

COMPARATIVE STUDIES ON SYNTHESIS AND STRUCTURE OF OLD AND NEW POLYMORPHS OF DESVENLAFAXINE - AN ANTIDEPRESSANT DRUG

Mahendra Khandpekar^{1*}, Jayanta Mheta², Sanjay Patil², Sonali Araj², Pandurang Satpute³

¹Materials Research Lab,
Department of Physics, Birla
College, Kalyan – 421 304, India.

²Department of Chemistry,
Changu Kana Thakur, Arts,
Commerce and Science College,
New Panvel, Raigad - 410 206,
India

³Department of Chemistry, Birla
College, Kalyan – 421 304, India.

Submitted: 18-08-2013

Revised: 09-10-2013

Accepted: 02-12-2013

*Corresponding author
Mahendra Khandpekar

E-mail address:
dr_mmk1968@yahoo.com

ABSTRACT

Desvenlafaxine succinate (pristiq) is an important non-hormonal drug used in the treatment of major depressive disorder and problems associated with menopause. This article summarizes the synthesis and investigation of new polymorphic form of Desmethylvenlafaxine. The new polymorph has been compared with the old polymorph using XRD, DSC, FTIR, SEM and HPLC techniques. Three prominent reflections with higher intensities lying at 20.3, 13.1 and 15.8 have been noted in the XRD measurements for the new polymorph. Higher intensity (XRD) peaks for the new polymorph indicates good crystalline quality. FTIR spectra shows close match between the polymorphs. DSC measurements show enhanced thermal stability for the new polymorph. Higher purity is indicated by the HPLC studies.

Key words: desvenlafaxine, polymorphism, structure, crystalline, purity

INTRODUCTION

Major depressive disorder is considered to be the most incapacitating conditions in the world Lourenco and Kennedy, 2009. The drug desvenlafaxine succinate (C₁₆ H₂₅ NO₂, Mol. Wt: 263.375g/mol) has long been used for the treatment of the major depressive disorder (De Martinis *et al.*, 2007; Abirami *et al.*, 2011. Popularly known as pristiq or O-desmethylvenlafaxine, it has being targeted as the first non-hormonal drug for treatment of menopause (Umand and Falconieri 2012, Archer *et al.*, 2009) several polymorphic forms each having distinct crystal structures and physical properties like melting point, X-ray diffraction pattern and infrared absorption fingerprint (Brittain, 2009). Moreover the crystalline forms may be distinguished on the basis of their thermal behavior different. Thermal behavior can be majored by techniques such as capillary melting point, differential scanning calorimetry (DSC), which have been used to distinguish the polymorphic forms (Giron, 2002).

In the present investigation the old as well as new polymorph of desvenlafaxine has

been prepared in our laboratory and the method of preparation has been outlined. The two samples of desvenlafaxine have been compared on the basis of XRD, IR, DSC (thermal), SEM and HPLC chromatographic studies. The structure of our new polymorph is found to be in close agreement with that of desvenlafaxine succinate monohydrate (Venu, *et al.*, 2008). The new polymorph reported in this paper is found to be more pure and thermally stable as compared to the old polymorph of desvenlafaxine as detailed below.

MATERIAL AND METHODS

All reagents, chemicals and solvents used for the synthesis were of AR grade. The XRD pattern of the samples was recorded on Shimadzu XRD 6000 with a solid state detector using Cu_α radiation (1.5418Å). The sample holder consisted of a round standard aluminum holder with a rough zero background. The sample was scanned between 2-40 (2θ) degrees with step size of 0.02° at a rate of 2°/min. The Infrared spectra was recorded on a FTIR infrared Shimadzu 8400 spectrophotometer in the range from 400 to 4000cm⁻¹.

