July 2022

Process for the preparation of Gadolinium-based contrast agents and its intermediates

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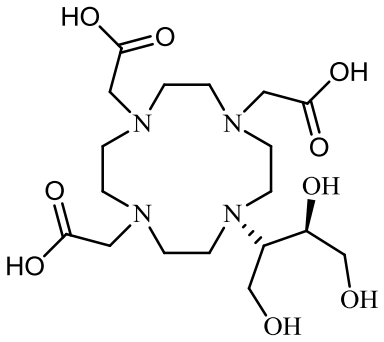
Process for the preparation of Gadolinium-based contrast agents and its intermediates

The present publication relates to a process for the preparation of 1,4,7-Tris(carboxymethyl)-10-(1-(hydroxymethyl)-2,3-dihydroxypropyl)-1,4,7,10-tetraazacyclododecane represented by the following structural formula-1, which is referred to as Butrol.



Formula-1.

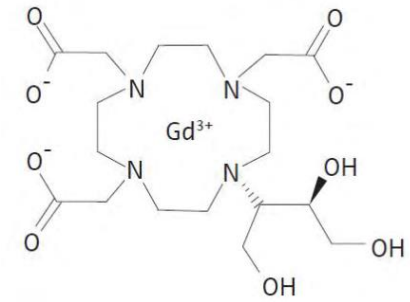
Butrol is an intermediate used for the preparation of 10-[(1SR,2RS)-2,3-dihydroxy-1-hydroxymethylpropyl]-1,4,7,10-tetraazacyclododecane-1,4,7–triacetic acid, gadolinium complex is known as Gadobutrol of formula-1a and calcium complex of 10-(2,3-Dihydroxy-l-(hydroxymethyl)propyl)-1,4,7,10-tetraaza-cyclodecane-1,4,7-triacetic acid is known as Calcobutrol of formula-1b.

Background of the invention:

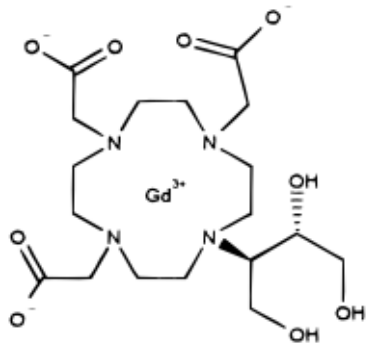
10-[(1SR,2RS)-2,3-dihydroxy-1-hydroxymethylpropyl]-1,4,7,10-tetraazacyclododecane-1,4,7–triacetic acid, gadolinium complex or 10-(2,3-dihydroxy-1-hydroxymethylpropyl)-1,4,7,10-tetraazacyclododecane-1,4,7-triacetic acid, Gd Complex of formula-1a is commonly known as Gadobutrol, it is a gadolinium-based contrast agent indicated for intravenous use in diagnostic MRI in adults and children (2 years of age and older) to detect and visualize areas with

disrupted blood brain barrier (BBB) and/or abnormal vascularity of the central nervous system s with the brand name of Gadavist®.

Food and Drug Administration label published on 14 March 2011 on Food and Drug administration website discloses chemical structure of Gadobutrol as follows:



The journal article Inorganic Chemistry 1997, 36 (26), 6086–6093 and the patent document US10072027B2 discloses chemical structure of Gadobutrol as follows:



Gadobutrol is a racemic metal coordination complex of gadolinium (Gd^{3+}). The carbons at 1-Hydroxymethyl and 2 hydroxy position of Gadobutrol are achiral. Therefore, both structure represetations of Gadobutrol in Food and Drug administration label and Inorganic Chemistry, 1997, 36 (26), 6086–6093 journal article can be used interchangeably. For convenience, applicants of the present application followed the chemical structure representation of Gadobutrol and its intermediates similar to Inorganic Chemistry 1997, 36 (26), 6086–6093.

Calcobutrol is an additive in the galenic formulations of Gadobutrol and solves the problem of preventing the release of free gadolinium in the formulations

(solutions).

