSES OF INFORMATION ONLY

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

AL	Albania	**ES**	Spain	**LS**	Lesotho	**SI**	Slovenia
AM	Armenia	**FI**	Finland	**LT**	Lithuania	**SK**	Slovakia
AT	Austria	**FR**	France	**LU**	Luxembourg	**SN**	Senegal
AU	Australia	**GA**	Gabon	**LV**	Latvia	**SZ**	Swaziland
AZ	Azerbaijan	**GB**	United Kingdom	**MC**	Monaco	**TD**	Chad
BA	Bosnia and Herzegovina	**GE**	Georgia	**MD**	Republic of Moldova	**TG**	Togo
BB	Barbados	**GH**	Ghana	**MG**	Madagascar	**TJ**	Tajikistan
BE	Belgium	**GN**	Guinea	**MK**	The former Yugoslav Republic of Macedonia	**TM**	Turkmenistan
BF	Burkina Faso	**GR**	Greece			**TR**	Turkey
BG	Bulgaria	**HU**	Hungary	**ML**	Mali	**TT**	Trinidad and Tobago
BJ	Benin	**IE**	Ireland	**MN**	Mongolia	**UA**	Ukraine
BR	Brazil	**IL**	Israel	**MR**	Mauritania	**UG**	Uganda
BY	Belarus	**IS**	Iceland	**MW**	Malawi	**US**	United States of America
CA	Canada	**IT**	Italy	**MX**	Mexico	**UZ**	Uzbekistan
CF	Central African Republic	**JP**	Japan	**NE**	Niger	**VN**	Viet Nam
CG	Congo	**KE**	Kenya	**NL**	Netherlands	**YU**	Yugoslavia
CH	Switzerland	**KG**	Kyrgyzstan	**NO**	Norway	**ZW**	Zimbabwe
CI	Côte d'Ivoire	**KP**	Democratic People's Republic of Korea	**NZ**	New Zealand		
CM	Cameroon			**PL**	Poland		
CN	China	**KR**	Republic of Korea	**PT**	Portugal		
CU	Cuba	**KZ**	Kazakstan	**RO**	Romania		
CZ	Czech Republic	**LC**	Saint Lucia	**RU**	Russian Federation		
DE	Germany	**LI**	Liechtenstein	**SD**	Sudan		
DK	Denmark	**LK**	Sri Lanka	**SE**	Sweden		
EE	Estonia	**LR**	Liberia	**SG**	Singapore		

INCLUSION COMPLEXES OF BETA-2-ANDRENERGICS FOR ORAL MUCOSAL DELIVERY

BACKGROUND OF THE INVENTION

This invention relates to a pharmaceutical composition for oral mucosal delivery comprising as an active ingredient an inclusion complex of a selective $ß_2$-adrenergic agonist or a salt thereof, and a cyclodextrin.

Salbutamol(4-hydroxy-3-hydroxymethyl-α-[(*tert*-butylamino)methyl]-benzyl alcohol) and other selective $ß_2$-adrenergic agonists, such as metaproterenol, terbutaline, pirbuterol, salmeterol, fenbuterol, orciprenaline, formoterol, hexaprenaline, reproterol, rimiterol, fenoterol, procaterol, mabuterol, bambuterol and bitolterol, are useful for the treatment of reversible obstructive airways diseases such as asthma and the reversible component of chronic obstructive pulmonary diseases.

Asthma is a chronic disease in which the patient suffers episodes of reversible airways obstruction. It is a common disorder occurring in about 4-5% of the population. Fatalities can occur and mortality rates are reported to be increasing.

The underlying cause of asthma is poorly understood, but resistance to airflow is increased by a number of factors:

1 Constriction of airway smooth muscle

2 The presence of excessive secretions within the airway lumen

3 Thickening of the airway epithelium due to oedema, infiltration of the mucosa by eosinophils and other inflammatory cells, hypertrophy and hypertrophy and hyperplasia.

As asthma is a chronic disease, management involves prophylatic measures to reduce airway resistance and maintain airflow as well as specific regimens for the treatment of acute attacks.

The standard drugs used in the management of asthma are $ß_2$-adrenergic agonists. $ß_2$-adrenergic agonists relax the bronchial smooth muscle to produce bronchodilatation by stimulating $ß_2$-adrenergic receptors. Short acting selective $ß^2$-agonists such as salbutamol or terbutaline are the initial drugs of choice; if inhaled, they produce a bronchodilating effect within 15 minutes.

Initially, therapy is usually administered by inhalation to deliver the drugs to the desired site of action. The doses are approximately 5% of the dose required with oral administration. In severe asthma, the oral route may also be necessary. Difficulties associated with the use of inhalers may be overcome by the use of spacing devices to act as reservoirs for the drug to make it easier for the patient (especially a child) to inhale each dose.

Chronic obstructive pulmonary disease (COPD) covers a range of disorders of progressive airflow limitation including chronic bronchitis and emphysema. Unlike asthma, the obstruction of airflow is relatively constant and essentially irreversible. COPD is a common disorder, frequently associated with cigarette smoking, infections, environmental pollution and

occupational dust exposure. Drug treatment includes symptomatic and palliative therapy using bronchodilating agents. First-line drug therapy for the treatment of COPD consists of bronchodilating agents to alleviate bronchospasm and any reversible component of airway obstruction. The drug of first choice is a $ß_2$-selective agonist such as salbutamol or terbutaline given by inhalation.

As stated above, salbutamol and related $ß_2$-adrenergic agonists are administered either by inhalation or by the orogastric route. When administered by inhalation, salbutamol produces significant bronchodilation within 15 minutes and effects are demonstrable for 3 to 4 hours. With aerosol therapy only about 10% of the inhaled dose actually enters the lungs: much of the remainder is swallowed. Successful aerosol therapy requires that the patient masters the technique of drug administration. Many patients, particularly children and the elderly, do not use optimal techniques. Additionally, many allergic asthmatics suffer from mucous congestion of the respiratory tract which further reduces the absorption of inhaled bronchodilators.

Salbutamol is rapidly absorbed from the gastro-intestinal tract. It is subject to first-pass metabolism in the liver and possibly the gut wall. The main metabolite is an inactive sulphate conjugate. It is rapidly excreted in the urine as metabolites and unchanged drug; there is some excretion in the faeces. It has been suggested that the majority of an inhaled dose is swallowed and absorbed from the gut (see Goodman & Gilman's The Pharmacological Basis of Therapeutics, Eighth Edition, Volume 1, Chap. 10 p204). The plasma half-life of salbutamol has been estimated to range from about 2 to as much as 7 hours.

Administration of salbutamol by inhalation results in the rapid onset (within 5 - 15 minutes) of bronchodilation which lasts for about 4 hours. Following conventional orogastric administration, the onset of action is within 30 minutes, with a peak effect between 2 to 3 hours after the dose, and a duration of action of up to 6 hours (see MARTINDALE, The Extra Pharmacopoeia, 31ST Edition, p 1591).

Administration of drugs by direct absorption through the oral mucosa has several advantages, particularly rapid systemic uptake with fast onset of therapeutic action and avoidance of presystemic metabolism. Both of these advantages are especially of relevance to the use of $ß_2$-adrenergic agonists in the treatment of reversible obstructive airways disease where rapid onset of action is desirable and where these compounds generally suffer extensive presystemic metabolism following orogastric administration. However, the low permeability of the membranes that line the oral cavity results in a low flux of the drug across the membrane. There is therefore a need to enhance the drug penetration to improve biovailability following oral mucosal drug delivery. There are several methods known in the art to deliver drugs to the oral mucosae. These include buccal and sublingual tablets or lozenges, adhesive patches, gels, solutions or sprays.

The absorption of drugs from mucosal membranes may be enhanced by (i) increasing drug solubility, (ii) pH modification to favour the unionized form of the drug, (iii) addition of mucoadhesive agents to improve contact between the delivery system and the membrane and (iv) incorporation of so-called penetration enhancers.

There are a number of penetration enhancers known to influence the permeability of drugs across epithelial membranes [for a recent review see

Walker, R.B. and Smith, E.W., Advanced Drug Delivery Reviews 1996, 18, 295-301].

Cyclodextrins and their derivatives have found extensive application as solubilizers and stabilizers due to their ability to form inclusion complexes with a wide variety of compounds [J. Szejtli, *Cyclodextrin Technology,* Kluwer Academic Press) and ([J. Szejtli & K-H Fromming, *Cyclodextrins in Pharmacy,* Kluwer Academic Press)]. Cyclodextrins have been used to enhance intestinal absorption of drugs primarily through increasing the solubility. Recently, cyclodextrins have been shown to have positive and negative effects on transdermal penetration of drugs [see Loftson, T. *et al,* International Journal of Pharmaceutics 1995, 115, 255-258), (Vollmer, U. *et al,* International Journal of Pharmaceutics 1993, 99, 51-58), (Legendre, J.Y. *et al,* European Journal of Pharmaceutical Sciences 1995, 3, 311-322) and (Vollmer, U. *et al,* Journal of Pharmacy and Pharmacology 1994, 46, 19-22)].