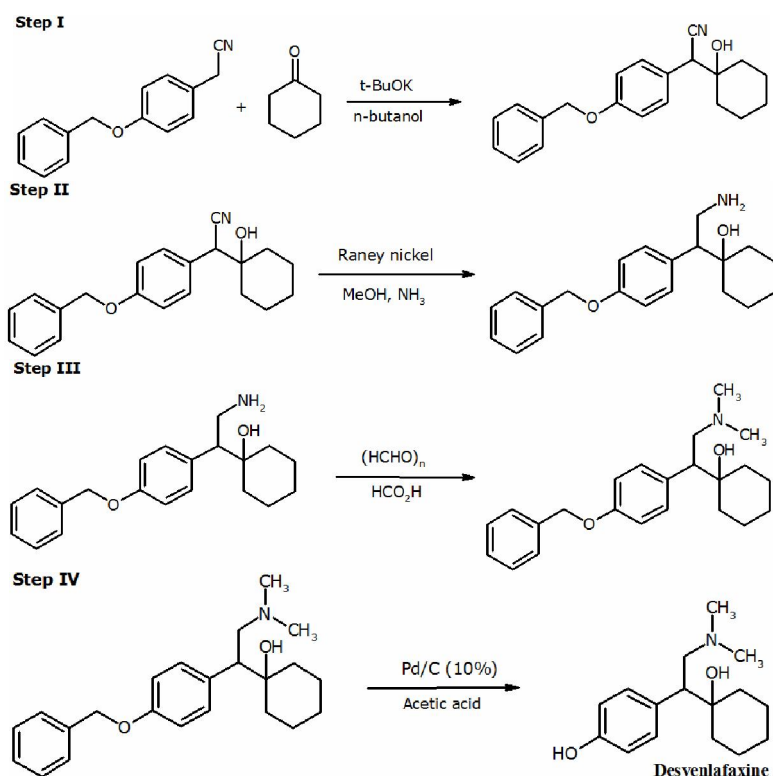


Figure 1. Reaction mechanism for synthesis of new polymorph of desvenlafaxine

Perkin Elmer (DSC7) analyzer was used for Differential Scanning Calorimetry Measurements. A Vergo make melting point apparatus was used for estimation of melting point. SEM was recorded using Jeol JSM 6500F scanning electron microscope. HPLC Chromatograph was recorded on a Perkin Elmer series 200 HPLC analyzer system.

Normal method of synthesis

For a batch quantity of 10g, desvenlafaxine was prepared by reacting O-desmethylvenlafaxine with methanol and ethyl acetate. To begin with methanol in a four-necked round bottom flask was stirred at room temperature and desmethylvenlafaxine base was added to it. This was followed by addition of ethyl acetate to the reaction mixture again under stirring. The mixture was heated till the temperature of the reaction mass was raised to 80°C. This temperature was maintained till complete dissolution of o-desmethylvenlafaxine occurs. The heating was then discontinued and

the material was allowed to cool naturally upto 30°C with continuous stirring so that product can be precipitated out. The product was then separated from the reaction mass by filtering it. The final product was then washed with a small quantity of methanol and dried at 60°C under vacuum to get the crystalline product.

Synthesis of old polymorph

4-[2-amino-1-(1-hydroxycyclohexyl)ethyl] phenol (2.12g; 0.009mol) was suspended in 21.2mL (16.79g) of methanol under nitrogen atmosphere. A white suspension was obtained to which 1.69mL (0.022mol) of formaldehyde (37%) was added followed by 4.46g (0.021mol) of sodium triacetoxyborohydride in portions. The resulting suspension was then stirred for 4h and 40min at room temperature. Following which 21.2mL Lof water was added, and the stirring was continued at room temperature for 10min. The methanol was then removed by distillation, and the resulting solution was washed twice with 10mL (8.67g) of toluene.

Table I. XRD reflections at 2θ degrees for old and new polymorphs of desvenlafaxine

Obs. No	New Polymorph	Old Polymorph
1	12.0	12.1
2	13.1	13.2
3	15.8	15.9
4	20.3	20.4
5	22.3	22.3

Thereafter, the pH was adjusted to 9.5 by adding 50% sodium hydroxide to it. The resulting suspension was cooled to 0-5°C and was filtered. The wet solid was finally dried under vacuum at 60°C until constant weight was obtained.

Synthesis of new polymorph

The reaction mechanism can be summarized as follows. Initially 4-benzyloxy-phehnyl acetonitrile and cyclohexanone was condensed in the presence of potassium tertiary butoxide as base in n-butanol to get DFL-I. The cyano group of DFL-I undergoes hydrogenation in methanolic ammonia and Raney nickel as catalyst to form DFL-IIA. DFL-IIA is then reacted with para formaldehyde and formic acid and isolated using sodium hydroxide solution to get dimethylated product DFL-III.A. DFL-III.A was then hydrogenated with Pd/C in methanol to get debenzylated product DFL-IV (Desvenlafaxine crude). The crude product was finally purified by charcoalisation in methanol and ethyl acetate to get final new crystalline polymorph of desvenlafaxine. The stepwise process of preparation of the new polymorph is shown in figure 1.

RESULTS AND DISCUSSION

XRD analysis

To confirm the phase formation the samples in powder form were exposed to X ray radiation. Table I lists the prominent XRD peaks for the polymorphs. Three strong peaks each are found in both new as well as old polymorph lying near 20.4°, 13.2° and 15.8°. The intensity ratio of the new polymorph was found to be ten times greater than the old

polymorph. The higher intensities in new polymorphs clearly indicate better phase formation. The highest intensity peak around 20.3° is found to be bifurcated in the old polymorph.

Thermal DSC studies

Thermal Differential Scanning Calorimetry (DSC) studies indicate sharp melting endotherm near the melting points of the respective polymorphs. Melting point of the older polymorph lies at 225°C as compared to the new polymorph which was found to lie at 230°C. The new polymorph thus has greater thermal stability than the old polymorph. The melting points were also confirmed using conventional melting point apparatus.

SEM analysis

The scanning electron microphotographs (SEM images) of the old and the new polymorphic forms are shown in figure 2 and figure 3. The crystalline aggregates in the old polymorph are clearly transformed into more regular, elongated needle shaped structures. The new polymorph is thus more ordered than the old polymorph exhibiting crystalline nature. Particle shape of new compound shows a remarkable change from previously existing one. The new polymorph is also found to have enhanced solubility.

