Abstract:
The present invention relates to an improved process for the preparation of high purity formoterol and its pharmaceutically acceptable salts of Formula-I(C).
AN IMPROVED PROCESS FOR THE PREPARATION OF HIGH PURITY FORMOTEROL AND ITS PHARMACEUTICALLY ACCEPTABLE SALTS

INTRODUCTION

The present invention relates to an improved process for the preparation of high purity formoterol base and its pharmaceutically acceptable salts. The particular salt envisaged by the invention is the fumarate salt. Formoterol base, \((\text{N-} [2\text{-hydróxy-}5\text{-[(IR)-1-hydroxy-2-[(IR)-2- (4\text{-methoxyphenyl})-l-methylethyl]-amino} ]\text{ethy}]\text{phenyl]}\text{fo πáamide})\) has the formula-I(A) and its fumarate dihydrate of the formula-I(C) given below is a well-known long acting and highly selective bronchodilator drug. The \(\beta_2\)-adrenoceptor agonists taken by inhalation are the administration of choice in the symptometric therapy of obstructive airway disease.

\[
\text{I(A)} \quad \text{I(B)}
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Formoterol is commercially available as a recemic mixture of (R, R) and (S, S) in a 1:1 ratio, and the generic name formoterol refers to this recemic mixture.

Formoterol is developed by Yamanouchi Pharmaceutical Company as a long-acting beta-2 adrenoceptor agonist. Formoterol fumarate dihydrate is available in the market as Foradil Aerolizer, a capsule dosage form containing a dry powder formulation of formoterol fumarate dihydrate for oral inhalation with the aerolize inhaler. It is indicated in the maintenance treatment of asthma and in the prevention of bronchospasm, including exercise-induced bronchospasm, in both adult and pediatric patients. Formoterol given by inhalation has much longer duration of action than any other bronchodilators in the market. Therefore it avoids the nocturnal asthma, which often causes considerable anxiety and debility to the patients. The product is also indicated in the treatment of patients with chronic obstructive pulmonary disease (COPD), including chronic bronchitis and emphysema.
BACKGROUND OF THE INVENTION

Formoterol is first disclosed in a Japanese patent application (Application No 13121 (1972) by Yamanouchi and its related priority applications are 39416 (1972), 51013 (1972), and 52925 (1972). The corresponding German Pat is DE 2 305 092 and the US Pat is 3 994 974. Later on it is also published in Chem. Phann. Bull, 1977, 25 (6), 1368-1377 by the same company.

The aforesaid patent describes a process for the preparation of Formoterol based on N-alkylation using a phenacyl bromide (Scheme-1). Accordingly, the bromo derivative of formula-II is reacted

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\text{Scheme-1}
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with benzyl protected secondary amine of formula-III to get a coupled keto derivative of formula-IV. The keto group is reduced to the corresponding nitro alcohol (oil) of formula-V using sodium borohydride. Successive reduction of nitro group by iron and HCl and the formylation of resulting aniline derivative with acetic formic anhydride gave the dibenzyl formoterol of formula-VII having four isomers RR, RS, SS, SR. Separation of RR and SS isomers is accomplished by converting the above dibenzyl formoterol into its fumarate salt and selective crystallization from isopropyl alcohol. The purified dibenzyl formoterol base of formula-VII is liberated from its salt and is subjected to hydrogenation using palladium-on-charcoal to get formoterol base of formula-I(A). The base is then converted to its pharmaceutically acceptable fumarate salt of formula-I(B).

The second process for formoterol is disclosed in ES 2 005 492 as shown in Scheme-2. Key step in this process is a coupling reaction between 3-formamido-4-benzyloxyphenyloxirane of the formula-VIII and the unprotected 2-(4-methoxyphenyl)-l-methylethylamine of the formula-IX to get the intermediate compound of formula-X. The O-debenzylation of the compound of formula-X is carried out by treating it with hydrofluoric acid to get formoterol of the formula-I(A).

![Scheme-2](attachment:image)

A modified process (Scheme 3) for formoterol is disclosed in WO 92/05147 (1992) and in the corresponding US pat 5434304 (1995). In this route, nitro epoxide of the formula-XI is reacted with benzyl protected amine derivative of formula-III to get the nitro alcohol derivative of formula-V in the form of four stereoisomers, namely RR, SS, RS, and SR. The dibenzyl formoterol of formula-VII is obtained either by reduction over platinum oxide of the...
nitro compound of formula-V and successive formylation of the resultant aniline derivative with formic acid or in a single step process using Raney nickel and formic acid. The crude dibenzyl formoterol thus obtained was then converted to its fumarate salt to remove unwanted isomers

Scheme-3

(RS and SR) by selective crystallization of the crude fumarate salt. The pure set of crystalline isomers (RR and SS) are isolated by filtration, neutralized with a base to get the dibenzylformoterol of formula-VII₄ and hydrogenated over Palladium-on-charcoal to get the formoterol of formula-I(A). The formoterol base was then converted to its pharmaceutically acceptable fumarate salt of formula—I(C).
Process disclosed in the first patent (US 3994974) for the preparation of formoterol fumarate has the following disadvantages.

(a) The chemical purity as well as enantiomeric purity of the intermediates and final product is not disclosed.

(b) Unwanted isomers of formoterol (RS and SR) are separated at a very late stage (dibenzyl formoterol (formula-VII) of the synthesis. This would lead to increase in cost and pollution, as the unwanted isomers are not recyclable.

(c) We observed that separation of unwanted isomers is not easy. It will require a number of crystallizations to remove these isomers from the required dibenzyl formoterol of formula-VII. This would lead to poor recovery of wanted formoterol.

(d) Process for the preparation of the stable dihydrate form of formoterol fumarate or its analysis is not mentioned in this patent.

Process disclosed in the second patent (ES 2005492), for formoterol fumarate suffers from following disadvantages.

(a) The process uses expensive and rare chemicals like crown ethers, hazardous reagents like hydrofluoric acid and carcinogenic solvents like benzene. Such process is not suitable for scale up operations, as it will have serious health and environmental problems.

(b) No information about the quality of formoterol fumarate is disclosed in this patent.

Process disclosed in the third patent (WO 92/05147, equivalent US pat 5434304) for formoterol fumarate dihydrate has the following disadvantages.

(a) Longer reaction time (69 hr) and higher temperature (90° C) are required to couple the nitro epoxide of formula-XI with benzyl protected secondary amine derivative of formula-III. Since nitro compounds are known to be thermally unstable at elevated temperatures, it is not advisable to carry out the reaction at such high temperatures for such prolonged time. The impact of higher temperature and longer reaction time will be severe on the yield and quality of required compound especially during scale up operation.
(b) Unwanted isomers (RS and SR) formed in the first step of the process are nearly 40% which were carried forward upto dibenzyl formoterol of formula-VII stage and separated at this stage via fumarate salt formation followed by selective crystallization. Such a process would require more reagents thereby making the process expensive and polluting. Also, the purification process at dibenzyl formoterol stage is not attractive as the unwanted isomers could not be eliminated to the required limit (0.3% as per pharmacoepial requirement) even after repeated crystallization of the fumarate salt. Such a process is not commercially viable.