Gadobutrol and its process for the preparation is described in US5980864. Gadobutrol preparation is also disclosed in the WO2012143355, Inorganic Chemistry 1997, 36, 6086- 6093, US6894151, WO2020012372 and WO2020040617.

Brief Description of the Drawings:

Figure-1: Illustrates the PXRD pattern of amorphous Calcobutrol sodium.

Detailed description of the Invention:

The "suitable solvent" used in the present invention can be selected from but not limited to "hydrocarbon solvents" such as n-pentane, n-hexane, n-heptane, cyclohexane, petroleum ether, benzene, toluene, xylene and mixtures thereof; "ether solvents" such as dimethyl ether, diethyl ether, diisopropyl ether, methyl tert-butyl ether, 1,2-dimethoxyethane, tetrahydrofuran, 1,4-dioxane and mixtures thereof; "ester solvents" such as methyl acetate, ethyl acetate, n-propyl acetate, isopropyl acetate, n-butyl acetate, isobutyl acetate, tert-butyl acetate and mixtures thereof; "polar-aprotic solvents" such as dimethylacetamide, dimethylformamide, dimethylsulfoxide, N-methylpyrrolidone (NMP) and mixtures thereof; "chloro solvents" such as dichloromethane, dichloroethane, chloroform, carbon tetrachloride and mixtures thereof; "ketone solvents" such as acetone, methyl ethyl ketone, methyl isobutyl ketone and mixtures thereof; "nitrile solvents" such as acetonitrile, propionitrile, isobutyronitrile and mixtures thereof; "alcohol solvents" such as methanol, ethanol, n-propanol, iso-propanol, n-butanol, iso-butanol, 2-butanol, tert-butanol, ethane-1,2-diol, propane-1,2-diol and mixtures thereof; "polar solvents" such as water; formic acid, acetic acid and the like or mixture of any of the afore mentioned solvents.

The term "base" used in the present invention refers to inorganic bases selected from "alkali metal carbonates" such as sodium carbonate, potassium carbonate, lithium carbonate, cesium carbonate and the like; "alkali metal bicarbonates" such as sodium bicarbonate, potassium bicarbonate, lithium

bicarbonate, cesium bicarbonate and the like; “alkali metal hydroxides” such as sodium hydroxide, potassium hydroxide, lithium hydroxide and the like; “alkyl metals” such as n-butyl lithium and like; “metal hydrides” such as lithium hydride, sodium hydride, potassium hydride and the like; “alkali metal phosphates” such as disodium hydrogen phosphate, dipotassium hydrogen phosphate; ammonia such as aqueous ammonia, ammonia gas, methanolic ammonia and like and “organic bases” selected from but not limited to methyl amine, ethyl amine, diisopropyl amine, diisopropylethyl amine (DIPEA), diisobutylamine, triethylamine, tert.butyl amine, pyridine, 4-dimethylaminopyridine (DMAP), N-methyl morpholine (NMM), nmethyl pyridine (NMP), 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU), 1,5-diazabicyclo[4.3.0] non-5-ene (DBN), 1,4-diazabicyclo[2.2.2]octane (DABCO), imidazole; “alkalimetal alkoxides” such as sodium methoxide, sodium ethoxide, potassium methoxide, potassium ethoxide, sodium tert.butoxide, potassium tert.butoxide and the like; “alkali metal amides” such as sodium amide, potassium amide, lithium amide, lithiumdiisopropyl amide (LDA), sodium bis(trimethylsilyl)amide (NaHMDS), potassiumbis(trimethylsilyl)amide, lithium bis(trimethysilyl)amide (LiHMDS) and the like; or mixtures thereof.