Cyclodextrins are water soluble cone-shaped cyclic oligosaccharides containing 6,7 or 8 glucopyranose units. The interior or "cavity" of the cone is hydrophobic whilst the exterior is hydrophillic. The size of the cavity increases with increasing number of glucose units. Several cyclodextrin derivatives such as alkyl, hydroxyalkyl and sulfoalkyl ethers have been prepared with improved solubility [see (J. Szejtli & K-H Fromming, *Cyclodextrins in Pharmacy,* Kluwer Academic Press) and (Stella, V.J. *et al,* Pharmaceutical Research 1995, 12 (9) S205)]. Suitably sized hydrophobic "guest" molecules may enter the "host" cavity to form a classical host-guest "inclusion compound" or "inclusion complex" with either the entire guest molecule included or only a portion thereof. The driving mechanism for cyclodextrin inclusion complexation is the affinity of the hydrophobic guest

molecule for the cavity of the cyclodextrin host molecule with displacement of cavity water molecules to form a thermodynamically more stable state. The term "complex stability" or stability of a given inclusion complex refers to the association/dissociation equilibrium of host and guest in solution. Complex stability depends on the number of intermolecular bonding interactions between the host and guest. Van der Waals forces and hydrophobic interactions are the main stabilising interactions in inclusion complexes (Bergeron, R.J. *et al,* Journal of the American Chemical Society 1977, 99, 5146). Depending on the nature and position of hydrogen bonding functionalities on a given guest, there may be hydrogen bonding between the guest and hydroxyl groups of the cyclodextrin or other hydrogen bonding groups in the case of cyclodextrin derivatives. Ionic interactions between the host and guest are also possible in the case of ionic cyclodextrins such as sulphobutyl ethers (Stella, V.J. *et al,* Pharmaceutical Research 1995. 12 (9) S205).

Cyclodextrin inclusion complexes may be prepared on the basis of liquid state, solid state or semi-solid state reactions between the components (J. Szejtli, *Cyclodextrin Technology,* Kluwer Academic Press). The first is accomplished by dissolving the cyclodextrin and guest in a suitable solvent or mixture of solvents and subsequently isolating the solid state complex by crystallisation, evaporation, spray drying or freeze drying. In the solid state method, the two components may be screened to uniform particle size and thoroughly mixed whereafter they are ground in a high energy mill with optional heating, screened and homogenized. In the semi-solid state reaction the two components are kneaded in the presence of small amounts of a suitable solvent, and the complex so-formed, is dried, screened and homogenized. The liquid state reaction generally provides optimum conditions for completeness.

Inclusion complexes of various cyclodextrins and salbutamol in both the liquid and the solid state have been reported in the literature [see (H.M. Cabal Marques, J. Hadgraft and I.W. Kellaway, *International Journal of Pharmaceutics,* 63 (1990) 259-266)]. Cabral Marques *et al* studied the interaction of salbutamol with beta-, alpha- and gamma-cyclodextrins. Using the methods of Higuchi and Connors (*Adv. Anal. Chem.,* 4(1965) 117-212) they determined by solution studies that the solubility of the salbutamol complexes increased in the order: Heptakis(2,6-di-*O*-methyl)-beta-cyclodextrin (DIMEB), > beta-cyclodextrin, >> gamma-cyclodextrin, >> alpha-cyclodextrin. This increase in solubility was attributed to the accessibility of the ring of the salbutamol molecule to interaction with the cyclodextrins. Overall, the cavity size of beta-cyclodextrins and its derivatives appear to be optimal for entrapment of the salbutamol molecule, and consequently provides the greatest solubilization effect. The authors also found that changes of temperature in the range 20-37°C had only a minimal effect on the solubility of salbutamol in both the absence and presence of cyclodextrins. From the solubility studies it was also concluded that a 1:1 molar complex was the only species formed under the conditions studied. Stability constants of 66-69 and 62-83 M^{-1} were reported for beta-cyclodextrin and DIMEB respectively.

The solid beta-cyclodextrin/salbutamol complex was prepared by freeze-drying (lyophilization), that is equimolar amounts of beta-cyclodextrin and salbutamol were dissolved in water, then subjected to freeze-drying for 48 hours while being protected from light. The formation of a solid state inclusion complex obtained from freeze-drying was determined by Differential Scanning Calorimetry. When guest molecules are incorporated in a cyclodextrin cavity their melting, boiling and / or sublimation points shift to different temperatures or disappear within the temperature range in

which the cyclodextrin is decomposed. The DSC thermogram for freeze dried salbutamol showed an endotherm at 431K, and the physical mix of freeze dried beta-cyclodextrin and salbutamol showed an endotherm at 423K. The thermogram of the freeze-dried complex showed no endothermic peak due to the phase transition of salbutamol. Thus the authors claim that freeze-drying resulted in a true inclusion complex being formed. However, the lack of a thermal event for the freeze dried beta-cyclodextrin/salbutamol could also indicate the amorphousness of the salbutamol in the interstitial spaces of the beta-cyclodextrin.

Cabral Marques *et al* (International Journal of Pharmaceutics, 63 (1990) 267-274) used Molecular Modelling and Proton-NMR to assess the mode of inclusion of salbutamol within the beta-CD cavity. Using Proton-NMR to assess the mode of inclusion is based on the shielding of the cyclodextrin and drug protons. If inclusion occurs, protons located within or near the cyclodextrin cavity should be strongly shielded. The NMR spectra showed upfield shifts of the cyclodextrin protons in the presence of salbutamol and the salbutamol protons shifted downfield in the presence of beta-cyclodextrin. The downfield shifts of the aromatic protons were greater than those of the aliphatic protons, suggesting that the aromatic ring of salbutamol interacts more strongly with the beta-cyclodextrin. The interior protons of the cyclodextrin molecule were shielded as a result of the anisotropy of the guest aromatic moiety. The highest shifts of beta-cyclodextrin protons occurred for a molar ratio of 1:1 (salbutamol: beta-cyclodextrin) indicating the probable stoichiometry of the complex. Molecular graphical computation showed that the minimum van der Waals energy positioning of salbutamol relative to beta-cyclodextrin occurs when the aromatic ring of salbutamol penetrates the cavity leaving the aliphatic chain externalised.

Cabral Marques *et al* (*International Journal of Pharmaceutics,* 77 (1991) 303-307) studied the fate of a freeze-dried 2-hydroxypropyl-ß-cyclodextrin (HP-ß-CD):salbutamol complex following pulmonary administration in order to evaluate the possibility of obtaining sustained release of salbutamol using HP-ß-CD as a carrier. Using a randomised cross-over design, the absorption and pharmacokinetics of HP-ß-CD salbutamol complex was investigated in four healthy New Zealand White male rabbits, after intravenous bolus (i.v.) by means of the marginal ear vein and pulmonary administration via intratracheal instillation (i.t.) at the bifurcation of the trachea. Although the terminal half-life of salbutamol did not change significantly after complexation, the pulmonary absorption of salbutamol as a complex was prolonged, as shown by its maximum plasma concentration which was observed approximately 23 minutes after instillation compared to approximately 14 minutes for the uncomplexed Salbutamol, and also by the increased absorption time. After i.v. dosing the availability of the complexed salbutamol was reduced to about 80% of that of the free drug. They concluded that complexation with HP-ß-CD did not sufficiently extend the salbutamol release profile to justify its use as a sustained release inhalation formulation.

Hirayama *et al* (Pharmaceutical Sciences 1995, 1, 517-520) investigated the effect of perbutanoyl-ß-cyclodextrin (TB-ß-CD), a hydrophobic cyclodextrin derivative, on plasma salbutamol levels after oral administration in dogs. The kneading method was used to prepare the sample of salbutamol/TB-ß-CD in a 1:1 molar ratio using methanol as the solvent. After oral administration of the salbutamol complex in dogs, a prolonged maintenance (at least 24 hours) of higher and constant salbutamol levels in plasma was obtained. The area under the plasma salbutamol concentration curve up to 24 hours after administration of the salbutamol/TB-ß-CD complex was about 5 times that

of salbutamol alone. Furthermore, the plasma level of salbutamol glucuronide, a major metabolite of salbutamol, was significantly lower after administration of the salbutamol/TB-ß-CD complex than after administration of the drug alone. This was attributed to the suppression of the metabolism of salbutamol in the gastrointestinal tract by TB-ß-CD complexation. The authors concluded that TB-ß-CD may be a useful carrier for orally administered water-soluble drugs which are extensively metabolized in the gastrointestinal tract.

Heptakis-(2,6-di-*O*-methyl)-ß-cyclodextrin (DIMEB) is derived from beta-cyclodextrin where methylation has occurred selectively at carbon 2 and 6 in each glucose subunit. Thus, there are 14 methyl groups per substituted cyclodextrin molecule. This is the beta-cyclodextrin molecule used by Cabral Marques *et al* (International Journal of Pharmaceutics, 63 (1990) 259-266). Randomly methylated-ß-cyclodextrin (RAMEB) is obtained from beta-cyclodextrin where methylation has occurred randomly at carbons 2, 3, or 6. Methylation may occur at all three positions, any two positions, or at one position only. Therefore, each glucose subunit may have one, two or three methyl groups. The degree of substitution is expressed as the average number of methyl groups per glucose subunit.

Salbutamol base and salbutamol sulphate have been complexed with various cyclodextrins in order to modify the *in vivo* release of salbutamol. Notably, salbutamol has been complexed with perbutanoyl-ß-cyclodextrin (Hirayama, F; Horikawa, T; Yamanaka, M; and Uekama, K.; *Pharmaceutical Sciences* 1995, 1:517-520) and 2-hydroxypropyl-ß-cyclodextrin (Cabral Marques, H. M.; Hadgraft, J.; Kellaway, I.W.; Taylor, G.; *International Journal of Pharmaceutics.* 77 (1991) 303-307) in order to evaluate the possibility of obtaining sustained release following oral and pulmonary administration.

