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Novel one pot synthesis of dexethylphenidate hydrochloride with chiral purity

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Environmental pollution generated due to industrial and other sources is big issue in our regular discussion; in order to prevent the pollution here we have initiated work involving green chemistry principles. Here, we have developed a process as "Green novel one pot synthesis of dexethylphenidate hydrochloride with significantly high yield and purity'. In the present work a special attention has been focus on the available regulations, the toxicological background for establishing limits, as well as the organic synthetic research with an analytical approach towards chiral assessment. This paper provides a complete overview of the topic with current available information, to address the overall chiral as well as hazardous issue during the development of new drug substances in R & D for the benefits to society.

Keywords: Chiral chemistry, Green chemistry, hazardous issues.

Introduction

Ethylphenidate (DEPH) is a psychostimulant and a close analog of methylphenidate. Ethylphenidate having *dl threo* mixture. Ethylphenidate have two chiral carbon atoms with four enantiomeric forms. Out of four forms, the studies of its *threo*-diastereomer revealed that *d-threo* isomer has been found to be more active with significant metabolic activity as compare to *l-threo* enantiomer. Dexethylphenidate acts as both a dopamine reuptake inhibitor and norepinephrine reuptake inhibitor, meaning it effectively boosts the levels of the norepinephrine and dopamine neurotransmitters in the brain, by binding to, and partially blocking the transporter proteins that normally remove those monoamines from the synaptic cleft[1]. Ethylphenidate metabolizes into methylphenidate and ritalinic acid[2]. Tiny amounts of ethylphenidate can be formed *in vivo* when ethanol and methylphenidate are coingested, via hepatic transesterification[3]. Ethylphenidate formation appears to be more common when large quantities of methylphenidate and alcohol are consumed at the same time, such as in non-medical use or overdose scenarios[4]. However, the transesterfication process of methylphenidate to ethylphenidate, as tested in mice liver, was dominant in the inactive (–)-enantiomer but showed a prolonged and increased maximal plasma concentration of the active (+)-enantiomer of methylphenidate[5].

Synthetic methods for preparing (2*R*)-2-phenyl-2-[(2*R*)-piperidin-2-yl]acetamide for the preparation of dexethylphenidate are reported in using a sequence involving the resolution of the amide derivative of the corresponding erythro isomer, conversion to the threo isomer, threo amide is hydrolysis to get corresponding acid in isolated form, isolated acid give methylphenidate by esterification with methanol and hydrochloric acid as catalyst[6–12]. Methylphenidate hydrolysed give its acid derivative, it is reacted with ethanol and hydrochloric acid give ethylphenidate[13].

Moreover, these processes involves tedious reaction conditions, loss of yield, long reaction time cycle, more energy consumption, loss of human hours and involvement of more inventories as well as unit operations.