(c) Selection of solvents like a mixture of isopropyl alcohol and ethyl acetate in the hydrogenation step (final step) is not advisable, as the solubility of formoterol base is poor in ethyl acetate and isopropyl alcohol.

(d) During process development work we observed that usage of water in recrystallization of formoterol lead to the formation of desformyl impurity of formoterol. Similar observation is reported by Gerald J Tanoury (Organic Process Research and Development 2002, 6, pp855-862) for (R,R) formoterol tartarate.

(e) The reported yields are not reproducible.

DESCRIPTION OF THE INVENTION

Formoterol fumarate has become a well-known bronchodilator that has now been on the market and has shown great promise as a valuable anti-asthmatic drug with few side effects. Keeping in view of the difficulties in commercialization of the above-mentioned processes for the preparation of formoterol fumarate, we aimed to develop a simple and economical process for commercial production of formoterol fumarate.

We observed that a promising approach for such a process is to (a) avoid the carrying forward of unwanted isomers (RS and SR) of nitro intermediate of formula-V to subsequent steps (b) remove the unwanted isomers formed in the first stage by simple crystallization technique (c) avoid high temperature and prolonged reaction times involving nitro intermediates (d) minimize or avoid the usage of reagents like iron powder or Raney Nickel in the process (e) avoid the purification of dibenzyl formoterol intermediate via fumarate salt as it requires several crystallizations (f) avoid the usage of hazardous reagent like hydrofluoric acid and
carcinogenic solvent like benzene (g) improve the hydrogenation process by employing better soluble solvent or solvent mixture in the process (h) avoid the usage of water during the crystallization/purification isolation of formoterol base.

Accordingly, the main objective of the present invention is to provide an improved process for the preparation of formoterol fumarate dihydrate of the formula-I(C) by avoiding the carrying forward of unwanted isomers of nitro intermediate of formula-V to subsequent steps.

Another main objective of the present invention is to provide an improved process for the preparation of formoterol fumarate dihydrate of the formula-I(C) by removing the unwanted isomers (RS and SR) formed in the second stage by simple crystallization technique.

Another objective of the present invention is to provide an improved process for the preparation of formoterol fumarate dihydrate of the formula-I(C) that uses minimum required quantity of reagents like iron powder, Raney nickel, acetic formic anhydride, etc.

Another objective of the present invention is to provide an improved process for the preparation of formoterol fumarate dihydrate of the formula-I(C) by avoiding the purification of dibenzylformoterol via fumarate salt.

Still another objective of the present invention is to provide an improved process for the preparation of formoterol fumarate dihydrate of the formula-I(C) by employing a better soluble solvent or solvent mixture in the hydrogenation step.

Another objective of the present invention is to provide an improved process for the preparation of formoterol fumarate dihydrate of the formula-I(C), which produces formoterol fumarate of more than 99.8% quality.

Another objective of the present inventions is to provide an improved process for the preparation of formoterol fumarate dihydrate of the formula-I(C) which maintains the unwanted isomers (RS and SR) below the pharmacopoeia limit (<0.3%).
Another objective of the present invention is to provide an improved process for the preparation of formoterol fumarate dihydrate of formula-I(C), which meets the specifications of the European Pharmacopoeia 2005 monograph. According to this monograph nine impurities are identified and the limits for these impurities are fixed. List of the nine impurities with their limit is given below.

| European Pharmacopoeia 2005 monograph listed impurities and their limits |
|---|---|---|
| ![Chemical Structure 1] | ![Chemical Structure 2] | ![Chemical Structure 3] |
| W Limit 0.3% | 'B' Limit 0.2% | 'G' Limit 0.2% |
| 'D' Limit 0.2% | 'E' Limit 0.1% | 'F' Limit 0.2% |
| ![Chemical Structure 7] | ![Chemical Structure 8] | ![Chemical Structure 9] |
| 'G' Limit 0.1% | 'H' Limit 0.1% | 'I' Limit 0.3% |

The present invention has been developed based on our finding that if one removes the isomeric impurities formed in the second stage itself the process would become simple and economically viable. It is also observed that the nitro intermediate of formula-V would crystallize readily from a number of solvents leaving both the isomeric impurities (RS and SR) in the mother liquor.
DETAILED DESCRIPTION OF THE INVENTION

Process of the present invention is as given in Scheme-4 below. The crude oily compound of formula-V is prepared as per the process disclosed in US pat 3 994 974. Accordingly, nitrophenacyl bromide of the formula-II is reacted with excess secondary amine of formula-III in methyl ethyl ketone solvent medium at reflux temperature to get the tertiary amine derivative of the formula-IV. Reduction of the keto group present in compound of formula-IV with sodium brohydride in alcoholic solvent medium gave the crude nitro alcohol derivative of formula-V.

The crude oily nitro alcohol compound of formula-V obtained in the reaction is triturated with a non-polar solvent such as diisopropyl ether to get a yellow solid after filtration of the solvent. In the prior (US 3994974 & WO 92/05147) art this intermediate was reported as yellow oil. The yellow solid thus obtained can be recrystallized from a number of solvents.
such as diethyl ether and diisopropyl ether, preferably diisopropyl ether. Recrystallization of the nitro alcohol derivative from diisopropyl ether gave the pure RR/SS mixture as a yellow crystalline solid with >99% purity. Melting point of this solid is 76.7-81.5°C.

Reduction of the nitro group present in compound of formula-V with Raney nickel in polar solvents such as methanol, ethanol or isopropyl alcohol preferably, methanol solvent medium under hydrogenation conditions gave the crystalline amino compound of formula-VI as dark yellow solid. Melting point of this intermediate is 94-99°C. In the prior art (US 3994974 & WO 92/05147) this intermediate was disclosed as oily solid. In the prior art process large excess (more than 5 molar equivalents) of iron powder was used to accomplish this conversion. The Raney nickel used in the process can be recycled simply by settling the reaction mass and decanting the supernatant liquid from Raney nickel. Therefore, present process is cost effective and environment friendly. The amino alcohol derivative of formula-VI can be recrystallized from a number of solvents such as diethyl ether or diisopropyl ether, preferably, diisopropyl ether. Recrystallization from diisopropyl ether gave the pure RR/SS mixture as a yellow crystalline solid with >99.4% purity. Melting point of this solid is 97.5-99.5°C.