Complexes of salbutamol base with alpha-cyclodexrin, beta-cyclodextrin, gamma-cyclodextrin and heptakis(2,6-di-O-methyl)-ß-cyclodextrin(DIMEB) were obtained in order to study the effect of temperature and cyclodextrin concentration on complex solubility (Cabral Marques, H.M.; Hadgraft, J. and Kellaway, I.W., *International Journal of Pharmaceutics,* 63 (1990) 259-266). Further, salbutamol base was complexed with beta-cyclodextrin in order that proton NMR could be employed to assess the mode of salbutamol inclusion within the beta-cyclodextrin cavity. The solid salbutamol inclusion complexes were prepared by freeze drying. Unfortunately freeze drying is an expensive drying technique and does not yield a product with acceptable physical characteristics. That is, the solid product obtained from freeze drying does not have a suitable particle size distribution, nor are the flow characteristics suitable for scale up or tabletting.

There is a need to be able to deliver $ß_2$-adrenergic agonists via the transmucosal routes.

SUMMARY OF THE INVENTION

According to a first aspect of the invention there is provided a pharmaceutical composition for oral mucosal delivery comprising as an active ingredient an inclusion complex of (a) a selective $ß_2$-adrenergic agonist or a pharmaceutically acceptable salt thereof and (b) an unsubstituted or substituted beta- or gamma-cyclodextrin, and a pharmaceutically acceptable carrier for oral mucosal delivery.

The selective $ß_2$-adrenergic agonist is preferably selected from the group consisting of salbutamol, metaproterenol, terbutaline, pirbuterol, formoterol,

salmeterol, fenbuterol, orciprenaline, isoprenaline, hexoprenaline, reproterol, rimiterol, fenoterol, procaterol, mabuterol, bambuterol, bitolterol, broxaterol, carbuterol, clenbuterol, coterol, eformoterol, tretoquinol and tulobuterol and the pharmaceutically acceptable salts thereof, such as for example the sulphate, methanesulfonate, hydrochloride, dihydrochloride, acetate or monoacetate salts.

The selective $ß_2$-adrenergic agonist is preferably salbutamol either in the form of the free base or in the form of a pharmaceutically acceptable salt such as the sulphate salt.

The inclusion complex preferably has a stoichiometry of (a) to (b) of 1:1 to 1:10 mol/mol, more preferably 1:1 to 1:5 mol/mol, most preferably 1:1 mol/mol.

The pharmaceutical composition may be formulated in the form of a buccal or sublingual tablet, lozenge, adhesive patch, gel, solution or spray.

The pharmaceutical composition is preferably for use in the treatment of a reversible obstructive airways disease such as asthma or the reversible component of chronic obstructive pulmonary diseases.

According to a second aspect of the invention there is provided the use of an inclusion complex of (a) a selective $ß_2$-adrenergic agonist or a pharmaceutically acceptable salt thereof and (b) an unsubstituted or substituted beta- or gamma-cyclodextrin, in the manufacture of a pharmaceutical composition for oral mucosal delivery for use in a method of treatment of a reversible obstructive airways disease such as asthma or the reversible component of chronic obstructive pulmonary diseases.

According to a third aspect of the invention there is provided a method of treating a patient suffering from a reversible obstructive airways disease which comprises administering to the oral mucosae of the patient an inclusion complex of (a) a selective $ß_2$-adrenergic agonist or a pharmaceutically acceptable salt thereof and (b) an unsubstituted or substituted beta- or gamma-cyclodextrin.

According to a fourth aspect of the invention there is provided an inclusion complex of salbutamol base and randomly substituted methyl-beta-cyclodextrin which has substantially the X-ray powder diffraction pattern of Figure 1 of the accompanying drawings or the Fourier Transform Infra-red spectrum of Figure 2 of the accompanying drawings.

According to a fifth aspect of the invention there is provided an inclusion complex of salbutamol base and 2-hydroxypropyl-beta-cyclodextrin which has substantially the X-ray powder diffraction pattern of Figure 5 of the accompanying drawings or the Fourier Transform Infra-red spectrum of Figure 6 of the accompanying drawings.

BRIEF DESCRIPTION OF THE DRAWINGS

Figure 1 shows an X-ray powder diffraction pattern of a 1:1 kneaded complex of salbutamol base and randomly methylated-ß-cyclodextrin obtained from Example 1;

Figure 2 shows a Fourier Transform infra-red spectrum of a 1:1 kneaded complex of salbutamol base and randomly methylated-ß-cyclodextrin obtained from Example 1;

Figure 3 shows a Differential Scanning Calorimetry thermogram of salbutamol base with a onset melting temperature of 157°C and a sharp endothermic melting peak at 159°C;

Figure 4 shows a Differential Scanning Calorimetry thermogram of a 1:1 kneaded complex of salbutamol base and randomly methylated-ß-cyclodextrin obtained from Example 1;

Figure 5 shows an X-ray powder diffraction pattern of an 1:1 kneaded complex of salbutamol base and 2-hydroxypropyl-ß-cyclodextrin obtained from Example 2;

Figure 6 shows a Fourier Transform infra-red spectrum of a 1:1 kneaded complex of salbutamol base and 2-hydroxypropyl-ß-cyclodextrin obtained from Example 2; and

Figure 7 shows a Differential Scanning Calorimetry thermogram a 1:1 kneaded complex of salbutamol base and 2-hydroxypropyl-ß-cyclodextrin obtained from Example 2.

DESCRIPTION OF EMBODIMENTS

The crux of the invention is a pharmaceutical composition for oral mucosal delivery which comprises as an active ingredient an inclusion complex of (a) a selective $ß_2$-adrenergic agonist or a pharmaceutically acceptable salt thereof and (b) an unsubstituted beta- or gamma-cyclodextrin, together with a pharmaceutically acceptable carrier for oral mucosal delivery.

Examples of suitable compounds (a) are salbutamol, metaproterenol, terbutaline, pirbuterol, formoterol, salmeterol, fenbuterol, orciprenaline, isoprenaline, hexoprenaline, reproterol, rimiterol, fenoterol, procaterol, mabuterol, bambuterol, bitolterol, broxaterol, carbuterol, clenbuterol, coterol, eformoterol, tretoquinol and tulobuterol. The compound may be used in the form of the free base, or in the form of a pharmaceutically acceptable salt such as a sulfate, methanesulfonate, hydrochloride, dihydrochloride, or monoacetate salt.

The second component of the inclusion complex is an unsubstituted or substituted beta- or gamma-cyclodextrin.

Highly water soluble cyclodextrins such as 2-hydroxypropylated or methylated or sulphoalkylated derivatives of beta-cyclodextrin are the preferred cyclodextrins of the invention. Gamma-cyclodextrin or 2-hydroxypropylated or methylated or sulphoalkylated derivatives of gamma-cyclodextrin may also be used in the same manner as the corresponding preferred beta-cyclodextrin derivatives. The degree of substitution of the cyclodextrin derivatives may vary between 1 to 20 substituents per cyclodextrin molecule but more preferably between 3 to 15 substituents per cyclodextrin molecule. When the cyclodextrin is 2-hydroxypropyl-beta-cyclodextrin, the preferred degree of substitution is between 3,9 and 5,1 hydroxypropyl groups per cyclodextrin molecule. When the cyclodextrin is randomly methylated-beta-cyclodextrin, the preferred degree of substitution is between 1,8 and 2 methyl groups per glucose unit.

The inclusion complex may be prepared from aqueous solutions, slurries or pastes of the drug active and cyclodextrin according to conventional methods. The molar ratio of drug active to cyclodextrin may vary between

1:1 and 1:10, but more preferably between 1:1 to 1:5 and most preferably about 1:1. Solutions are prepared by dissolving the cyclodextrin in a sufficient quantity of purified, deionized water which may be optionally buffered between pH 7,4 and 8,5. The drug active is added to the solution with stirring until dissolved. The solution may be dried by spray drying, freeze drying or by evaporation of the aqueous phase under reduced pressure and/ or increased temperature. Alternatively, the drug active and cyclodextrin are mixed in the dry form. The powder mixture is wetted with water, optionally containing a buffer, pH 7,4 - 8,5, while mixing vigorously until a paste or slurry is formed. The paste or slurry is mixed for 0,25 to 2 hours and is then dried in an oven or *in vacuo* at elevated temperature. The dried complex obtained may be crushed or milled and sieved to the desired particle size.

A pharmaceutically acceptable buffer, capable of buffering in the pH range 7,4-8,5 may be used in the formation of the inclusion complex, particularly when the drug active is present as a salt. Preferred buffers include tromethamine, triethanolamine, diethanolamine and phosphate buffer. The concentration of the buffer may vary from 0,1 to 5 molar equivalents relative to the drug active.

The administration of a selective $ß_2$-adrenergic agonist through the mucosal tissue of the mouth avoids the problems associated with administration of these drugs by inhalation (i.e. only approximately 10% of the drug entering the lungs, difficulty with inhalation techniques resulting in therapeutic blood levels not being attained) and by oral administration (i.e. slower onset of action and extensive metabolism in the gastrointestinal tract).

Absorption of the drug from the pharmaceutical composition of the invention

through the oral mucosae is rapid such that the drug reaches the systemic circulation within minutes, which is highly advantageous for the rapid relief of bronchoconstriction associated with a reversible obstructive airways disease such as asthma or the reversible component of chronic obstructive pulmonary diseases. Further, any unpleasant taste and irritant properties of the active are reduced by presenting the drug to the oral mucosal membranes in the form of a cyclodextrin inclusion complex.