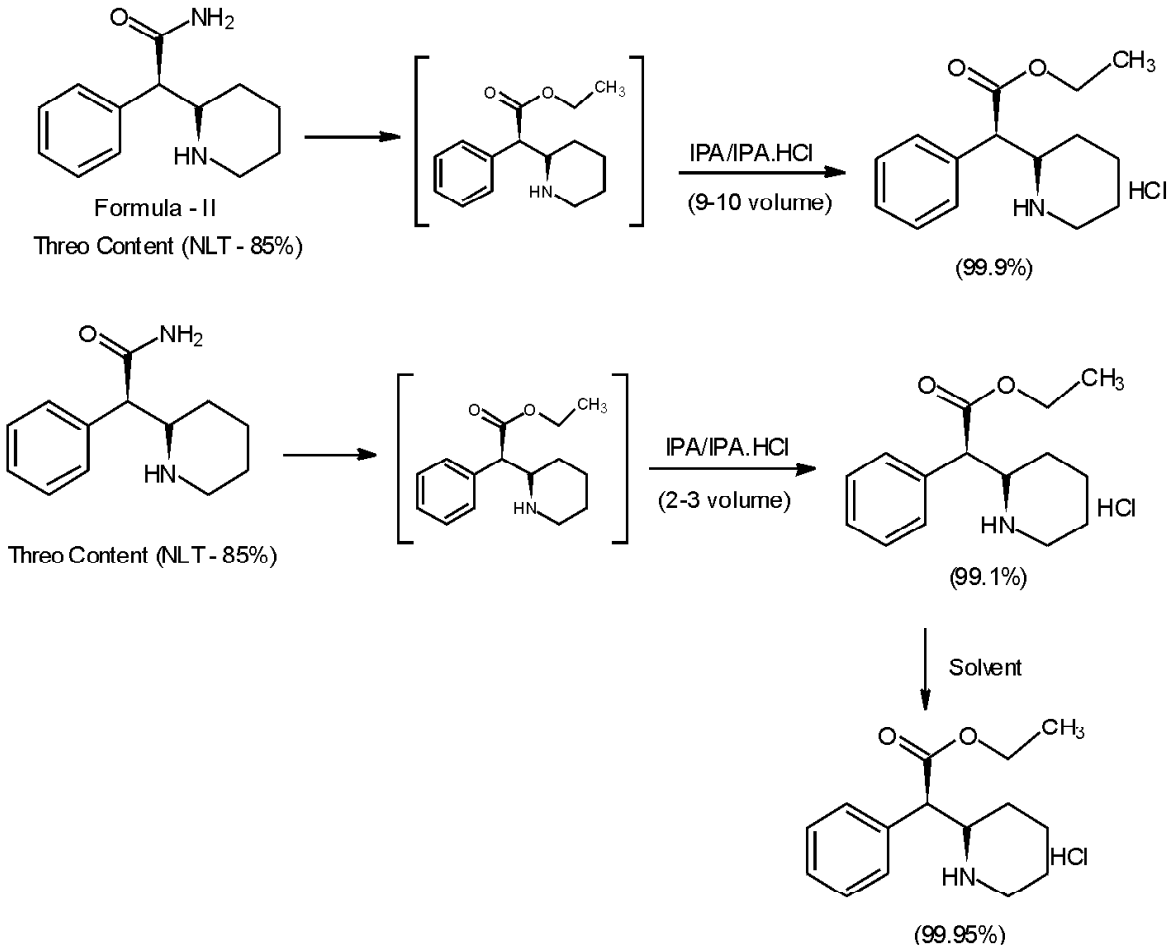
Experimental

Materials and reagent:

d-Threo-2-phenyl-2-(piperidin-2-yl)acetamide, ethanol, sulphuric acid, isopropanol, isopropanolic hydrochloric acid, activated charcoal and *n*-butanol.

Preparation of dexethylphenidate hydrochloride from d-threo-2-phenyl-2-piperidyl acetamide:

A mixture of ethanol (500 ml), and *d-threo*-2-phenyl-2-(piperidine-2-yl)acetamide (100 g, 1.0 mole) was cooled to



Scheme 1. One pot route of synthesis of dexethylphenidate hydrochloride.

2–8°C and sulfuric acid (224.4 g, 5.0 mole) added over 30–40 min. The reaction mass was heated at temperature 80 to 95°C for 15–30 min and maintained at reflux for 30 h to distil some volume of ethanol. Further it is maintained at reflux for 5 h. Reaction mixture was concentrated under vacuum at 70 to 75°C. The thick residue was cooled to 20–25°C and water (1000 ml) was added and the pH was adjusted to 11–12.5 with caustic soda lye. The reaction mixture was extracted two time with dichloromethane (2×200 ml). Extracted mass concentrated under vacuum and isopropanol (800 ml) added into the oily mass followed by charcoal treatment. The treated mass was then cooled up to 5–10°C. Isopropanolic hydrochloric acid (80 g, 1.1 mole) was added. The reaction mixture was heated at 55–65°C than cool to 0–5°C and the solid collected by filtration under vacuum and washed with isopropanol to give dexethylphenidate hydrochloride (95.0 g, 84.15%) having HPLC purity: Threo content: 99.9%, Erythro content: 0.10% Chiral purity – 100.0% [CHIRALPAK IB (4.6×250) mm, 5 μm at 210 to 230 nm and eluted with *n*-hexane/EtOH/DEA 80/20/0.1 v/v/v], SOR $[\alpha]_{D20:}$ + 88.0° (*c* = 1.0% w/v in methanol).