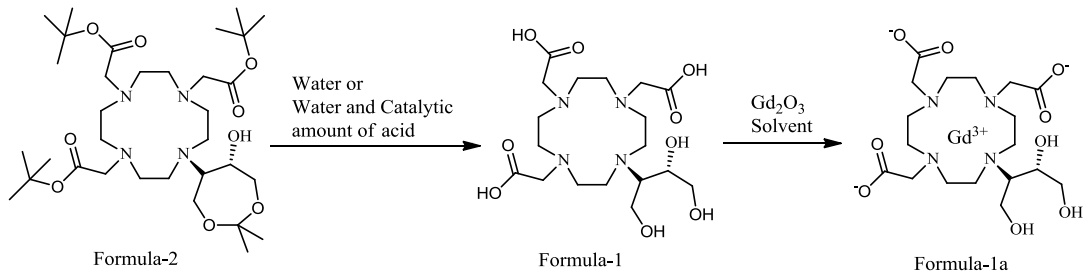
As used herein the term “acid” in the present invention refers to inorganic acid and organic acid; inorganic acid is selected from such as hydrochloric acid, hydrobromic acid, sulfuric acid, nitric acid, phosphoric acid, sulfuric acid; organic acids such as acetic acid, maleic acid, malic acid, oxalic acid, succinic acid, fumaric acid, trifluoroacetic acid, methane sulfonic acid, p-toluene sulfonic acid; chiral acids such as S-(+) mandelic acid, R-(-) mandelic acid, L-(+)tartaric acid, D-(-)tartaric acid, L-malic acid, D-malic acid, D-maleic acid, (-)-naproxen, (+)-naproxen, (1R)-(-)-camphor sulfonic acid, (IS)-(+)-camphor sulfonic acid (1R)-(+)-bromocamphor-10-sulfonic acid, (1S)-(-)-bromocamphor-10-sulfonic acid, (-)-Dibenzoyl-L-tartaric acid, (-)-Dibenzoyl-L-tartaricacid monohydrate, (+) -Dibenzoyl-D-tartaric acid, (+)-Dibenzoyl-D-tartaric acid monohydrate, (+)-dipara-tolyl-D-tataric acid, (-)-diparatolyl-L-tataricacid, L(-)-pyroglutamic acid, L(+)-pyroglutamic acid, (-)-lactic

acid.

First embodiment of the present invention provides a process for the preparation of 1,4,7-tris(carboxymethyl)-10-(1-(hydroxymethyl)-2,3-dihydroxy propyl)-1,4,7,10-tetraazacyclododecane formula-1 comprising hydrolysis of 1,4,7-tris(tert-butoxycarbonylmethyl)-10-(6-hydroxy-2,2-dimethyl-1,3-dioxepane-5-yl)-1,4,7,10-tetraazacyclododecane compound of formula-2 using water, optionally in presence of catalytic amount of an acid in a solvent to provide 1,4,7-tris(carboxymethyl)-10-(1-(hydroxymethyl)-2,3-dihydroxypropyl)-1,4,7,10-tetraaza cyclododecane compound of formula-1.

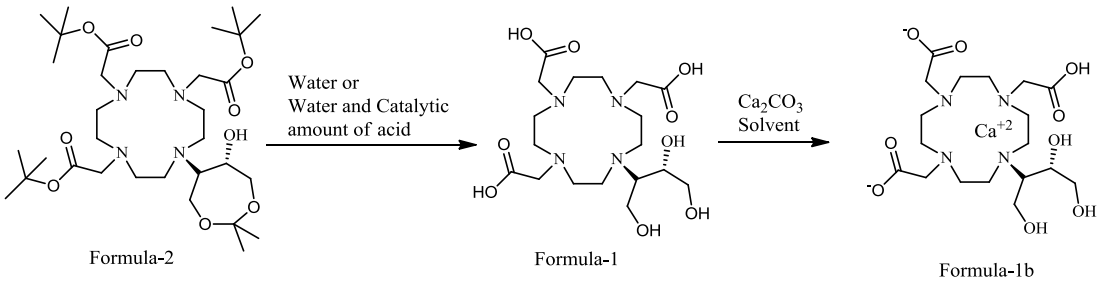
Acid in step-a) is same as defined above; wherein the acid is used in less than about 0.5 equivalents with respect to formula-2; solvent in step-a) is selected from alcohol solvents, ether solvents, ketone solvents, ester solvents, amide solvents, water and/or mixtures thereof.