The present invention achieves these advantages by molecular encapsulation of the selective $ß_2$-adrenergic agonist in a cyclodextrin molecule, so forming a molecular inclusion complex which may be used in the solid form for the preparation of a pharmaceutical composition for oral mucosal delivery, such as buccal or sublingual tablets, lozenges, adhesive patches, gels, solutions and sprays.

Administration of a single dose of a sublingual tablet containing 4mg salbutamol according to the invention resulted in relief of asthma within 2 minutes in two asthmatic patients.

The complex according to the invention may be incorporated into a shearform matrix designed for immediate release as described in Fuisz Technologies Ltd patents (Eur. Pat. Appl. EP 95-650038 and PCT Int. Appl. WO 95/34293).

The pharmaceutical composition of the invention may also contain, in addition to the pharmaceutically acceptable carrier for oral mucosal delivery, other optional ingredients as are discussed below.

Penetration enhancers may be used to promote the passage of the drug

active across the mucosal membranes. Typical permeation enhancers include fatty acids and their salts such as sodium caprate, sodium caprylate and sodium oleate, and bile salts such as sodium glycodeoxycholate, sodium glycocholate, sodium cholate and sodium taurodeoxycholate. Other penetration enhancers may include tensides or non-ionic surfactants such as polyethylene glycol 660 hydroxystearate or polyoxyethylene lauryl ethers, fusidates such as sodium taurodihydrofusidate, azone and chitosan. Combinations of permeation enhancers such as polyoxyethylene 8 lauryl ether and sodium glycocholate or mixed micelles such as sodium caprate and sodium glycocholate may also be used. The penetration enhancers may also be used in combination with beta- or gamma-cyclodextrins or their methyl, hydroxypropyl or sulphoalkyl derivatives. Typical concentrations of penetration enhancers are between 0,1 and 5,0%, more preferably between 0,25 to 3% by mass of the inclusion complex.

As stated above, the selective $ß_2$-adrenergic agonist may be used in the form of the free base or a pharmaceutically acceptable salt. When acidic penetration enhancing excipients are used such as bile acids or fatty acids, or pharmaceutically acceptable salts of bile acids, salt formation between the basic component of the $ß_2$-adrenergic agonist and the acidic component of the bile or fatty acid may occur.

Buffering agents may be incorporated into the pharmaceutical composition of the invention to control the microenvironmental pH surrounding the drug delivery system in the alkaline range, so as to maximise the percentage of the unionized form of the drug, as drugs in the unionized form cross mucosal membranes more readily than the corresponding ionized form.

The pharmaceutical composition may contain suitable flavouring and

sweetening agents such as mint, spearmint, aspartame, sucrose, xylitol, saccharin and the like.

Typical sublingual or buccal tablets may include lubricants such as magnesium stearate, calcium stearate and sodium stearyl fumarate to facilitate tablet compression. Diluents such as lactose, microcrystalline cellulose, maize starch and the like may be used. In order to prevent movement of the dosage form from the site of administration, mucoadhesive agents such as chitosan, carbopol 934P, and hydroxypropyl cellulose and the like may be used in conventional concentrations.

Typical disintegrants to enhance sublingual or buccal tablet disintegration include sodium carboxymethylcellulose, sodium starch glycolate, polyplasdone XL, and dried starch.

Another aspect of the invention is the specific inclusion complex of salbutamol base and methyl-beta-cyclodextrin having substantially the X-ray powder diffraction pattern of Figure 1 or the Fourier Transform Infra-red spectrum of Figure 2 of the accompanying drawings.

A further aspect of the invention is the specific inclusion complex of salbutamol base and 2-hydroxypropyl-ß-cyclodextrin having substantially the X-ray powder diffraction pattern of Figure 5 or the Fourier Transform Infra-red spectrum of Figure 6 of the accompanying drawings.

The following examples illustrate the present invention.

Example 1

Salbutamol base (2,00g) and methyl-beta-cyclodextrin (11,57g) are mixed together in a mortar. Purified, deionized water (6ml) is added in aliquots with mixing to form a homogenous paste. The paste is dried in an oven at 40°C and atmospheric pressure. The dried complex is crushed with a pestle and passed through a 250µm mesh sieve. At all processing stages, the compound is protected from light. The complex contains 14,1% mass/mass salbutamol base as determined by HPLC.

Example 2

Salbutamol base (2,00g) and 2-hydroxypropyl-beta-cyclodextrin (12,6g) are mixed together in a mortar. Purified, deionized water (10ml) is added in aliquots with mixing to form a homogenous paste. Continue grinding for 0,5 hours. The paste is dried in an oven at 40°C and 5 millibar. The dried complex is crushed with a pestle and passed through a 250µm mesh sieve. At all processing stages, the compound is protected from light. The complex contains 13,24% mass/mass salbutamol base as determined by HPLC.

Example 3

The unit composition of a sublingual tablet containing the equivalent of 4 mg salbutamol base is as follows:

Salbutamol base/methyl-beta-cyclodextrin complex (from Example 1)	28,5mg
Xylitol	21,0 mg
Sodium Stearyl Fumarate	0,5 mg

The complex is blended with the xylitol. The lubricant, sodium stearyl fumarate, is screened in and the mixture is blended and formed into sublingual tablets by compression at 10 - 30 N.

Example 4

The unit composition of a sublingual tablet containing the equivalent of 4 mg salbutamol base is as follows:

Salbutamol base/2-hydroxypropyl-ß-CD (from Example 2)	30,2 mg
Microcrystalline Cellulose	8,6 mg
Sodium Starch Glycollate	10,0 mg
Chitosan	0,6 mg
Magnesium Stearate	0,6 mg

The complex is blended with the microcrystalline cellulose, sodium starch glycollate and chitosan. The lubricant, magnesium stearate, is screened in and the mixture is blended and formed into sublingual tablets by compression at 10 - 30 N.

Example 5

The unit composition of a sublingual tablet containing the equivalent of 4 mg salbutamol base is as follows.

Salbutomol sulphate/2-hydroxypropyl-ß-CD	30,8 mg
Tromethamine	25,0 mg
Microcrystalline cellulose	8,2 mg
Sodium starch glycollate	10,0 mg
Xylitol	25,3 mg
Menthol	0,1 mg
Mangnesium stearate	0,6 mg

Example 6

Tulobuterol base (10,0 g) and randomly methylated beta-cyclodextrin (57,0 g) are mixed together in a mortar. Purified, deionised water (30 mL)

is added in aliquots with mixing to form a homogeneous paste. Grinding is continued for a further 1 hour. The paste is dried in an oven at 50°C and 5 millibar. The dried complex is crushed with a pestle and passed through a 250μm mesh sieve. The complex contains 14,93% mass/mass tulobuterol base as determined by HPLC.

Example 7

The unit composition of a sublingual tablet containing the equivalent of 2 mg tulobuterol base is as follows:

Tulobuterol base/randomly methylated beta-cyclodextrin	13,40 mg
Xylitol	43,10 mg
Anhydrous Lactose	43,00 mg
Sodium stearyl fumarate	0,50 mg

The complex is blended with the xylitol and anhydrous lactose. The lubricant, sodium stearyl fumarate is screened in and the mixture is blended and formed into sublingual tablets by compression to 10-30N.

Inclusion complexes of the other $ß_2$-adrenergic agonists listed above and any suitable beta- or gamma-cyclodextrin can be manufactured in the same manner as exemplified for salbutamol and tulobuterol and can be formulated in the same manner as exemplified for salbutamol and tulobuterol.

The procedures used to obtain the results shown in Figures 1 to 7 are as follows:

X-ray powder diffraction patterns were obtained using a Rigaku D Max 3 powder diffractometer with a graphite monochromator and Cu radiation. Samples were mounted in Al rings, or on glass slides and run from 2° -

52° 2θ, with a step size of 0.02°θ and a fixed time of 1s.

Fourier Transform infra-red transmission spectra were obtaining using a Perkin Elmer Spectrum 2000 spectrometer. Data was collected from 4400 cm^{-1} to 600 cm^{-1} with a resolution of 4 cm^{-1}, strong apodization and a gain of 1. Samples were prepared as powders in KBr matrix and data was collected from diffuse reflectance cells.

Differential scanning calorimetry thermograms were obtained using Perkin Elmer DSC 7 Differential Scanning Calorimeter. Sampling was done in vented aluminium pans (50µl). The starting temperature was 50°C, final temperature was 200°C, and the rate of temperature increase was 10°C/minute. The carrier gas was nitrogen. The instrument was calibrated with an indium standard prior to the sample being analysed.

The treatment or prevention of bronchospasm with selective $ß_2$-adrenergic agonists via the oral transmucosal route has the following advantages over currently available treatments:

1 Less complicated treatment modality than inhalation, particularly when used during an attack and especially significant for pediatric use.

2 Better compliance than inhalers in cases where the presence of excessive secretions within the airway lumen or thickening of the airway epithelium (due to oedema, infiltration of the mucosa by eosinophils and other inflammatory cells, hypertrophy and hyperplasia) results in reduced access of the inhaled drug to the site of action.

3 Similar time of onset of action when compared with inhalers and significantly faster than that of orogastric tablets or syrup.