Preparation of dexethylphenidate hydrochloride from d-threo-2-phenyl-2-piperidyl acetamide [threo isomer NLT 85%]:

A mixture of ethanol (500 ml), and *d-threo*-2-phenyl-2-(piperidine-2-yl)acetamide (100 g, 1.0 mole) was cooled to 2–8°C and sulfuric acid (224.4 g, 5.0 mole) added over 30–40 min. The reaction mass was heated at temperature 80 to 95°C for 15–30 min and maintained at reflux for 30 h to distil some volume of ethanol. Further it is maintained at reflux for 5 h. Reaction mixture was concentrated under vacuum at 70 to 75°C. The thick residue was cooled to 20–25°C and water (1000 ml) was added and the pH was adjusted to 11–12.5

with caustic soda lye. The reaction mixture was extracted two time with dichloromethane (2×200 ml). Extracted mass concentrated under vacuum and isopropanol (300 ml) added into the oily mass followed by charcoal treatment. The treated mass was then cooled up to 5–10°C. Isopropanolic hydrochloric acid (80 g, 1.1 mole) was added. The reaction mixture was heated at 55–65°C than cool to 0–5°C and the solid collected by filtration under vacuum and washed with isopropanol to give dexethylphenidate hydrochloride (97.50 g, 86.37%) having HPLC purity: Threo content: 99.10%. Erythro content: 0.90%, Chiral purity – 99.50% and SOR $[\alpha]_{D20:}$ + 87.50° (*c* = 1.0% w/v in methanol).

Purification of crude dexethylphenidate hydrochloride:

Mixture of *n*-butanol (540 ml) and crude dexethylphenidate hydrochloride (90 g) was heated up to 110–120°C and maintained for 10–15 min. The solid mass was cooled and collected by filtration under vacuum and washed with *n*-butanol (90 ml) and dried at 75–80°C under vacuum to get pure 86.0 g dexethylphenidate hydrochloride having HPLC purity: Threo content: 99.95%, Erythro content: 0.05%, Chiral purity – 100.0% and SOR $[\alpha]_{D20:}$ +88.0° (*c* = 1.0% w/v in methanol).

Results and discussion

The preferred embodiment of the present invention is to provide a green novel *in situ* process for preparation of dexethylphenidate hydrochloride. The esterification can be done by reacting formula II with ethanol and acid catalyst.

Fine observations of researchers is that the use of 9–10 volumes of the solvent gives higher quality instead of 2–3 volumes of solvent at particular stage. The difference is compared in Table 1.

Table 1

	Pure	Crude
Solvent	isopropanol	isopropanol
Solvent volume	9–10	2–3
HPLC purity	~99.9%	~99.1%

2-3 volumes of solvent of methanol, ethanol, *n*-propanol, isopropanol, *n*-butanol, isobutanol, tert-butanol or acetone and mixture thereof, added into oily mass of ethylphenidate free base, give less purity as compared to 9-10 volumes.

Dexethylphenidate hydrochloride of formula II is purified in different solvents. The suitable solvents include methanol, ethanol, isopropanol, *n*-butanol, isobutanol, tert-butanol, acetone, acetonitrile or mixture thereof at 80 to 100°C and filtered at 0–25°C give pure dexethylphenidate hydrochloride.

Hence, this process of purification in present work make the product pharmacopoeially acceptable worldwide.

Final molecule characterised by ^{1}H NMR, ^{13}C NMR, FTIR, CHNO and Mass analysis:

^{1}H NMR:

The Proton Magnetic Resonance Spectrum (^{1}H NMR spectrum) of dexethylphenidate hydrochloride in $CDCl_3$ was recorded at 400.13 MHz instrument which exhibits the followings signals in the ppm scale described Table 2 and Fig. 1.

^{13}C NMR:

The ^{13}C NMR spectrum of dexethylphenidate hydrochloride in $CDCl_3$ was taken at 100.13 MHz which shows followings signals in the ppm scale described Table 3 and Fig. 2.

Table 2

Sr. No.	ppm (H)	Type of signal	Number of protons	Type of proton
1.	1.36	Triplet	3H	Protons of -CH_3 group attached on -CH_2 of ester.
2.	3.64	Multiplet	2H	Protons of -CH_2- group of -OCH_3 of ester.
3.	1.67	Quarterate	2H	Protons of -CH_2- group of cyclic ring of piperidine.
4.	2.89	Multiplet	1H	1 Carbons of -CH- group between of cyclic ring of piperidine and benzene.
5.	1.84 to 4.35	Multiplet	7H	Protons of -CH_2- group of cyclic ring of piperidine.
6.	9.03	Broad singlet	1H	Protons of -NH- group of cyclic ring of piperidine.
7.	7.28 to 7.37	Multiplet	5H	Protons of aromatic ring
8.	10.12	Broad singlet	1H	Protons of HCl- group.