In the first aspect of first embodiment, the compound of formula-1 can be converted into Gadobutrol of formula-1a by treating the compound of formula-1 with gadolinium oxide in a solvent to provide Gadobutrol of formula-1a.



Scheme-1

In the second aspect of first embodiment, the compound of formula-1 can be converted into Calcobutrol of formula-1b by treating the compound of formula-1 with calcium carbonate or calcium oxide or calcium hydroxide in a solvent to provide the Calcobutrol of formula-1b.



Scheme-2

In third aspect of the first embodiment, intermediate butrol of formula 1 of the present invention can be converted into Gadobutrol or Calcobutrol by processes known in the art, such as Inorganic Chemistry 1997, 36, 6086- 6093 or as the process described in the present application.

In fourth aspect of first embodiment hydrolysis facilitates the removal of t-butoxy and removal of 2,2-dimethyl protecting group.

Calcobutrol of formula-1b optionally converted to its sodium salt by treating with sodium source. The sodium source is selected from sodium bases such as sodium carbonate, sodium bicarbonate, sodium hydroxide, sodium methoxide, sodium hydrogen citrate, sodium citrate, sodium acetate, sodium propionate, sodium butyrate, sodium isobutyrate, sodium tartrate, sodium oxalate, sodium benzoate, sodium sorbate, sodium malate, monosodium succinate, disodium succinate.

The compound of formula-1a produced by the processes of the present invention can be further micronized or milled to get desired particle sizes to achieve desired solubility profile based on different forms of pharmaceutical composition requirements. Techniques that may be used for particle size reduction include but not limited to a single or multi-stage micronization using cutting mills, pin/cage mills, hammer mills, jet mills, fluidized bed jet mills, ball mills and roller mills. Milling or micronization may be performed before drying or after drying of the product.

Second embodiment of the present invention provides the use of Gadobutrol of formula-1a and/or Calcobutrol of formula-1b of the present invention for the preparation of various pharmaceutical formulations.

Third embodiment of the present invention provides pharmaceutical composition comprising Gadobutrol of formula-1a and/or and Calcobutrol of formula-1b and their polymorphs or mixture thereof obtained according to the present invention and at least one pharmaceutically acceptable excipient.

Fourth embodiment of the present invention provides the process for the preparation of Calcobutrol sodium comprising treating Calcobutrol with sodium bicarbonate in solvent.

In first aspect of fourth embodiment wherein solvent is selected from alcohol solvents, ether solvents, ketone solvents, ester solvents, amide solvents, water and/or mixtures thereof.

In second aspect of fourth embodiment of the present invention provides a substantially pure compound of Calcobutrol sodium having HPLC (High performance liquid chromatography) purity greater than about 99% or greater than about 99.5% or greater than about 99.6% or greater than about 99.8% or greater than about 99.9% as measured by HPLC (High performance liquid chromatography) method.

In third aspect of fourth embodiment Calcobutrol sodium is in amorphous form.

"Substantially pure" or “pure” in relation to Calcobutrol sodium or amorphous form of Calcobutrol sodium prepared by the process of the present invention is substantially free from the impurities. The said compound of Calcobutrol sodium or amorphous form of Calcobutrol sodium obtained according to the present invention is substantially pure having a purity of greater than about 99%, preferably greater than about 99.5% by HPLC.

As used herein, the term "pharmaceutical compositions" or "pharmaceutical formulations" include tablets, pills, powders, liquids, suspensions, emulsions, granules, capsules, suppositories, or injection preparations.