The crystalline amino compound of formula-VI is converted to the N-formyl derivative of formula-VII using a formylating reagent such as formic acid or aceticformic anhydride. Crystallization from isopropyl alcohol gave the pure RR/SS mixture (99.95%) as white to off white crystalline solid. Present process avoids formation and repeated crystallizations of the fumarate salt of formula-VII. Therefore, this process is simple and cost effective for commercial scale up. In the prior art processes (US 3994974 & WO 92/05147) this intermediate was converted to fumarate salt and purified by repeated recrystallizations.

Debenzylation of the compound of formula-VII using Pd/C in methanol-ethyl acetate solvent medium gave the formoterol base of formula-I(A). The Pd/C used in the process can be 1-20% Pd/C, preferably, 5-10% Pd/C. The reaction can be done at 0-1000psi hydrogen pressure, preferably, between 35-70 psi. The formoterol base obtained from the hydrogenation step can be recrystallized from a solvent such as isopropyl alcohol or ethanol, preferably, isopropyl
alcohol. For example, recrystallization of the formoterol base in isopropyl alcohol gave the pure RR/SS mixture in 99.95% purity. The pure formoterol base is then converted to the fumarate salt by suspending the base in a hydrocarbon solvent and adding a solution of fumaric acid in isopropyl alcohol. Trituration of the resulting formoterol fumarate salt of formula-I(B) with solvents such as ethyl acetate, aqueous isopropyl alcohol, and acetonitrile gave pure formoterol fumarate. Later on it was converted to its dihydrate form by triturating the pure formoterol fumarate with double distilled water and isolated as a white to off-white crystalline solid.

The Purity of formoterol fumarate dihydrate prepared according to the present process has >99.8% purity with all the European Pharmacopoeia 2005 monograph listed impurities well below the specified limit.

Accordingly, the present invention provides an improved process for the preparation of formoterol fumarate dihydrate of the formula-I(C),

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\text{I(C)}
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which comprises:

(i) Triturating the crude oily compound of formula-V with a non-polar solvent to make it a solid

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\text{V}
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(ii) Recrystallization of solid compound of formula-V from a solvent to make it >99.0% pure
(iii) Reduction of nitro derivative of formula-V with a metal catalyst under hydrogenation conditions to get crystalline amino derivative of formula-VI

(iv) Recrystallization of the resulting amino derivative of formula-VI from a solvent to get > 99.4% quality

(V) Formylation of the crystalline amino compound of formula-VI with a formylating reagent to get diastereomerically pure formanilide derivative of formula-VII

(vi) Debenzylation of the formanilide derivative of formula-VII under hydrogenation conditions in the presence of a metal catalyst and isolation of the formoterol base of formula-I(A), from a solvent medium
(vii) Recrystallization of formoterol base of formoterol-I(A) from a solvent to get >99.8% quality.

![Chemical structure of I(A)](image)

I(A) RR, SS - >99.9%
RS, SR - <0.1%

(viii) Reaction of a suspension of pure formoterol base of formula-(IA) in hydrocarbon solvent with an alcoholic solution of fumaric acid to get the formoterol fumarate of formula-(IB),

![Chemical structure of I(B)](image)

(ix) Purification of formoterol fumarate of formula-I(B) from a solvent or a mixture thereof followed by leaching with water to get pharmaceutical grade formoterol fumarate dihydrate (>99.8%) of formula-I(C),

![Chemical structure of I(C)](image)

I(C) RR, SS - >99.9%
RS, SR - <0.1%

The non-polar solvent employed in step (i) to solidify the nitro derivative of formula-V is selected from ethers like diisopropyl ether, diethyl ether, dioxane, methyl tert-butyl ether, hydrocarbons like hexane, heptane, cyclohexane, toluene, xylene, etc, preferably, diisopropyl ether. The volume of solvent used in step (i) to solidify the nitro derivative of formula-V is in the range of 5-8 times to its weight, preferably, 5-7 times and the temperature at which the compound of formula-V can be isolated is in the range of 0-35°C, preferably, 20-30°C.

The solvent employed in step (ii) for recrystallization of nitro derivative of formula-V is selected from ethers like diethyl ether, diisopropyl ether, dioxane, methyl tert-butyl ether,
preferably, diisopropyl ether. The volume of solvent used in step (ii) to crystallize nitro alcohol derivative of formula-V is in the range of 5-15 times preferably, 5-10 to the weight of nitro alcohol derivative. The temperature at which the crystalline compound of formula-V can be isolated in step (ii) is in the range of 5-40°C preferably, 25-30°C. The purity of compound of formula-V after recrystallization from diisopropyl ether in step (ii) is more than 99% and the unwanted isomeric impurities are less than 1%.

The metal catalyst used in step (iii) to reduce crystalline nitro derivative of formula-V is Raney nickel. The hydrogenation conditions applied in step (iii) include a polar solvent like methanol, isopropyl alcohol, ethyl acetate preferably, methanol and the pressure of hydrogen is 1-100psi, preferably, 40-60psi at a temperature of 20-50°C, preferably, 30°C.

The solvent employed in step (iv) for recrystallization of the compound of formula-VI is selected from ethers like diisopropyl ether or diethyl ether, hydrocarbons like hexane, heptane, cyclohexane, toluene, xylene, etc., preferably, diisopropyl ether. The volume of solvent used in step (iv) to crystallize amino alcohol derivative of formula-VI is in the range of 5-15 times to its weight, preferably, 5-10 times. The temperature at which the compound of formula-VI can be isolated in step (iv) is in the range of 0-35°C, preferably, 20-30°C. The purity of the recrystallized compound of formula-VI in step (iv) is more than >99.4% and the isomeric impurities are below 0.2%.

The reagent employed for formylation of crystalline amino derivative of formula-VI in step (v) is selected from formic acid, aceticformic anhydride, etc., preferably, aceticformic anhydride. The solvent employed in step (v) for formylation of amino derivative of formula-VI is tetrahydrofuran or 2-methyl tetrahydrofuran. The volume of solvent used in step (v) is in the range of 1-20 times to its weight, preferably, 5-10 times and the reaction temperature is in the range of 0-80°C. The temperature at which the compound of formula-VII can be isolated in step (v) is in the range of 0-35°C, preferably, 20-30°C. The solvent employed in step (v) for crystallization of compound of formula-VII is selected from ethyl acetate, methanol, isopropyl alcohol, or a mixture thereof, preferably, isopropyl alcohol. The volume of solvent used in step (v) to crystallize
formamide derivative of formula-VII is in the range of 5-15 times to its weight, preferably, 5-10 times. The temperature at which the crystalline compound of formula-VII can be isolated in step (v) is in the range of 0-35°C, preferably, 20-30°C. The purity of the recrystallized compound of formula-VII in step (v) is more than >99.9% and the isomeric impurities are below 0.1%.