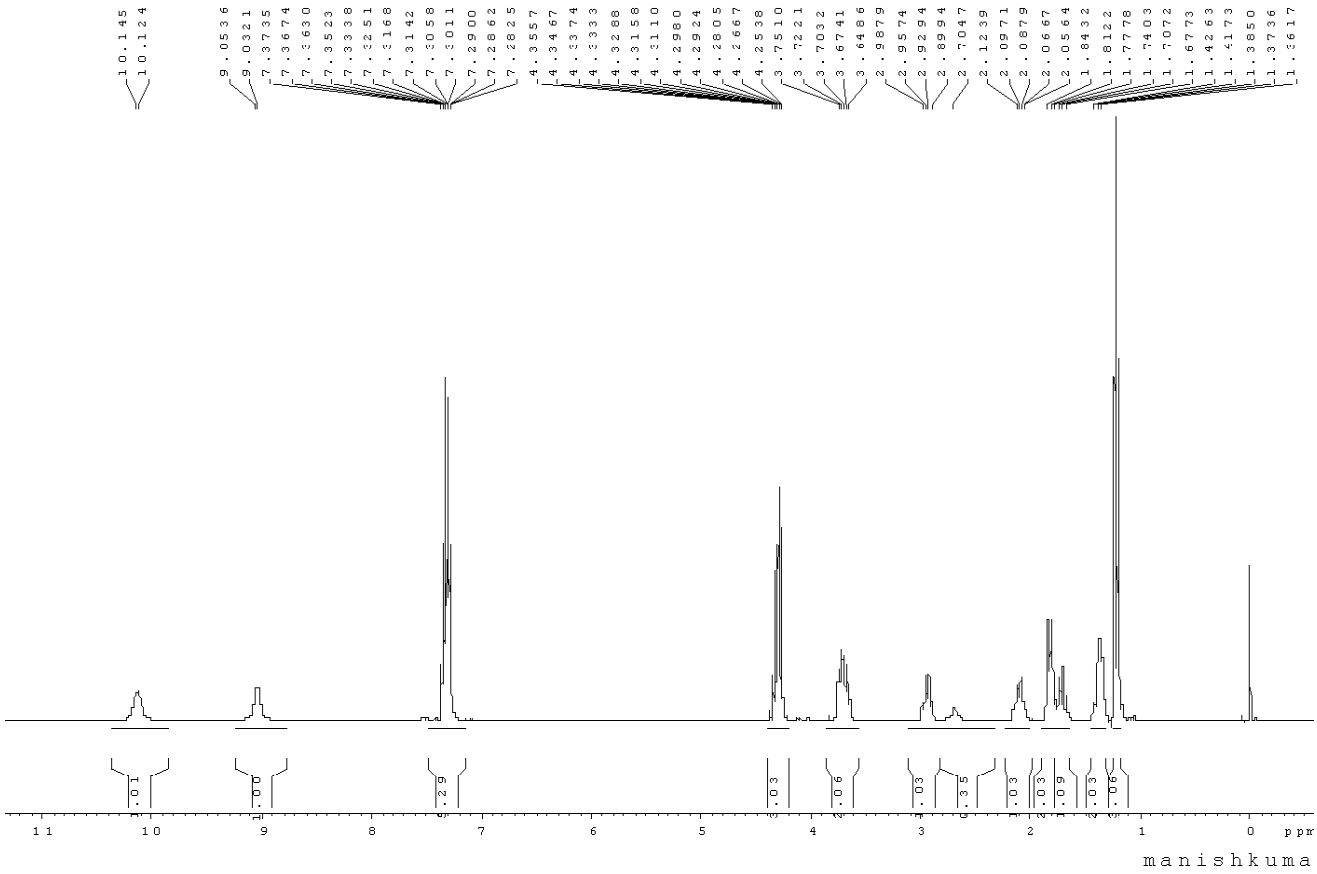


Fig. 1

Table 3

Sr. No.	ppm	Type of carbon
1.	13.87	1 carbon of -CH_3 group attached on -CH_2 of ester.
2.	21.93	1 Carbons of -CH_2- group of cyclic ring of piperidine.
3.	22.53 to 58.81	4 Carbons of -CH_2- group of cyclic ring of piperidine.
4.	54.07	1 Carbons of -CH- group between of cyclic ring of piperidine and benzene.
5.	62.33	1 carbon of -CH_2- group of -CH_3 of ester.
6.	76.81 to 134.27	6 Carbons of aromatic ring
7.	171.38	1 Carbons of -C=O carbonyl group.