The term “pharmaceutically acceptable excipients” selected from but not limited to binders, diluents, disintegrants, surfactants and lubricants. Suitable binders that can be include polyvinylpyrolidone, copovidone, starches such as pregelatinized starch, cellulose derivatives such as hydroxypropylmethyl cellulose, ethylcellulose, hydroxypropylcellulose and carboxymethylcellulose, gelatine, acacia, agar, alginic acid, carbomer, chitosan, dextrates, cyclodextrin, dextrin, glycerol dibehenate, guargum, hypromellose, maltodextrin, poloxamer, polycarbophil, polydextrose, polyethylene oxide, polymethacrylates, sodium alginate, sucrose, mixtures thereof; suitable diluents that can be include anhydrous lactose, lactose monohydrate, modified lactose, dibasic calcium phosphate, tribasic calcium phosphate, microcrystalline cellulose, silicified microcrystalline cellulose, powdered cellulose, maize starch, pregelatinized starch, calcium carbonate, sucrose, glucose, dextrates, dextrins, dextrose, fructose, lactitol, mannitol, sorbitol starch, calcium lactate or mixtures thereof; suitable disintegrants that can be include magnesium aluminometa silicate (or magnesium aluminum silicate), starch, pregelatinized starch, sodium starch glycolate, crospovidone, croscarmellose sodium, low-substituted hydroxypropyl cellulose, alginic acid, carboxy methyl cellulose sodium, sodium alginate, calcium alginate and chitosan; suitable lubricants that can be include (but are not limited to) magnesium stearate, stearic acid, palmitic acid, talc, and aerosil. Suitable surfactants that can be include (but are not limited to) polysorbate 80, polyoxyethylene sorbitan, polyoxyethylene-polyoxy-propylene copolymer and sodium lauryl sulphate; beta-cyclodextrin include (but are not limited to) sulfobutylalkyl ether-beta-cyclodextrin, betadex-sulfobutylether sodium, or hydroxypropyl-beta-cyclodextrin.

Gadobutrol of formula-1a and their polymorphs produced by the present invention is indicated for intravenous use in diagnostic MRI in adults and children (2 years of age and older) to detect and visualize areas with disrupted blood brain barrier (BBB) and/or abnormal vascularity of the central nervous system.

The best mode of carrying out the present invention was illustrated by the below mentioned examples. These examples are provided as illustration only and hence should not be construed as limitation to the scope of the invention.

Examples:

Example-1: Preparation of 1-Formyl-7-(6-hydroxy-2,2-dimethyl-1,3-dioxepane-5-yl)-1,4,7,-10-tetraazacyclododecane

Mixture of 1,4,7,10-Tetraazacyclododecane (100 g), toluene (500 ml) and 1,1-dimethoxy-N,N-dimethyl methanamine (76 g) is heated to 95-100°C and stirred at the same temperature. Cooled the reaction to 70°C and distilled off solvent completely. 4,4-Dimethyl-3,5,8-trioxabicyclo[5,1,0]octane (83.68 g) was added to the obtained compound at 25-30°C, heated to 115-120°C and stirred at the same temperature. Cooled the reaction mixture to 90-95°C, water is added to it and further cooled to 25-30°C. Methanol (400 ml) was added to mixture at 25-30°C, stirred at the same temperature and distilled off solvent completely. Co-distilled with acetonitrile. Recrystallized the obtained compound using acetonitrile to get the pure title compound.

Yield: 107.0 g; Purity by HPLC: 99.20%.