4 Potential for 50% dose reduction relative to tablet or syrup dose due to avoidance of presystemic hepatic metabolism.

5 More convenient than inhalers for use in public.

6 More convenient than inhalers for prevention of exercise-induced brochospasm, where the drug should be administered 15 minutes before exercise.

CLAIMS

1 A pharmaceutical composition for oral mucosal delivery comprising as an active ingredient an inclusion complex of (a) a selective $ß_2$-adrenergic agonist or a pharmaceutically acceptable salt thereof and (b) an unsubstituted or substituted beta- or gamma-cyclodextrin, and a pharmaceutically acceptable carrier for oral mucosal delivery.

2 A pharmaceutical composition according to claim 1 wherein the selective $ß_2$-adrenergic agonist is selected from the group consisting of salbutamol, metaproterenol, terbutaline, pirbuterol, formoterol, salmeterol, fenbuterol, orciprenaline, isoprenaline, hexoprenaline, reproterol, rimiterol, fenoterol, procaterol, mabuterol, bambuterol, bitolterol, broxaterol, carbuterol, clenbuterol, coterol, eformoterol, tretoquinol and tulobuterol and the pharmaceutically acceptable salts thereof.

3 A pharmaceutical composition according to claim 1 or claim 2 wherein the selective $ß_2$-adrenergic agonist is salbutamol in the form of the free base or in the form of a pharmaceutically acceptable salt.

4 A pharmaceutical composition according to any one of claims 1 to 3 wherein the cyclodextrin is selected from the group consisting of unsubstituted beta-cyclodextrin, 2-hydroxypropylated beta-cyclodextrin, methylated beta-cyclodextrin and sulphoalkylated beta-cyclodextrin.

5 A pharmaceutical composition according to any one of claims 1 to 3 wherein the cyclodextrin is selected from the group consisting of unsubstituted gamma-cyclodextrin, 2-hydroxypropylated gamma-

cyclodextrin, methylated gamma-cyclodextrin and sulphoalkylated gamma-cyclodextrin.

6 A pharmaceutical composition according to any one of claims 1 to 5 wherein the inclusion complex has a stoichiometry of (a) to (b) of 1:1 to 1:10 mol/mol.

7 A pharmaceutical composition according to claim 6 wherein the inclusion complex has a stoichiometry of (a) to (b) of 1:1 to 1:5 mol/mol.

8 A pharmaceutical composition according to claim 7 wherein the inclusion complex has a stoichiometry of (a) to (b) of 1:1 mol/mol.

9 A pharmaceutical composition according to any one of claims 1 to 8 formulated in a form selected from the group consisting of a buccal tablet, a sublingual tablet, a lozenge, an adhesive patch, a gel, a solution and a spray.

10 A pharmaceutical composition according to any one of claims 1 to 9 for use in the treatment of a reversible obstructive airways disease.

11 The use of an inclusion complex of (a) a selective $ß_2$-adrenergic agonist or a pharmaceutically acceptable salt thereof and (b) an unsubstituted or substituted beta- or gamma-cyclodextrin, in the manufacture of a pharmaceutical composition for oral mucosal delivery for use in a method of treatment of a reversible obstructive airways disease.

12 The use according to claim 11 wherein the reversible obstructive

airways disease is asthma or the reversible component of chronic obstructive pulmonary diseases.

13 The use according to claim 11 or claim 12 wherein the selective $ß_2$-adrenergic agonist is selected from the group consisting of salbutamol, metaproterenol, terbutaline, pirbuterol, formoterol, salmeterol, fenbuterol, orciprenaline, isoprenaline, hexoprenaline, reproterol, rimiterol, fenoterol, procaterol, mabuterol, bambuterol, bitolterol, broxaterol, carbuterol, clenbuterol, coterol, eformoterol, tretoquinol and tulobuterol and the pharmaceutically acceptable salts thereof.

14 The use according to claim 13 wherein the selective $ß_2$-adrenergic agonist is salbutamol in the form of the free base or in the form of a pharmaceutically acceptable salt.

15 The use according to any one of claims 11 to 14 wherein the cyclodextrin is selected from the group consisting of unsubstituted beta-cyclodextrin, 2-hydroxypropylated beta-cyclodextrin, methylated beta-cyclodextrin, and sulphoalkylated beta-cyclodextrin.

16 The use according to any one of claims 1 to 14 wherein the cyclodextrin is selected from the group consisting of unsubstituted gamma-cyclodextrin, 2-hydroxypropylated gamma-cyclodextrin, methylated gamma-cyclodextrin and sulphoalkylated gamma-cyclodextrin.

17 The use according to any one of claims 1 to 16 wherein the inclusion complex has a stoichiometry of (a) to (b) of 1:1 to 1:10 mol/mol.

18 The use according to claim 17 wherein the inclusion complex has a stoichiometry of (a) to (b) of 1:1 to 1:5 mol/mol.

19 The use according to claim 18 wherein the inclusion complex has a stoichiometry of (a) to (b) of 1:1 mol/mol.

20 The use according to any one of claims 11 to 19 wherein the pharmaceutical composition is selected from the group consisting of a buccal tablet, a sublingual tablet, a lozenge, an adhesive patch, a gel, a solution or a spray.

21 A method of treating a patient suffering from a reversible obstructive airways disease comprising administering to the oral mucosae of the patient an inclusion complex of (a) a selective $ß_2$-adrenergic agonist or a pharmaceutically acceptable salt thereof and (b) an unsubstituted or substituted beta- or gamma-cyclodextrin.

22 A method according to claim 21 wherein the reversible obstructive airways disease is asthma or the reversible component of chronic obstructive pulmonary diseases.

23 An inclusion complex of salbutamol base and randomly substituted methyl-beta-cyclodextrin which has substantially the X-ray powder diffraction pattern of Figure 1 of the accompanying drawings or the Fourier Transform Infra-red spectrum of Figure 2 of the accompanying drawings.

24 An inclusion complex of salbutamol base and 2-hydroxypropyl-beta-cyclodextrin which has substantially the X-ray powder diffraction

pattern of Figure 5 of the accompanying drawings or the Fourier Transform Infra-red spectrum of Figure 6 of the accompanying drawings.

FIGURE 1

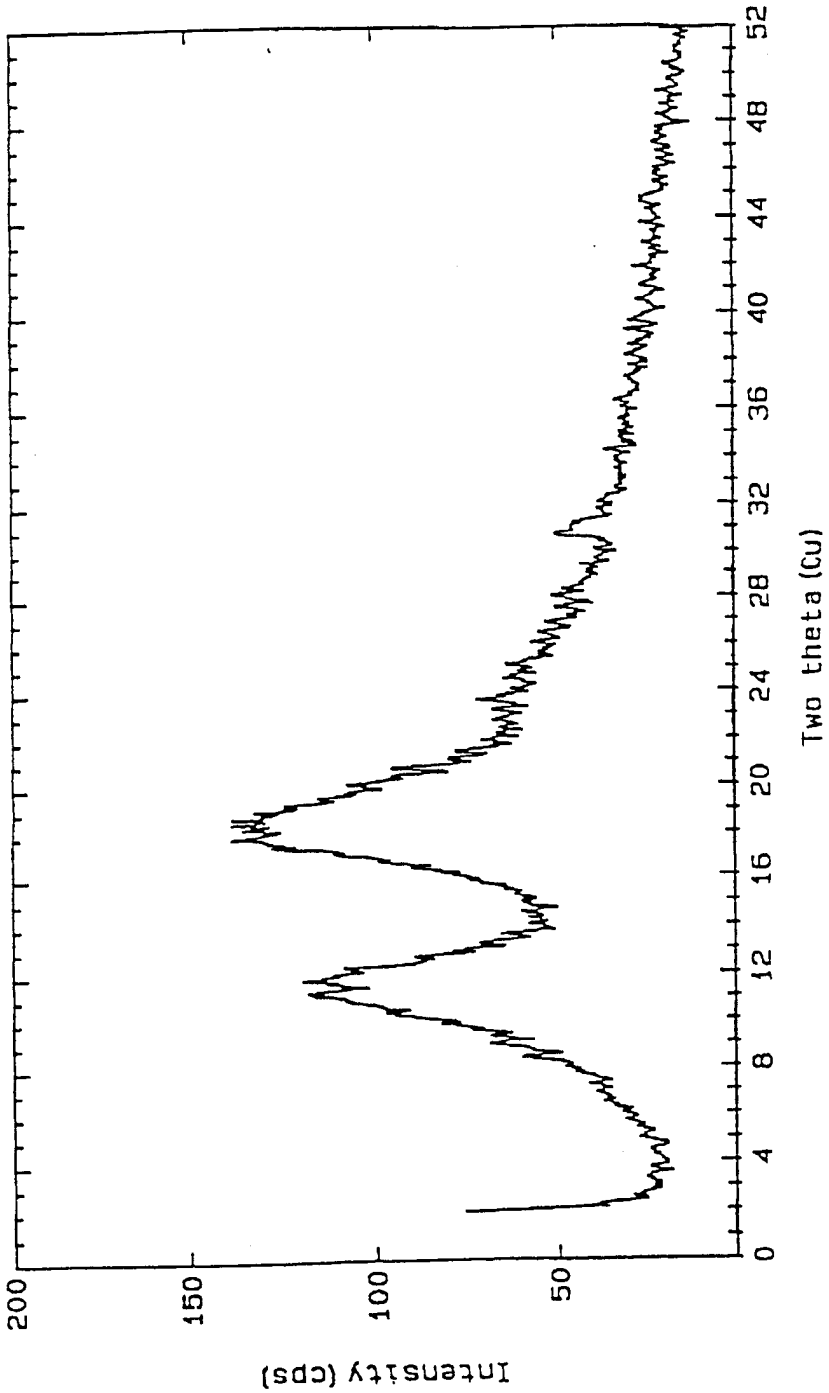

Intensity (cps)
200
150
100
50
0
4
8
12
16
20
24
28
32
36
40
44
48
52
Two theta (Cu)