The metal catalyst used in step (vi) for debenzylation of dibenzyl formoterol of formula-VII is 5-10% wet Palladium-on-Charcoal, preferably, 10% wet. The solvent employed in step (vi) for debenzylation of compound of formula-VII is selected from ethyl acetate, methanol, or a mixture thereof, preferably, a 60:40 or 50:50 mixture of ethyl acetate and methanol. The volume of solvent used in step (vi) for debenzylation of dibenzyl formoterol of formula-VII is in the range of 15-25 times to its weight, preferably, 15-20 times. The hydrogen pressure applied in step (vi) is 1-100psi, preferably, 40-60psi. The temperature of reaction in step (vi) is in the range of 20-50°C, preferably, 25-30°C. The solvent employed in step (vi) for isolation of the formoterol base of formula-I(A) is selected from esters like methyl acetate or ethyl acetate, alcohols like methanol, isopropyl alcohol, hydrocarbons like hexane, heptane, cyclohexane, toluene, xylene, nitriles like acetonitrile, etc., preferably, ethyl acetate. The volume of solvent used in step (vi) for isolation of formoterol base of formula-I(A) is in the range of 15-25 times to its weight, preferably, 15-20 times. The isolation temperature in step (vi) is in the range of 30-80°C, preferably, at 35-40°C.

The solvent employed in step (vii) for crystallization of the formoterol base of formula-I(A) is selected from esters like methyl acetate or ethyl acetate, alcohols like methanol, isopropyl alcohol, either or a mixture thereof, preferably, isopropyl alcohol. The volume of solvent used in step (vii) for crystallization of formoterol base of formula-I(A) is in the range of 5-20 times to its weight, preferably, 10-11 times. The isolation temperature of formoterol base of formula-I(A) in step (vii) is in the range of 25-70°C, preferably, 30-35°C. The HPLC purity of the pure formoterol base of formula-I(A) obtained in step (vii) according to the present process is > 99.8%.
The solvent used in step (viii) to suspend the pure crystalline formoterol base of formula-I(A) is selected from hexane, heptane, cyclohexane, toluene, xylene, etc, preferably, toluene.

The volume of hydrocarbon solvent used in step (viii) to suspend formoterol base is in the range of 5-20 times to its weight, preferably, 10-15 times. The alcoholic solvent used in step (viii) to dissolve fumaric acid is selected from methanol, ethanol, isopropanol, t-butanol, preferably, isopropanol. The volume of alcoholic solvent used to dissolve fumaric acid in step (viii) is in the range of 2-6 times to its weight, preferably, 2-4 times, most preferably, 2 times. The isolation temperatures of formoterol fumarate of formula-I(B) in step (viii) is in the range of 10-60°C, preferably, at 25-30°C.

The solvent employed in step (ix) for purification of formoterol fumarate of formula (I(B) is selected from toluene, ethyl acetate, aqueous (1-20%) isopropyl alcohol, methanol, acetonitrile, acetone or a mixture thereof. The volume of solvent used to purify formoterol fumarate of formula-I(B) in step (ix) is in the range of 1-30 times to its weight, preferably, 5-25 times, most preferably, 20 times. The purification temperature of the compound of formula-I(B) in step (ix) is in the range of 25-90°C preferably, 50-85°C and most preferably, in the range of 60-70°C. The isolation temperature of the compound of formula-I(B) in step (ix) is in the range of 10-80°C, preferably, at 30-50°C, most preferably, at 35-45°C. The trituration temperature in step (ix) of the compound of formula-I(B) in water is in the range of 0-40°C, preferably, 20-35°C, most preferably, 25-30°C. The isolation temperature of the pharmaceutically acceptable dihydrate form of formoterol fumarate of formula-I(C) in step (ix) is in the range of 0-40°C, preferably, 20-35°C most preferably, 25-30°C. The percentage of isomeric purity of compound of formula-I(C) in step (ix) is more than 99.9% by HPLC. The percentage of isomeric impurity of compound of formula-I(C) in step (ix) is less than 0.1% by HPLC.
ADVANTAGES OF THE INVENTION

1. The present invention provides an improved process for the preparation and isolation of crystalline high purity (>99% by HPLC) intermediates of formoterol of formulae-V and VI.

2. Usage of high purity intermediates of formulae-V and VI in the subsequent steps of formoterol synthesis helped in cost reduction.

3. Present process avoids the purification of dibenzylformoterol via its fumarate salt, which is tedious and low yielding.

4. Present process employs better soluble solvents like ethyl acetate and methanol in the debenzylation step of formoterol base synthesis.

5. Present process produces >99.9% (by HPLC) purity formoterol fumarate dihydrate with all the impurities listed in European Pharmacopoeia 2005 Monograph below the specified limits.

Having thus described the present invention with reference to certain preferred embodiments, the invention will be further illustrated by the examples, which follow. These examples are provided for illustrative purposes only and are not intended to limit the scope of the invention in any way.

Example 1:

(a) Preparation of 2-{Benzyl-[2-(4-methoxyphenyl)-l-methylethyl]amino}-l-(4-benzyloxy-3-nitrophenyl)-ethanol of formula-V

Into a 5-L four-necked round-bottomed flask equipped with a mechanical stirrer, a thermometer pocket and reflux condenser, is charged 188 g (0.358 mol) of 2-{Benzyl-[2-4-methoxyphenyl]-1-methylethyl]amino} -1-(4-benzyloxy-3-nitrophenyl)-ethanone (IV) and 2.5 L methanol. To this stirred suspension, 35 g (0.921 mol) of sodium borohydride is added in 10 equal portions at RT (25-30° C). After addition, the resulting solution is stirred for over
night at 25-30° C. Upon evaporation of methanol, the resulting residue is dissolved in toluene (2.0 L) and washed with water (2.5 L). The toluene solution is then treated with activated charcoal and filtered. Evaporation of toluene from the filtrate under reduced pressure gave 205 g of yellow oily compound of formula-V. HPLC purity: RR and SS isomers: 58.57%; RS and SR isomers: 41.43%.

Purification of compound of formula-V:

Into a 2-L, four-necked round-bottomed flask, the above oily residue (205g) is charged and triturated with diisopropyl ether (1200 mL) at RT (25-30° C) for over night. The resulting yellow coloured solid (109 g) is isolated by filtration. This solid compound is further purified by recrystallization from diisopropyl ether (650 mL) and isolated the crystalline solid at 25-30° C to get 85 g of yellow crystalline compound of formula-V.