FTIR:

IR spectrum of dexethylphenidate hydrochloride was recorded in KBr pellet in the range 400–4000 cm^{-1}. Assignments for the characteristics bands in the infra-red spectrum confirmed the formation of compound and given in following Table 4.

Table 4

Sr. No.	Band at frequency (cm^{-1})	Due to stretching of
1.	2930 to 2709	Aromatic -C-H stretching
2.	1731	Carbonyl group of ester
3.	2576 to 2418	Piperidine ring -C-H stretching
4.	1604	Aromatic -C= C- stretching
5.	1173	Ester group -C-O stretching

CHN Analysis:

CHN and O analysis of dexethylphenidate hydrochloride confirmed the formation of compound and given in following Table 5.

Mass analysis:

Mass analysis of dexethylphenidate hydrochloride con-

Table 5

Sr. No.	Element	Theoretical value (%)	Observed values (%)	Observed value
1.	C	63.48	63.69	Matches with theoretical value
2.	N	4.94	4.87	Matches with theoretical value
3.	H	7.81	7.79	Matches with theoretical value
4.	O	11.28	11.19	Matches with theoretical value

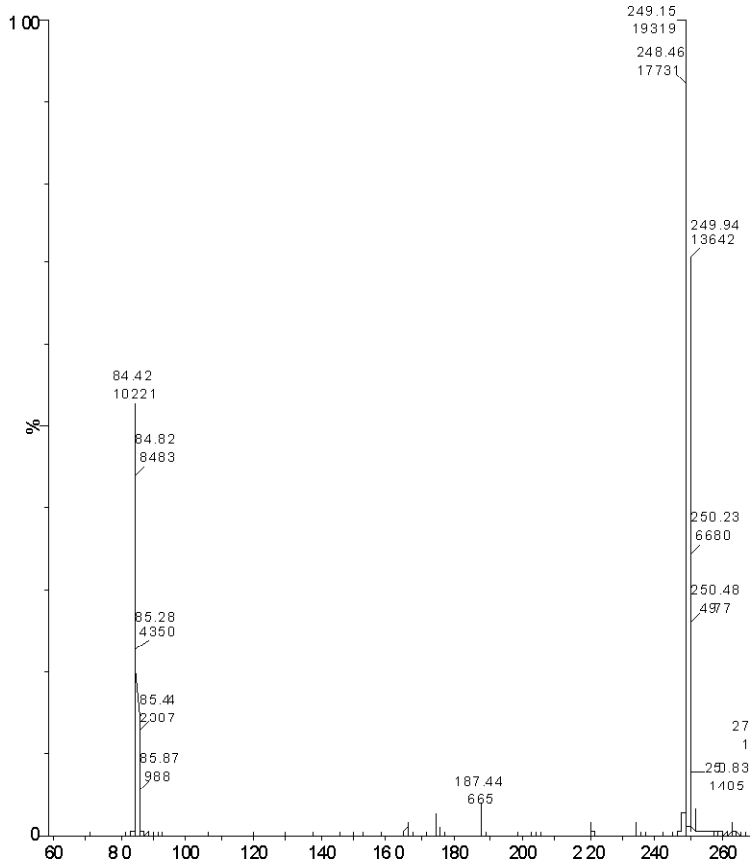


Fig. 2

firmed the formation of compound and given in following Fig. 2. Base peak on 247 m/e.

Conclusion

The synthesis of dexethylphenidate hydrochloride and its structural confirmation was made by spectroscopic and analytical data i.e. Spectra, Mass, Proton NMR and Carbon-13 NMR, CHN analysis, ROS also support formation of the product[14].

The above results are complying the formation of product by applying one pot synthesis in one step instead of three steps and best achievement of green chemistry route. We have avoid the use of hazardous chemicals, number of solvents, catalyst and reagents. This process is commercially highly effective as it save man powder, time, utility, health and safety of man; it's frankly for environment because we have reduced bulk waste generation and same is the basic principal of green chemistry.

One more important benefit of this process is genotoxic impurity causing cancer (Cancer; "something wrong with the genes"...), we have avoided more toxic and carcinogenic

chemical (thionyl chloride, phosphorus trichloride, phosphorus pentachloride, phosphorus oxychloride and many more like those are using for acylation of acid to acid chloride) and intermediate (acid chloride intermediate) those are responsible for cancer.

So many factors are responsible for making a product free from hazardous waste and impurities as per guideline of ICH. In this process we have considered all the parameter like environment, health and safety, economical viable and too much beneficial for nation.

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