FIGURE 2

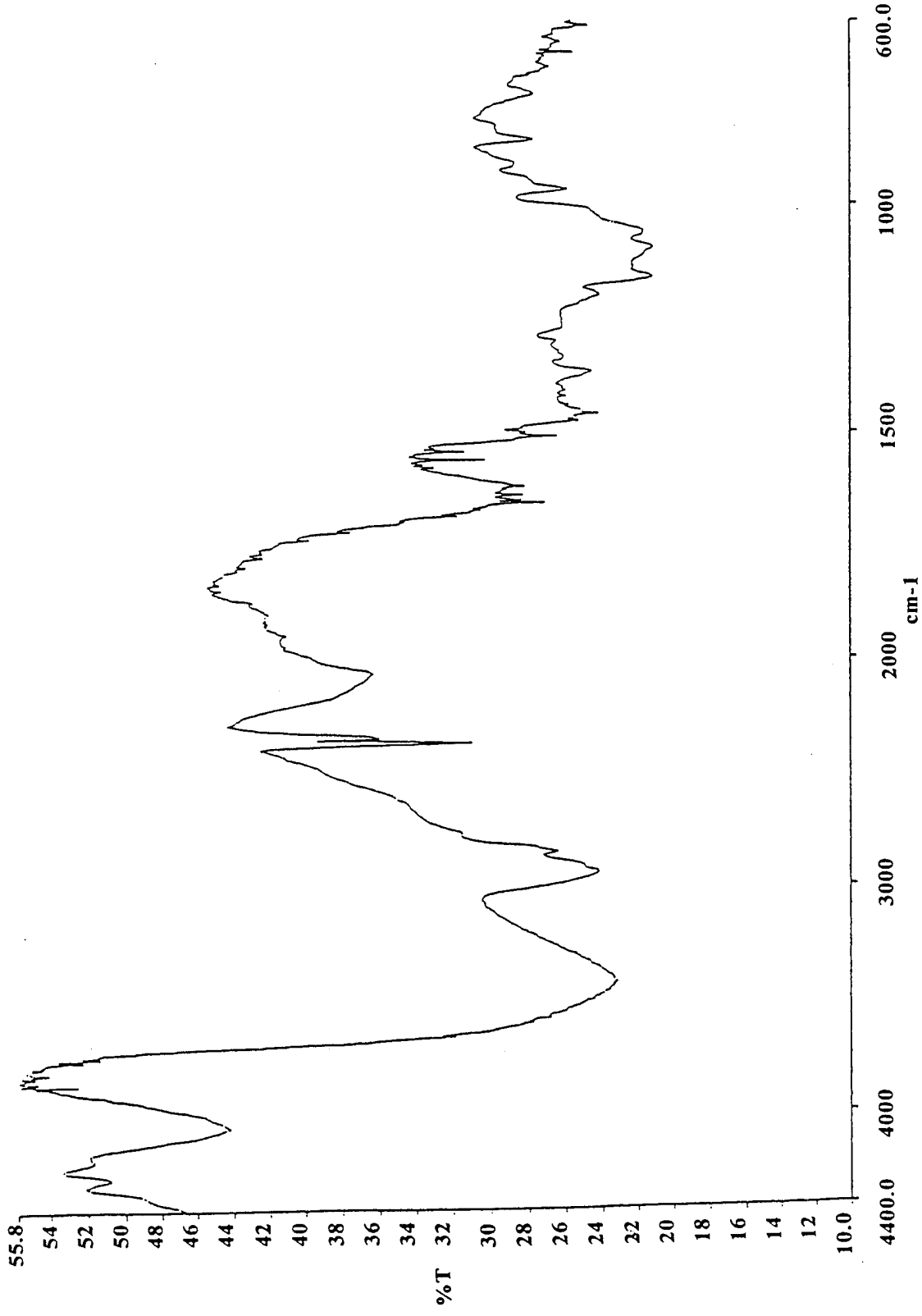

55.8
54
52
50
48
46
44
42
40
38
36
34
32
30
28
26
24
22
20
18
16
14
12
10.0
%T
4400.0
4000
3000
2000
1500
1000
600.0
cm-1

FIGURE 3

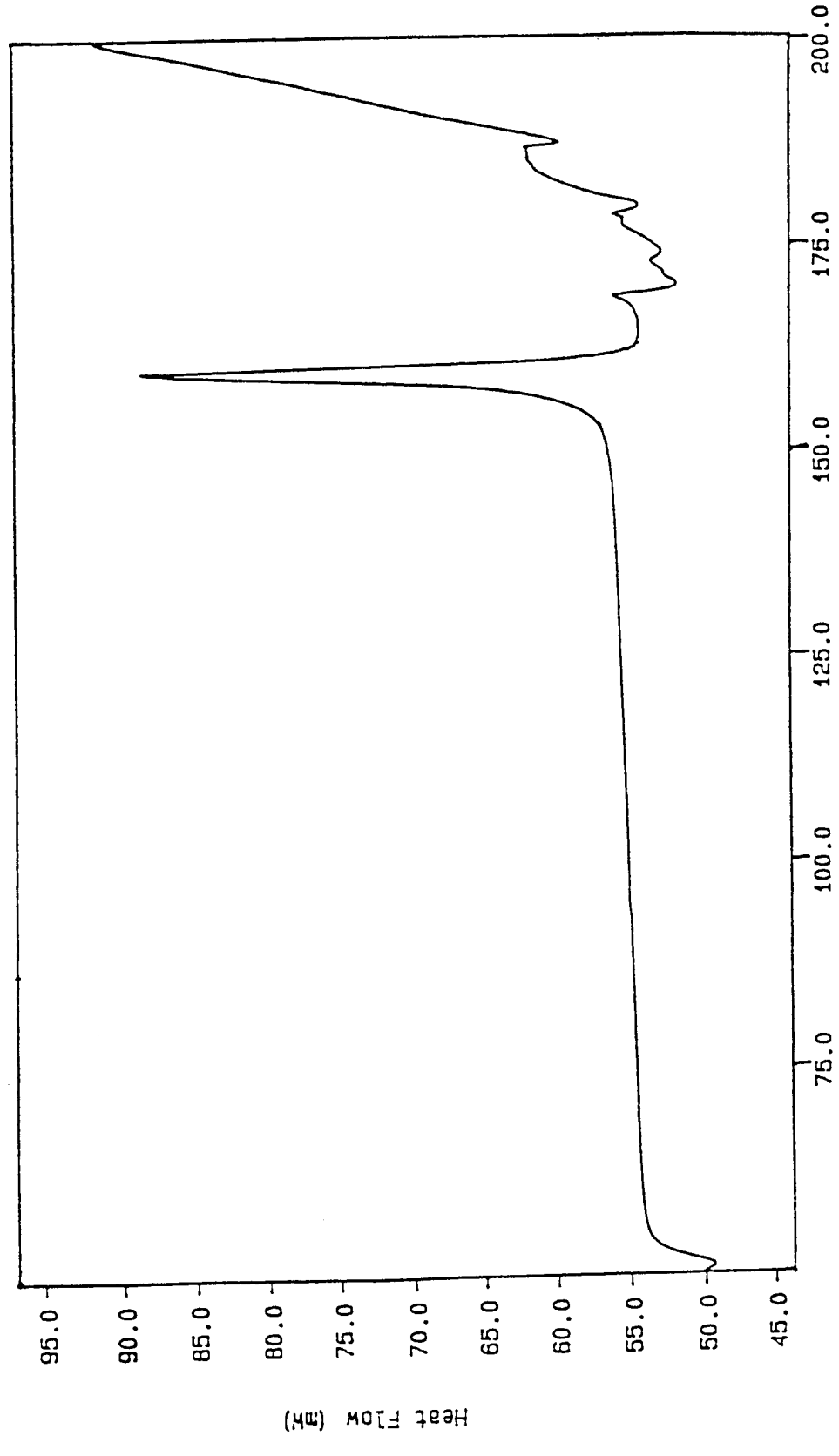

Heat Flow (mW)
95.0
90.0
85.0
80.0
75.0
70.0
65.0
60.0
55.0
50.0
45.0
75.0
100.0
125.0
150.0
175.0
200.0
Temperature (°C)
50ul CRUCIBLES WITH PINHOLES
TEMP 1: 50.0 C TIME 1: 0.0 min RATE 1: 10.0 C/min
TEMP 2: 200.0 C