Melting point: 76.7-81.5° C
HPLC purity : RR and SS isomers: > 99.4%; RS and SR isomers: < 0.6 %

1H NMR (300 MHz; CDCl₃; δ ppm): 1.12 (s, 3H, -CH₃); 2.46-2.48 & 2.70-2.75 (m, 2H, NCH(CH₃)CH₂-); 2.58-2.61 (m, 2H, -NCH₂Ph); 3.1 1-3.15 (m, 1H, -NCH(CH₃)CH₂-); 3.50-3.53 & 3.79-3.86 (m, 2H, -CH(OH)CH₂NCH₂Ph-); 3.65 (bs, 1H, -CH(OH)-CH₂-); 3.79 (s, 3H, -OCH₃); 4.48-4.51 (m, 1H, -CH(OH)CH₂NCH₂Ph-); 5.21 (s, 2H, -OCH₂C₆H₃); 6.80-6.82 (d, 2H, Ar-Hydrogens); 6.97-6.96 (d, 2H, Ar-Hydrogens); 7.04-7.06 (d, 1H, Ar-Hydrogens); 7.12-7.13 (m, 2H, Ar-Hydrogens); 7.25-7.28 (m, 4H, Ar-Hydrogens); 7.32-7.45 (m, 5H, Ar-Hydrogens); 7.76 (s, 1H, Ar-Hydrogen)

13C NMR (300 MHz; CDCl₃; δ ppm): 12.9, 40.1, 54.3, 55.2, 55.7, 57.1, 67.9, 71.2, 113.7, 115.1, 123.0, 126.9, 127.2, 128.1, 128.4, 128.6, 128.7, 129.9, 131.2, 135.4, 135.6, 138.7, 140.0, 151.0, and 158.0

Mass : 527(M+1)

(b) Preparation of 1-(3-amino-4-benzyloxyphenyl)-2-[benzyl-[2-(4-methoxyphenyl)-1-methylethyl]-amino]ethanol of formula-VI

Into a 2-L stainless steel hydrogenation vessel, is charged crystalline nitro alcohol derivative of formula V (15 g) and methanol (500 mL). To this solution wet Raney nickel catalyst (3-5 g) (previously washed with methanol) is charged in the presence of nitrogen atmosphere.
The vessel is connected to a Parr hydrogenator and hydrogenated at 40-60 psi H\textsubscript{2} pressure and at RT (25-30° C). After completion of hydrogen gas consumption, the catalyst is removed by filtration under nitrogen atmosphere and the solvent is distilled off from the filtrate to get 11.5 g of brownish yellow compound of formula-VI.

HPLC purity: RR and SS isomers: 98.84% and RS and SR isomers: 0.45%

Purification of compound of formula-VI:

The above crude compound (11.5 g) is dissolved in diisopropyl ether (57.5 mL) at 65-70°C and the solution is treated with activated charcoal and filtered. The filtrate is then slowly cooled to RT (25-30° C) and filtered to get 9.0 g of brownish yellow crystalline compound of formula-VI.

MR: 97.5-99.5° C

HPLC purity: RR and SS isomers: 99.83% and RS and SR isomers: 0.06%

1\textsuperscript{HNMR} (300 MHz; CDCl\textsubscript{3}; \delta ppm): 0.98-1.00 (s, 3H, -CH\textsubscript{3}); 2.54-2.60 (m, 3H, -NCH(CH\textsubscript{3})\textsubscript{-CHH- and -NCH\textsubscript{2}Ph}); 2.72-2.77 (m, IH, -NCH(CH\textsubscript{3})CHHH-); 3.09-3.11 (m, IH, -NCH(CH\textsubscript{3})\textsubscript{-CH\textsubscript{2}-}); 3.48-3.51 & 3.82-3.89 (2 d, 2H, -CH(OH)CH\textsubscript{2}NCH\textsubscript{2}Ph-); 3.61 (bs, IH, -CH(OH)-CH\textsubscript{2}-); 3.78 (s, 3H, -OCH\textsubscript{3}); 3.82 (s, 2H, -NH\textsubscript{2}); 4.44-4.47 (m, IH, -CH(OH)CH\textsubscript{2}NCH\textsubscript{2}Ph-); 5.06 (s, 2H, -OCH\textsubscript{2}Ph); 6.61-6.63 (d, IH, Ar-Hydrogens); 6.73 (s, IH, Ar-Hydrogen); 6.79-6.82 (m, 3 H\textsubscript{5} Ar-Hydrogens); 6.96-6.98 (d, 2H, Ar-Hydrogens); 7.12-7.16 (d, 2H, Ar-Hydrogens); 7.23-7.34 (m, 3H\textsubscript{5} Ar-Hydrogens); 7.36-7.39 (m, 3H\textsubscript{5} Ar-Hydrogens); 7.40-7.45 (m, 2H\textsubscript{5} Ar-Hydrogens)

13\textsuperscript{C NMR} (300 MHz; CDC13; \delta ppm): 12.68, 40.34, 54.39, 55.18, 55.56, 57.42, 68.92, 70.50, 111.85, 112.76, 113.70, 115.84, 126.98, 127.47, 127.89, 128.29, 128.42, 128.78, 129.95, 131.61, 135.56, 136.43, 137.20, 139.12, 145.81, and 157.92.

Mass: 497 (M+1)

c) Preparation of N-[5-(2-{Benzyll[2-(4-methoxyphenyl)-l-methylethyl]amino}-l-hydroxy ethyl)-2-benzyloxyphenyl]-formamide of formula-VII

Into a 1-L 4 necked round bottomed flask fitted with a mechanical stirrer, a dropping funnel, a reflux condenser, thermometer pocket, and a nitrogen bubbler, is charged acetic anhydride (31.52 g) and cooled to 0° C using an ice/salt bath. Formic acid (15.96 mL) is added
dropwise at a rate of about 1 mL/min under vigorous stirring and efficient cooling so that the temperature of the reaction mixture is kept below 50°C. After 30 min, the reaction mixture is heated to 50-55°C. After 2 hr, the reaction mixture is cooled to 5-10°C. To this solution, a previously dissolved solution of crystalline amino derivative of formula VI (42 g) in THF (260 mL) is added at 5-10°C. After addition, the cooling bath is removed and the reaction is stirred for over night at room temperature. The solvent is removed under reduced pressure. The oily residue is dissolved in ethyl acetate and washed with water, 5% aq. NaHCO₃ solution, and aq. sodium carbonate successively. The organic layer is treated with charcoal followed by filtration to get a clear solution. The solvent is removed under reduced pressure and the residue is stirred with diisopropyl ether to get (43.0 g) of crystalline compound of formula-VII. The product is recrystallised from isopropyl alcohol (430 mL) and isolated at 25-30°C to get 40.9 g of highly pure white crystalline compound of formula-VII.