Example-2: Preparation of 1,4,7-Tris(tert-butoxycarbonylmethyl)-10-(6-hydroxy-2,2-dimethyl-1,3-dioxepane-5-yl)-1,4,7,10-tetraazacyclododecane of formula-2

Mixture of 1-Formyl-7-(6-hydroxy-2,2-dimethyl-1,3-dioxepane-5-yl)-1,4,7,-10-tetra-azacyclododecane (100 g)**,** sodium hydroxide (58 g), water (100 ml) and methanol (200 ml) was heated to 60-65°C and stirred at the same temperature. Distilled off the solvent completely from the reaction mixture. Water and toluene were added to

obtained compound at 25-30°C, heated the mixture to 50-55°C and stirred at the same temperature. Separated the organic and aqueous layers and aqueous layer was extracted with toluene. Combined the organic layers. Sodium carbonate (107 g) and tert-butyl bromoacetate (198.1 g) slowly added to toluene layer at 25-30°C and stirred at the same temperature. Water was added to the reaction mixture at 25-30°C and stirred at the same temperature. Filtered the obtained solid and washed with water. Water was added to wet solid and acidified using acetic acid. Methyl tertiary butyl ether was added to mixture at 25-30°C and basified using aqueous ammonia solution. Separated the both organic layer and the aqueous layer was extracted with methyl tertiary butyl ether. Combined the organic layers and distilled off the solvent completely. Water was added to obtained compound at 25-30°C and stirred at the same temperature. Filter the solid, washed with water dried to get the tile compound. Yield: 120 g; Purity of HPLC: 99.34%

Example-3: Preparation of Butrol of formula-1

1,4,7-Tris(tert-butoxycarbonylmethyl)-10-(6-hydroxy-2,2-dimethyl-1,3-dioxepane-5-yl)-1,4,7,10-tetraazacyclododecane (60 g) and water (300 ml) at 25-30°C was heated to 95-100°C and stirred at the same temperature. Cooled the reaction mixture to 25-30°C. The reaction mixture washed with dichloromethane. Distilled off the solvent and co-distilled with isopropanol. To the obtained compound isopropanol (300 ml) was added at 60-65°C and stirred at the same temperature. Cooled the mixture to 25-30°C. Filtered the solid, washed with isopropanol and dried to get the title compound. Yield: 30 g.

Example-4: Preparation of Gadobutrol of formula-1a

Mixture of 1,4,7-Tris(tert-butoxycarbonylmethyl)-10-(6-hydroxy-2,2-dimethyl-1,3-dioxepane-5-yl)-1,4,7,10-tetraazacyclododecane (200 g), trifluoroacetic acid (8.65 g) and water (200 ml) at 25-30°C was heated to 95-100°C and stirred the reaction mixture at the same temperature. Cooled the reaction mixture to 25-30°C, dichloromethane added and separated both organic and aqueous layers. Aqueous layer washed with dichloromethane. Gadalonium oxide (66 g) was added to obtained

aqueous layer, heated to 95-100°C and stirred at the same temperature. Cooled the reaction mixture to 25-30°C, filtered the reaction mixture and washed with water. To the filtrate Indion 225 H resin was added and stirred at 25-30°C. The mixture was filtered and washed with water. Basic resin was added to the filtrate and stirred the mixture. The mixture was filtered and washed with water. The obtained filtrate was treated with carbon. Distilled off the solvent from the filtrate completely under vacuum. To the obtained compound water (200 ml) and ethanol (400 ml) was added and heated to 80-85°C. Ethanol (3000 ml) was slowly added to the mixture 80-85°C and stirred at the same temperature. Cool the mixture to 25-30°C and stirred at the same temperature. Filtered the solid and washed with ethanol. Water (100 ml) and methanol (600 ml) were added to the obtained compound at 25-30°C and heated the 60-65°C temperature. Methanol (2400 ml) added at 61-62°C and stirred at the same temperature. Cooled the mixture to 25-30°C, filter the solid, washed with ethanol and dried to get the title compound.

Yield: 120 g; Purity by HPLC: 99.92%

Example-5: Purification of Gadobutrol

Ethanol (250 ml) was added to the mixture of water (250 ml) and Gadobutrol (250 g) at 25-30°C and stirred at the same temperature. Filtered the mixture and filtrate was heated to 80-85°C and stirred at the same temperature. Ethanol (3250 ml) was slowly added to mixture at 80-85°C and stirred at the same temperature. Cooled the mixture to 25-30°C and stirred at the same temperature. Filtered the solid, washed with ethanol and dried to get the title compound.