FIGURE 4

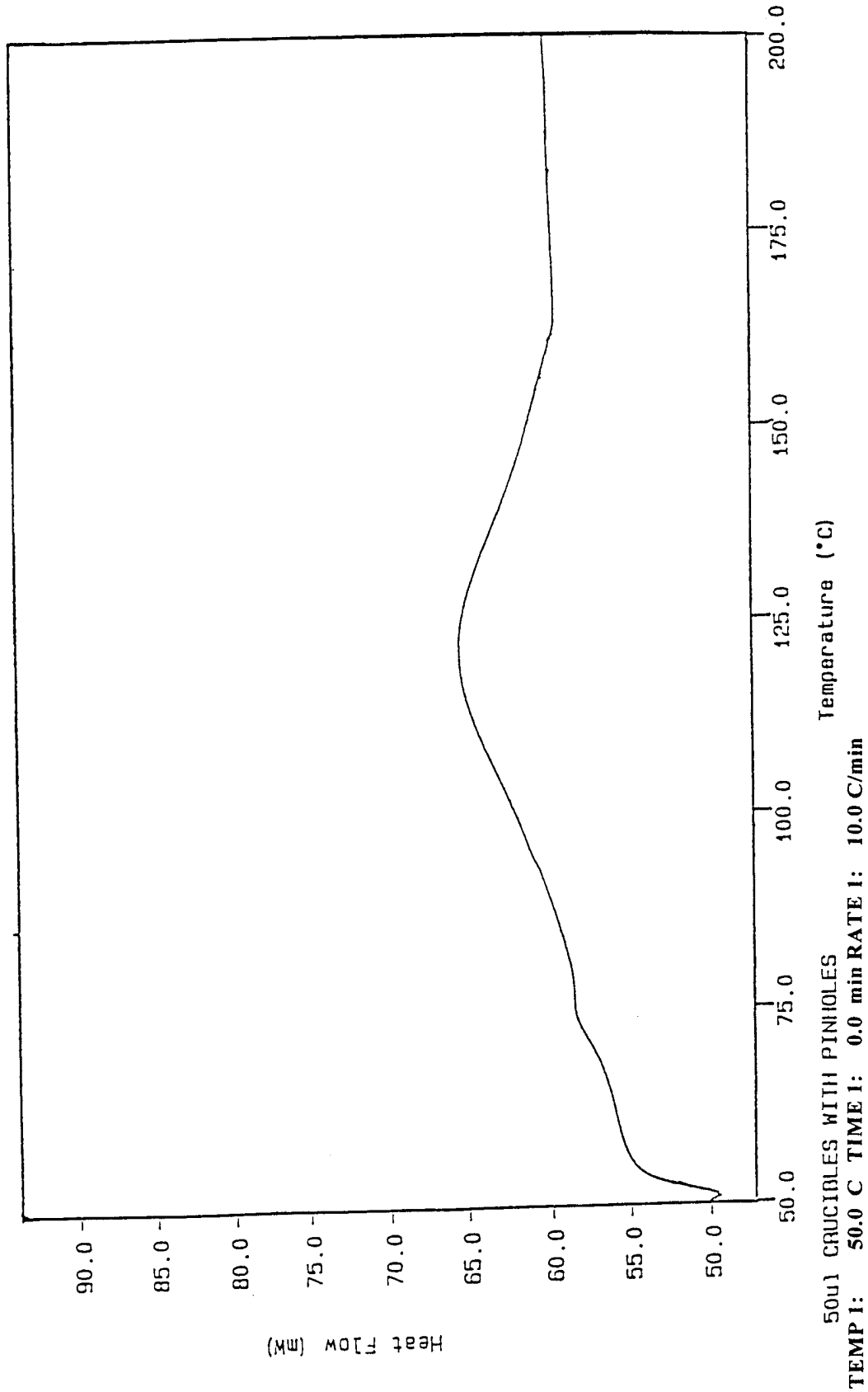

Heat Flow (mW)
90.0
85.0
80.0
75.0
70.0
65.0
60.0
55.0
50.0
50.0
75.0
100.0
125.0
150.0
175.0
200.0
Temperature (°C)
50ul CRUCIBLES WITH PINHOLES
TEMP 1: 50.0 C TIME 1: 0.0 min RATE 1: 10.0 C/min
TEMP 2: 200.0 C

FIGURE 5

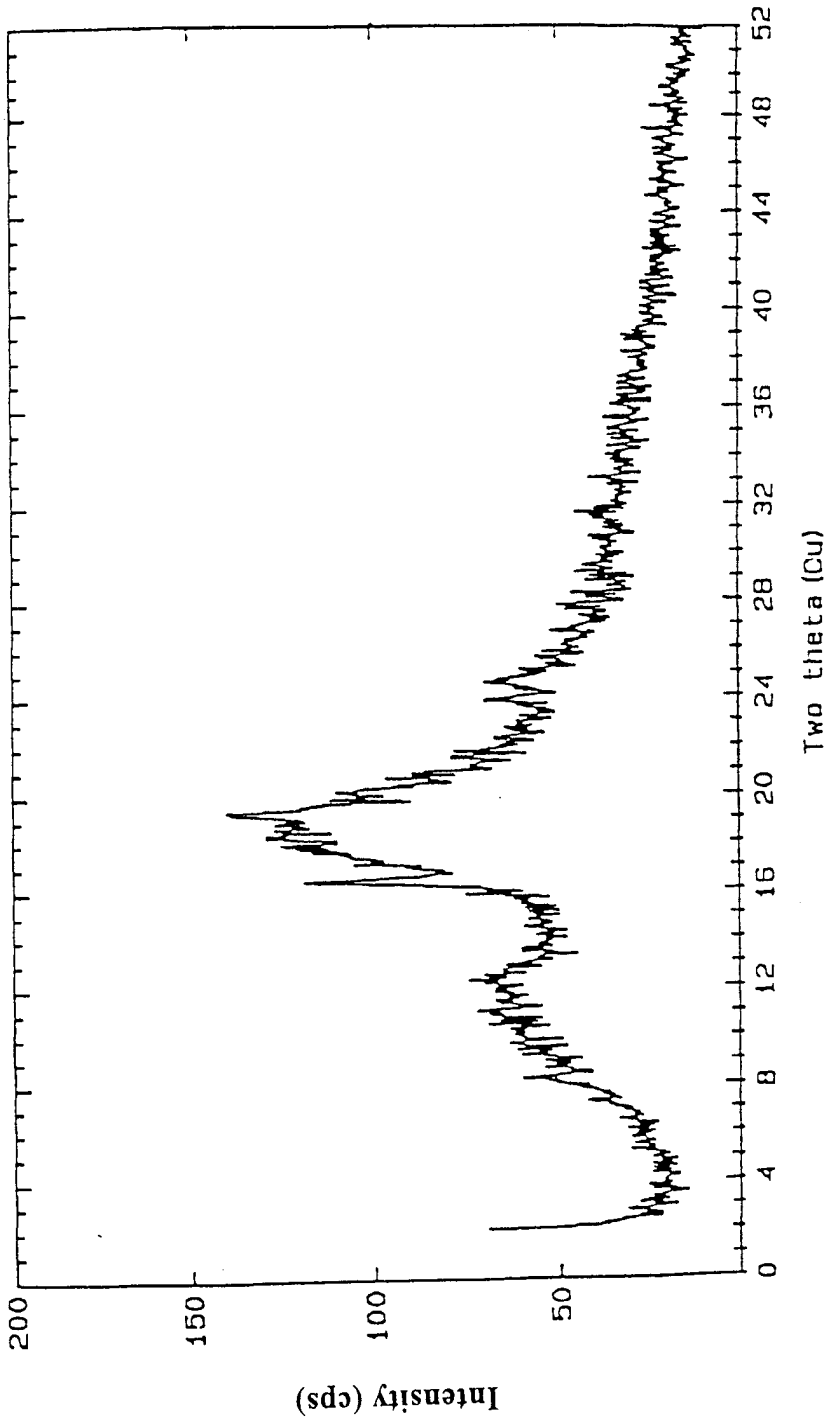

Intensity (cps)
200
150
100
50
0
4
8
12
16
20
24
28
32
36
40
44
48
52
Two theta (Cu)