MR : 112.7-1 14.2°C
HPLC purity : RR and SS isomers: 99.95% and RS and SR isomers: 0.05%

(d) Preparation of N-(2-Hydroxy-5-[1-hydroxy-2-[2-(4-methoxyphenyl)-1 -methyl ethylamino] ethyl ]phenyl-formamide of formula-I (A)
Into a 1-L stainless steel hydrogenation vessel is charged a previously dissolved solution of crystalline compound of formula-VII (40 g) in ethyl acetate (250 mL). To this solution, a suspension of 16 g of Palladium-on-charcoal (10% wet) in methanol (250 mL) is charged. The vessel is connected to a Parr hydrogenator and hydrogenated at 40-60 psi. After completion of hydrogen consumption, the catalyst is removed by filtration under nitrogen atmosphere and the solvent is distilled off from the filtrate under reduced pressure at 30-40°C. The titled compound is isolated at 35-40°C by the addition of ethyl acetate (350 mL) and recrystallized from isopropyl alcohol (250 mL) and isolated at 30-35°C to get 23.0 g of white to off-white crystalline pure formoterol base of formula-I(A).
HPLC purity : RR and SS isomers: 99.95% and RS and SR isomers: 0.05%
MP : 145.1-145.6°C

(e) Preparation of formoterol fumarate of formula-I(B)
Into a 500 mL 4 necked round bottomed flask fitted with a mechanical stirrer, addition funnel and thermometer pocket, is charged formoterol base (23 g) and toluene (230 mL). To this stirred suspension, is added a previously dissolved solution of fumaric acid (3.68 g) in isopropyl alcohol (46 mL) at RT (25-30°C). After stirring for 5 hr at RT, the compound of formula-I(B) is recovered by filtration. The wet compound is suspended in 460 mL of 95% aqueous isopropyl alcohol and heated to 65-75°C. After maintaining for 1-2 hr the reaction mass was cooled to 40-45°C, maintained for 1-2 hr, and filtered. The wet cake is taken in a flask and suspended in 460 mL of acetonitrile and heated to 75-80°C. After maintaining for 1-2 hr, the reaction mass was cooled to 40-45°C, maintained for 1-2 hr, filtered, and dried at 60°C to get 19.0 g of formoterol fumarate of formula-I(B).

(f) Preparation of formoterol fumarate dihydrate of formula-I(C)

The above compound of formula-I(B) (19.0 g) is triturated with water (120 mL) at RT (25-30°C) for 30 minutes. The resultant suspension is filtered, washed the wet cake with water, and dried at 60°C to get 20.0 g of pharmaceutically acceptable formoterol fumarate dihydrate of formula-I(C) as white to off-white solid.

MR: 140.7-141.2°C
HPLC purity: 99.83%
Impurity 'A': 0.127%
Impurity 'E': 0.04%

Rest of the impurities B, C, D, F, G, H, I are not detected.
Isomeric purity (HPLC): RR and SS isomers: 99.95%; RS and SR isomers: 0.05%


(a) Purification of compound of formula-V:

Into a 2-L four-necked round-bottomed flask, the oily residue (20 g) prepared as per the process given in example-1(a) is charged and triturated with diethyl ether (120 mL) at RT (25-30°C) for over night. The resulting yellow coloured solid (10 g) is isolated by filtration.
The compound is further purified by recrystallization from diethyl ether (65 mL) and isolated at 25-30° C to get 8.2 g of yellow crystalline compound of formula-V.

Melting point: 76.0-80.1° C

HPLC purity: RR and SS isomers: > 99.45%; RS and SR isomers: < 0.55 %

(b) Preparation of 1-(3-amino-4-benzyloxyphenyl)-2-[benzyl-[2-(4-methoxyphenyl)-l-methylethyl]-amino}ethanol of formula-VI

Into a 1-L necked round bottomed flask fitted with a mechanical stirrer, a dropping funnel, a reflux condenser, thermometer pocket, and a nitrogen bubbler, is charged a previously dissolved solution of thermomter-ethyl)-2-benzyloxyphenyl]-formamide (80 g) in Toluene (150 mL) and 20% acetic acid solution (100 mL) are added at 75-80° C simultaneously. After addition, the reaction is stirred for 1-2 hours at 75-80° C. The inorganic salt was removed by filtration and the toluene layer is separated. The toluene layer is then washed with water and then treated with carbon and filtered. The solvent is removed from the filtrate under reduced pressure. To the resulting residue, diisopropyl ether (200 mL) is added and isolated the compound of formula-V (18.5 g) as a brownish yellow solid. Part of the compound of formula-VI (10 g) is recrystallised from diisopropyl ether (100 mL) and isolated at 25-30° C to get 18.3 g highly pure light brownish yellow crystalline compound of formula-VI.

HPLC purity: RR and SS isomers: 99.75% and RS and SR isomers: 0.16%

Remaining part of the compound of formula-VI (8.5 g) is recrystallized from diethyl ether (80 mL) and isolated at 20-25° C to get 5.9 g of highly pure brownish yellow crystalline compound of formula-VI.

HPLC purity: RR and SS isomers: 99.75% and RS and SR isomers: 0.16%

(c) Preparation of N-[5-(2-{Benzyl[2-(4-methoxyphenyl)-l-methylethyl]amino}-l-hydroxy ethyl)-2-benzyloxyphenyl]-formamide of formula-VII

Into a 1-L 4 necked round bottomed flask fitted with a mechanical stirrer, a reflux condenser, thermometer pocket, and a nitrogen bubbler, is charged a previously dissolved solution of
crystalline amino derivative of formula VI (42 g) in THF (260 mL). To this stirred solution Formic acid (15.96 mL) is added dropwise at a rate of about 1 mL/min under vigorous stirring at 20-25° C and the reaction is stirred for over night at room temperature. The solvent is removed under reduced pressure. The oily residue is dissolved in ethyl acetate and washed with water and 5% sodium carbonate solution successively. The organic layer is treated with charcoal followed by filtration to get a clear solution. The solvent is removed under reduced pressure and the residue is stirred with diisopropyl ether to get (37.0 g) of crystalline compound of formula-VII. The product is recrystallised from isopropyl alcohol (400 mL) and isolated at 25-30° C to get 35.1 g of highly pure white crystalline compound of formula-VII.

MR : 111.7-115.0° C
HPLC purity : RR and SS isomers: 99.92% and RS and SR isomers: 0.08%

(d) Preparation of N-(2-Hydroxy-5-{[(l-hydroxy-2-[2-(4-methoxyphenyl)]-l-methyl
ethylamino]ethyl}phenyl-formamide of formula-I (A)

(i) Into a 1-L stainless steel hydrogenation vessel is charged a previously dissolved solution of crystalline compound of formula-VII (40 g) in ethyl acetate (260 mL). To this solution, a suspension of 16 g of Palladium-on-charcoal (10% wet) in methanol (240 mL) is charged. The vessel is connected to a Parr hydrogenator and hydrogenated at 40-60 psi. After completion of hydrogen consumption, the catalyst is removed by filtration under nitrogen atmosphere and the solvent is distilled off from the filtrate under reduced pressure at 30-40° C. The titled compound is isolated at 35-40° C by the addition of ethyl acetate (350 mL) and recrystallized from isopropyl alcohol (250 mL) and isolated at 30-35° C to get 23.0 g of white to off-white crystalline pure formoterol base of formula-I(A).