Yield: 200 g; Purity by HPLC: 99.95%

Example-8: Preparation of Calcobutrol

Mixture of 1,4,7-Tris(tert-butoxycarbonylmethyl)-10-(6-hydroxy-2,2-dimethyl-1,3-dioxepane-5-yl)-1,4,7,10-tetraazacyclododecane (150 g), trifluoroacetic acid (2.59 g) and water (600 ml) at 25-30°C was heated to 95-100°C and stirred the reaction mixture at the same temperature. Cooled the reaction mixture to 25-30°C, dichloromethane added and separated both organic and aqueous layers. Aqueous

layer washed with dichloromethane. Calcium carbonate (22.7 g) was added to obtained aqueous layer at 28-30°C and stirred at the same temperature. Filtered the reaction mixture and washed with water. Distilled off the solvent completely from the filtrate under vacuum and further co-distilled with ethanol. Ethanol (3000 ml) was added to obtained compound at 55-60°C and stirred at the same temperature. Cool the mixture to 5-10°C and stirred at the same temperature. Filtered the solid and washed with ethanol. Methanol (750 ml) added to obtained compound at 25-30°C, heated the reaction mixture to 60-65°C and stirred at the same temperature. Cooled the mixture to 25-30°C and stirred at the same temperature. Filter the solid, washed with methanol and dried to get the title compound.

Yield: 83 g; Purity by HPLC: 99.56%.

Example-6: Preparation of Calcobutrol sodium

Mixture of Calcobutrol (150 g), water (750 ml) and sodium bicarbonate (25.8 g) stirred at 25-30°C. Filter the reaction mixture, washed with water and distilled off solvent completely. Acetone (750 ml) added to obtained compound at 25-30°C, heated to 40-45°C and stirred at the same temperature. Cooled the mixture to 25-30°C and stirred at the same temperature. Filter the solid, washed with acetone and dried to get the title compound.

Yield: 120 g; Purity by HPLC: 99.80%; PXRD pattern of the obtained compound is depicted in figure-1.

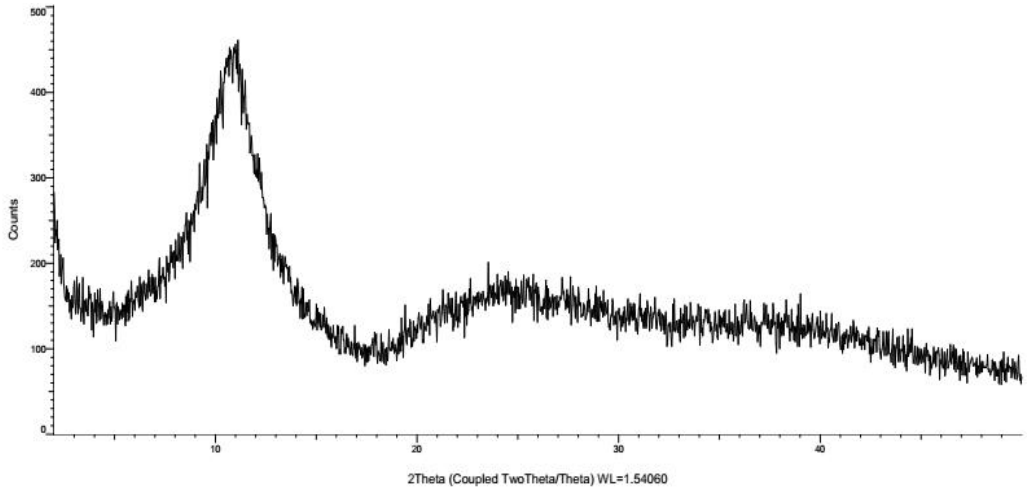

Counts
500
400
300
200
100
0
10
20
30
40
2Theta (Coupled TwoTheta/Theta) WL=1.54060

Figure-1

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