FIGURE 6

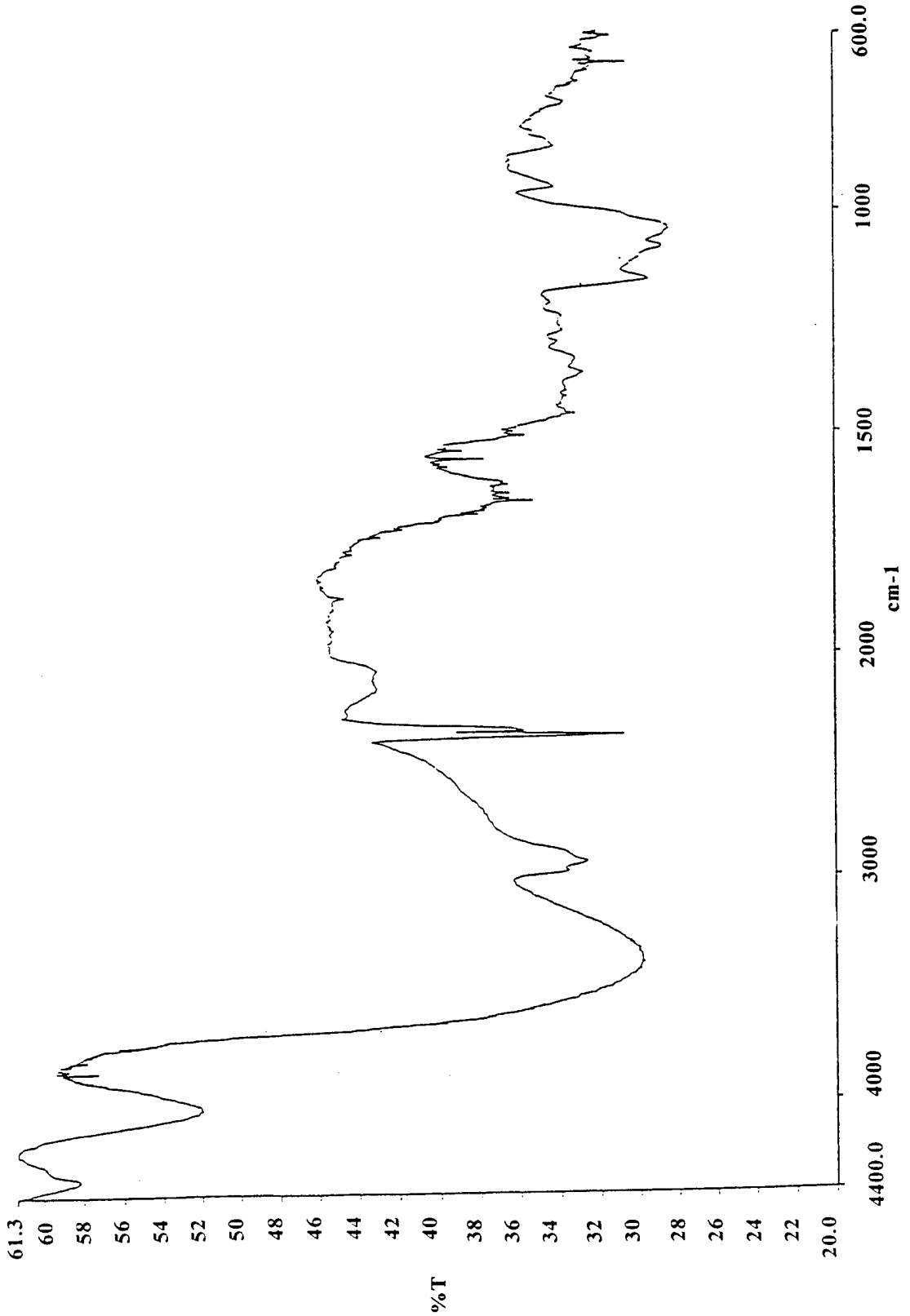
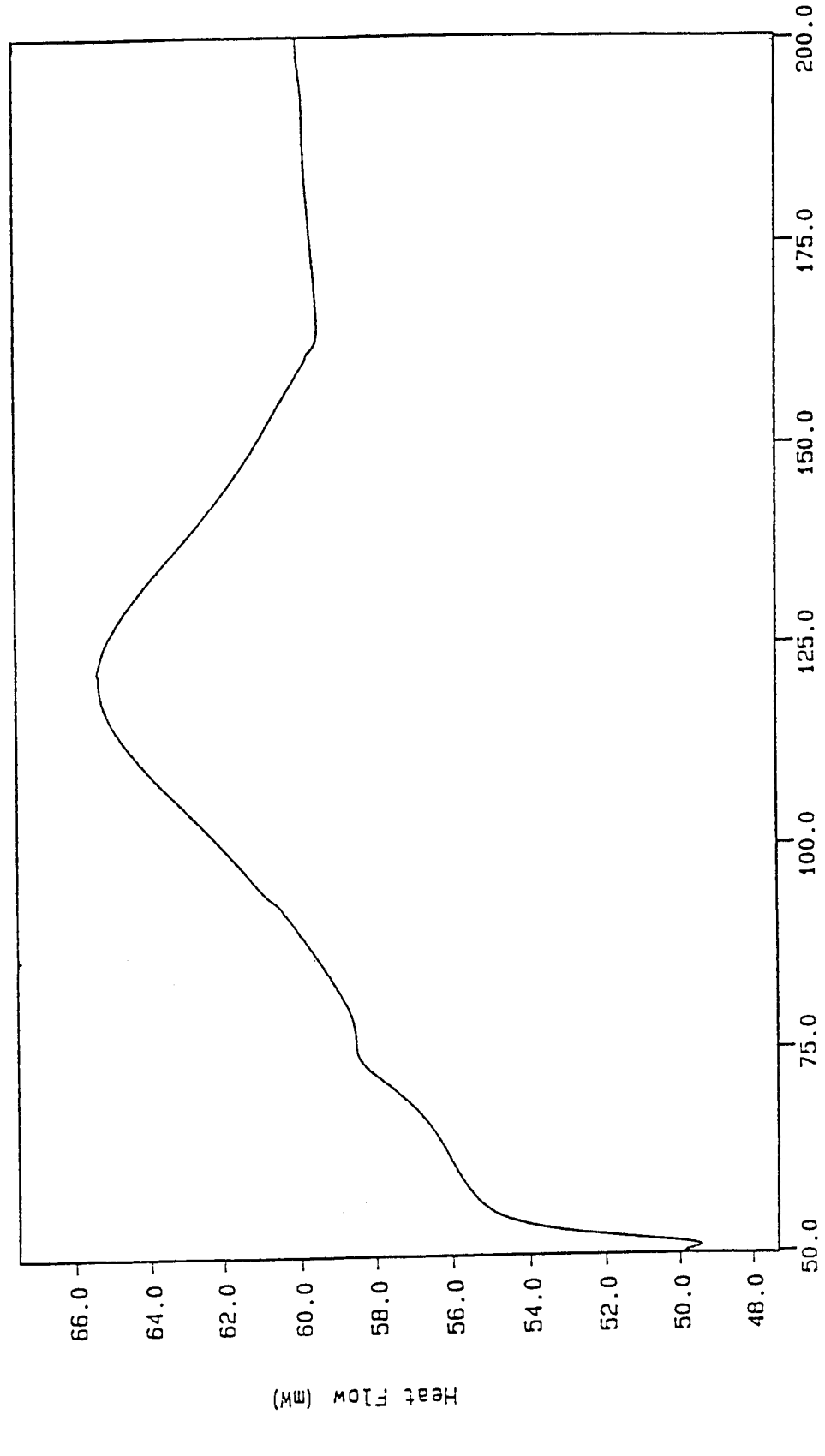

%T
61.3
60
58
56
54
52
50
48
46
44
42
40
38
36
34
32
30
28
26
24
22
20.0
4400.0
4000
3000
2000
1500
1000
600.0
cm-1

FIGURE 7


66.0
64.0
62.0
60.0
58.0
56.0
54.0
52.0
50.0
48.0
Heat Flow (mW)
50.0
75.0
100.0
125.0
150.0
175.0
200.0
Temperature (°C)
50ul CRUCIBLES WITH PINHOLES
TEMP 1: 50.0 C TIME 1: 0.0 min RATE 1: 10.0 C/min
TEMP 2: 200.0 C

INTERNATIONAL SEARCH REPORT

International Application No
PCT/GB 97/02947

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 C08B37/00 A61K47/48 A61K31/135

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 C08B A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	US 5 080 903 A (AYACHE JOSIANE ET AL) 14 January 1992 * see in particular claims 1-4; col. 2, lines 65-68 * ---	1-24
Y	WO 96 01129 A (FARMARC NEDERLAND BV ;PENKLER LAWRENCE JOHN (ZA); GLINTENKAMP LUET) 18 January 1996 * see p.13, l.3-18, preparation examples 7 & 8;claims 1,10 * ---	1-24
A	EP 0 251 459 A (EURO CELTIQUE SA) 7 January 1988 * see claims 1,2; p. 3, l. 15-25 & 40 * --- -/--	1-22

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"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)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"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

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"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.

"&" document member of the same patent family

1

Date of the actual completion of the international search	Date of mailing of the international search report
5 February 1998	20. 02. 98

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Isert, B

Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

International Application No
PCT/GB 97/02947

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	LEMESLE-LAMACHE: "Study of beta-cyclodextrin and ethylated beta-cyclodextrin salbutamol complexes, in vitro evaluation of sustained release bahaviour of salbutamol" INT. J. PHARM., vol. 141, no. 1,2, 1996, pages 117-124, XP002054595 * see the abstract *	1-24
A	MARQUES ET AL.: "Studies of cyclodextrin inclusion complexes. I The salbutamol-cyclodextrin comple as studied by phase solubility and DSC " INT. J. PHARM., vol. 63, 1990, pages 259-266, XP002054596 cited in the application * see the abstract; p.265, conclusion *	1-24
Y	" * "	23
A	MARQUES ET AL.: "Studies of cyclodextrin inclusion complexes. IV. The pulmonary absorption of salbutamol from a complex with 2-hydroxypropyl-beta-cyclodextrin in rabbits" INT. J. PHARM., vol. 77, 1991, pages 303-307, XP002054597 cited in the application * see the abstract; p.307, conclusion *	1-24
Y	* " *	24
Y	DARROUZET H: "PREPARING CYCLODEXTRIN INCLUSION COMPOUNDS" MANUFACTURING CHEMIST, vol. 64, no. 11, 1 November 1993, page 33/34 XP000423501 " see the whole document *	23,24

1

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No
PCT/GB 97/02947

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
US 5080903 A	14-01-92	FR 2619718 A	03-03-89
		AT 138565 T	15-06-96
		CA 1328621 A	19-04-94
		DE 3855323 D	04-07-96
		DE 3855323 T	10-10-96
		EP 0306422 A	08-03-89
		ES 2087855 T	01-08-96
		JP 1100117 A	18-04-89
WO 9601129 A	18-01-96	AU 3075395 A	25-01-96
		EP 0768897 A	23-04-97
		ZA 9505582 A	26-02-96
EP 0251459 A	07-01-88	DE 3780223 A	13-08-92
		JP 2052930 C	10-05-96
		JP 7080788 B	30-08-95
		JP 62292733 A	19-12-87
		US 4834985 A	30-05-89