HPLC purity : RR and SS isomers: 99.94% and RS and SR isomers: 0.06%
MP : 144.1-145.4° C

(ii) Preparation of N-(2-Hydroxy-5-{[(l-hydroxy-2-[2-(4-methoxyphenyl)]-l-methylethylamino]ethyl}phenyl-formamide of formula-I (A)

Into a 1-L stainless steel hydrogenation vessel is charged a previously dissolved solution of crystalline compound of formula-VII (40 g) in ethyl acetate (250 mL). To this solution, a
suspension of 16 g of Palladium-on-charcoal (10% wet) in methanol (250 mL) is charged. The vessel is connected to a Parr hydrogenator and hydrogenated at 40-60 psi. After completion of hydrogen consumption, the catalyst is removed by filtration under nitrogen atmosphere and the solvent is distilled off from the filtrate under reduced pressure at 30-40° C. The titled compound is isolated at 35-40° C by the addition of isopropyl alcohol (250 mL) and recrystallized from isopropyl alcohol (250 mL) and isolated at 30-35° C to get 20.0 g of white to off-white crystalline pure formoterol base of formula-I(A).

HPLC purity : RR and SS isomers: 99.95% and RS and SR isomers: 0.05%

MP : 142.1-145.0° C

(e) Preparation of formoterol fumarate of formula-I(B)

(i) Into a 500 mL 4 necked round bottomed flask fitted with a mechanical stirrer, addition funnel and thermometer pocket, is charged formoterol base (23 g) and isopropyl alcohol (230 mL). To this stirred suspension, is added a previously dissolved solution of fumaric acid (3.68 g) in isopropyl alcohol (46 mL) at RT (25-30° C). After stirring for 5 hr at RT, the compound of formula-I(B) is recovered by filtration. The wet compound is suspended in 460 ml of 95% aqueous isopropyl alcohol and heated to 65-75° C. After maintaining for 1-2 hr.

The reaction was cooled to 40-45° C and maintained for 1-2 hr and filtered. The wet cake is taken in a flask and suspended with 460 ml of acetonitrile and heated to 75-80° C. After maintaining for 1-2 hr, the reaction was cooled to 40-45° C and maintained for 1-2 hr and filtered and after drying at 60° C to get 19.60 g of formoterol fumarate of formula-I(B).

(ii) Into a 500 mL 4 necked round bottomed flask fitted with a mechanical stirrer, addition funnel and thermometer pocket, is charged formoterol base (23 g) and Acetonitrile (230 mL).

To this stirred suspension, is added a previously dissolved solution of fumaric acid (3.68 g) in isopropyl alcohol (46 mL) at RT (25-30° C). After stirring for 5 hr at RT, the compound of formula-I(B) is recovered by filtration. The wet compound is suspended in 460 ml of 95% aqueous isopropyl alcohol and heated to 65-75° C. After maintaining for 1-2 hr. The reaction was cooled to 40-45° C and maintained for 1-2 hr and filtered. The wet cake is taken in a flask and suspended with 460 ml of acetonitrile and heated to 75-80° C. After maintaining for
1-2 hr, the reaction was cooled to 40-45° C and maintained for 1-2 hr and filtered and after
drying at 60° C to get 18.50 g of formoterol fumarate of formula-I(B).

(iii) Into a 500 mL 4 necked round bottomed flask fitted with a mechanical stirrer, addition
funnel and thermometer pocket, is charged formoterol base (23 g) and acetone (230 mL). To
this stirred suspension, is added a previously dissolved solution of fumaric acid (3.68 g) in
isopropyl alcohol (46 mL) at RT (25-30° C). After stirring for 5 hr at RT, the compound of
formula-I(B) is recovered by filtration. The wet compound is suspended in 460 ml of 95%
aqueous isopropyl alcohol and heated to 65-75° C. After maintaining for 1-2 hr, the reaction
was cooled to 40-45° C and maintained for 1-2 hr and filtered. The wet cake is taken in a
flask and suspended with 460 ml of acetonitrile and heated to 75-80° C. After maintaining for
1-2 hr, the reaction was cooled to 40-45° C and maintained for 1-2 hr and filtered and after
drying at 60° C to get 17.1 g of formoterol fumarate of formula-I(B).

(f) Preparation of formoterol fumarate dihydrate of formula-I(C)

(i) The compound of formula-I(B) (19.0 g) is prepared as described in the example l(e) is
triturated in water (180 mL) at RT (25-30° C) for 30 minutes. The solution is filtered, washed
the cake with water and after drying at 60° C to get 18.20 g of pharmaceutically acceptable
dihydrate from of formoterol fumarate salt of formula -I(C) as white to off-white solid.

MR: 141.7-143.2° C
HPLC purity: 99.86%
Isomeric purity (HPLC): RR and SS isomers: 99.95%; RS and SR isomers: 0.05%

(ii) The compound of formula-I(B) (19.0 g) is prepared as described in the example l(e) is
triturated in water (240 mL) at RT (25-30° C) for 30 minutes. The solution is filtered, washed
the cake with water and after drying at 60° C to get 20.0 g of pharmaceutically acceptable
dihydrate from of formoterol fumarate salt of formula -I(C) as white to off-white solid.
HPLC purity: 99.85%
Isomeric purity (HPLC): RR and SS isomers: 99.95%; RS and SR isomers: 0.05%
We claim:

1. An improved process for the preparation of high purity (chemically (>99.8%) and diastereomerically (>99.9%) pure Formoterol fumarate dihydrate of formula - I(C)

   ![Chemical Structure I(C)]

   I (C) RR, SS ->99.9%
   RS, SR <-0.1%

which comprises:

   (i) Triturating the crude oily compound of formula-V with a non-polar solvent to make it a solid

   ![Chemical Structure V]

   V RR, SS ->99%
   RS, SR <-1%

   (ii) Recrystallization of solid compound of formula-V from a solvent to make it >99.0% pure

   ![Chemical Structure VI]

   (iii) Reduction of nitro derivative of formula-V with a metal catalyst under hydrogenation conditions to get crystalline amino derivative of formula-VI
(iv) Recrystallization of the resulting amino derivative of formula-VI from a solvent to get >99.4% quality

![Formula VI]

(V) Formylation of the crystalline amino compound of formula-VI with a formylating reagent to get diastereomerically pure formanilide derivative of formula-VII

![Formula VII]

(Vi) Debenzylation of the formanilide derivative of formula-VII under hydrogenation conditions in the presence of a metal catalyst and isolation of the formoterol base of formula-I(A) from a solvent medium

![Formula I(A)]

(vii) Recrystallization of formoterol base of formoterol-I(A) from a solvent to get >99.8% quality.

![Formula I(A)]

(viii) Reaction of a suspension of pure formoterol base of formula-(IA) in hydrocarbon solvent with an alcoholic solution of fumaric acid to get the formoterol fumarate of formula-(IB),
(ix) Purification of formoterol fumarate of formula-I(B) from a solvent or a mixture thereof followed by leaching with water to get pharmaceutical grade formoterol fumarate dihydrate (>99.8%) of formula-I(C).

2. An improved process for the preparation of formoterol fumarate dihydrate of formula - I(C) as claimed in claim 1, wherein the non-polar solvent employed in step (i) to solidify the nitro derivative of formula-V is selected from ethers like diisopropyl ether, diethyl ether, dioxane, methyl tert-butyl ether, hydrocarbons like hexane, heptane, cyclohexane, toluene, xylene, etc, preferably, diisopropyl ether.

3. An improved process for the preparation of formoterol fumarate dihydrate of formula - I(C) as claimed in claim 1-2, wherein the solvent employed in step (ii) for recrystallization of nitro derivative of formula-V is selected from ethers like diethyl ether, diisopropyl ether, dioxane, methyl tert-butyl ether, preferably, diisopropyl ether.

4. An improved process for the preparation of formoterol fumarate dihydrate of formula - I(C) as claimed in claim 1-3, wherein the purity of compound of formula-V after recrystallization from diisopropyl ether in step (ii) is more than 99% and the unwanted isomeric impurities are less than 1%.

5. An improved process for the preparation of formoterol fumarate dihydrate of formula - I(C) as claimed in claim 1-4, wherein the metal catalyst used in step (iii) to reduce crystalline nitro derivative of formula-V is Raney nickel.
6. An improved process for the preparation of formoterol fumarate dihydrate of formula - I(C) as claimed in claim 1-5, wherein the hydrogenation conditions applied in step (iii) include a polar solvent like methanol, isopropyl alcohol, ethyl acetate preferably, methanol and the pressure of hydrogen is 1-100psi, preferably, 40-60psi at a temperature of 20-50°C, preferably, 30°C.

7. An improved process for the preparation of formoterol fumarate dihydrate of formula - I(C) as claimed in claim 1-6, wherein the solvent employed in step (iv) for recrystallization of the compound of formula-VI is selected from ethers like diisopropyl ether or diethyl ether, hydrocarbons like hexane, heptane, cyclohexane, toluene, xylene, etc., preferably, diisopropyl ether.

8. An improved process for the preparation of formoterol fumarate dihydrate of formula - I(C) as claimed in claim 1-7, wherein the purity of the recrystallized compound of formula-VI in step (iv) is more than >99.4% and the isomeric impurities are below 0.2%.

9. An improved process for the preparation of formoterol fumarate dihydrate of formula - I(C) as claimed in claim 1-8, wherein the reagent employed for formylation of crystalline amino derivative of formula-VI in step (v) is selected from formic acid, aceticformic anhydride, etc., preferably, aceticformic anhydride.

10. An improved process for the preparation of formoterol fumarate dihydrate of formula - I(C) as claimed in claim 1-9, wherein the solvent employed in step (v) for formylation of amino derivative of formula-VI is tetrahydrofuran or 2-methyl tetrahydrofuran.

11. An improved process for the preparation of formoterol fumarate dihydrate of formula - I(C) as claimed in claim 1-10, wherein the temperature at which the compound of formula-VII can be isolated in step (v) is in the range of 0-35°C, preferably, 20-30°C.

12. An improved process for the preparation of formoterol fumarate dihydrate of formula - I(C) as claimed in claim 1-11, wherein the solvent employed in step (v) for crystallization of compound of formula-VII is selected from ethyl acetate, methanol, isopropyl alcohol, or a mixture thereof, preferably, isopropyl alcohol.
13. An improved process for the preparation of formoterol fumarate dihydrate of formula - I(C) as claimed in claim 1-12, wherein the purity of the recrystallized compound of formula-VII in step (v) is more than >99.9% and the isomeric impurities are below 0.1%.

14. An improved process for the preparation of formoterol fumarate dihydrate of formula- I(C) as claimed in claim 1-13, wherein the solvent employed in step (vi) for debenzylation of compound of formula-VII is selected from ethyl acetate, methanol, or a mixture thereof, preferably, a 60:40 or 50:50 mixture of ethyl acetate and methanol.

15. An improved process for the preparation of formoterol fumarate dihydrate of formula - I(C) as claimed in claim 1-14, wherein the solvent employed in step (vi) for isolation of the formoterol base of formula-I(A) is selected from esters like methyl acetate or ethyl acetate, alcohols like methanol, isopropyl alcohol, hydrocarbons like hexane, heptane, cyclohexane, toluene, xylene, nitriles like acetonitrile, etc., preferably, ethyl acetate.

16. An improved process for the preparation of formoterol fumarate dihydrate of formula - I(C) as claimed in claim 1-15, wherein the solvent employed in step (vii) for crystallization of the formoterol base of formula-I(A) is selected from esters like methyl acetate or ethyl acetate, alcohols like methanol, isopropyl alcohol, either or a mixture thereof, preferably, isopropyl alcohol.

17. An improved process for the preparation of formoterol fumarate dihydrate of formula - I(C) as claimed in claim 1-16, wherein the HPLC purity of the pure formoterol base of formula-I(A) obtained in step (vii) according to the present process is > 99.8%.

18. An improved process for the preparation of formoterol fumarate dihydrate of formula - I(C) as claimed in claim 1-17, wherein the solvent used in step (viii) to suspend the pure crystalline formoterol base of formula- I(A) is selected from hexane, heptane, cyclohexane, toluene, xylene, etc, preferably, toluene.
19. An improved process for the preparation of formoterol fumarate dihydrate of formula - I(C) as claimed in claim 1-18, wherein the alcoholic solvent used in step (viii) to dissolve fumaric acid is selected from methanol, ethanol, isopropanol, t-butanol, preferably, isopropanol.

20. An improved process for the preparation of formoterol fumarate dihydrate of formula - I(C) as claimed in claim 1-19, wherein the solvent employed in step (ix) for purification of formoterol fumarate of formula (I(B) is selected from toluene, ethyl acetate, aqueous (1-20%) isopropyl alcohol, methanol, acetonitrile, acetone or a mixture thereof.

21. An improved process for the preparation of formoterol fumarate dihydrate of formula - I(C) as claimed in claim 1-20, wherein the percentage of isomeric purity of compound of formula- I(C) in step (ix) is more than 99.9% by HPLC.

22. An improved process for the preparation of formoterol fumarate dihydrate of formula - I(C) as claimed in claim 1-21, wherein the percentage of isomeric impurity of compound of formula-I(C) in step (ix) is less than 0.1% by HPLC.

23. An improved process for the preparation of formoterol fumarate dihydrate of formula - I(C) substantially as reported herein with reference to examples 1 and 2.