FTIR studies

For identification of fundamental groups present Fourier Transform Infrared Spectral (FTIR) analysis using KBr pellet technique was carried out for the new polymorph. Table II shows a comparative chart of the IR peaks for old and new polymorphs.

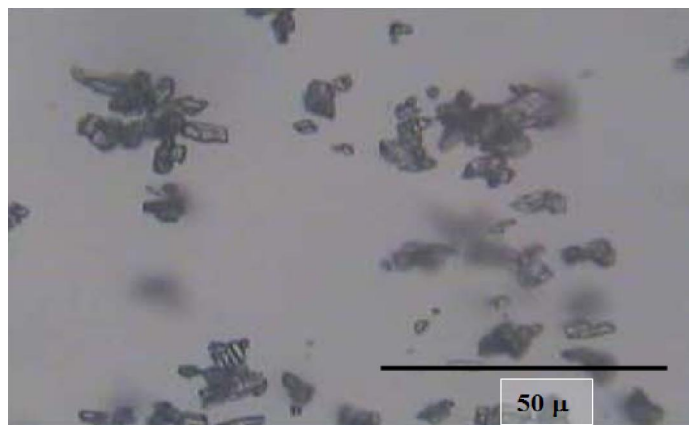


Figure 2. SEM image of old polymorph of desvenlafaxine



Figure 3. SEM image of new polymorph of desvenlafaxine

Between wave numbers 400cm^{-1} to 4000cm^{-1} , a close match in the IR vibrations with an error of 2cm^{-1} has been observed. Presence of two new peaks has been noted at 3128.32cm^{-1} and at 3028.03cm^{-1} in the new polymorph. The peak at 764.40cm^{-1} in the old polymorph is seen to shift by about 18cm^{-1} on the lower wave number side in the new polymorph.

HPLC chromatographic analysis

High performance liquid chromatography (HPLC) is essentially a separation technique which is used invariably for the separation of organic molecules/ions. HPLC is also extremely useful to judge the purity of the sample. Table III shows chromatographic measurements on old and new polymorphs of desvenlafaxine. The retention peaks (retention time) and hence the area for the new

polymorphs is found to be enhanced, Thus the new polymorph can be ascertained to be more pure than the old polymorph.

In a nutshell the new polymorph is found to be much more ordered (elongated needle shaped structures) as against aggregates found in the case of the old polymorph. The new polymorph is thus more pure (crystalline) and exhibits enhanced solubility as compared to the old polymorph. The purity of the new polymorph remains supported further by the HPLC measurements. The XRD structure is found to be in close agreement with that reported by Venu *et al.*, 2008. XRD studies on new polymorph of desvenlafaxine show better phase formation (with enhanced intensity peaks) as compared to that of the old polymorph. The new polymorph is also found to have greater thermal stability than the old

Table II. Comparative IR chart showing peaks for old and new polymorphs

Peak No.	Old polymorph (cm ⁻¹)	New polymorph (cm ⁻¹)
1	451.31	*
2	518.89	516.89
3	545.82	545.02
4	764.40	746.40
5	806.19	806.19
6	837.05	837.05
7	952.77	952.77
8	1033.77	1029.92
9	1095.49	*
10	1153.35	1153.35
11	1184.21	1184.21
12	1247.86	1247.86
13	*	1269.07
14	1290.29	*
15	1352.01	1350.08
16	1396.37	1396.37
17	1415.65	1415.65
18	1450.37	1452.30
19	1515.94	*
20	1602.74	1602.74
21	1645.17	1647.10
22	1878.54	1876.61
23	2150.48	2152.41
24	2335.64	*
25	2441.71	2339.49
26	2530.43	2530.43
27	2636.71	2636.71
28	2715.79	1715.59
29	2761.87	2759.95
30	2848.67	2848.67
31	2933.53	2933.53
32	—	3028.03
33	—	3128.20
34	3166.90	3166.90
35	3458.13	3456.20

polymorph which is clearly indicated by 5°C rise in melting point of the new polymorph. Majority of the vibrational (FTIR) peaks are found to be present in both old as well as new polymorphs confirming the presence of fundamental groups of desvenlafaxine.

CONCLUSION

The new polymorphic form of desvenlafaxine has been synthesized. More ordered, needle like elongated crystallites have

been obtained for the new polymorphs as evidenced by SEM measurements. The detailed processes for making different polymorphic forms have been outlined and the relevant reaction mechanisms have been proposed. The new polymorph has been compared with the old polymorph using XRD, DSC, FTIR, SEM and HPLC techniques. Three prominent reflections with higher intensities lying at 20.3, 13.1 and 15.8 have been noted in the XRD measurements for the new polymorph. Higher

Table III. Chromatographic measurements of old and new polymorph of Desvenlafaxine

	RT	% Area	RT Ratio
Desvenlafaxine (Old- Peak 2)	23.500	0.09	1.265
Desvenlafaxine (New -Peak 2)	23.860	0.04	1.273
Desvenlafaxine (Old)	18.577	99.91	—
Desvenlafaxine (New)	18.737	99.96	—

intensity (XRD) peaks for the new polymorph indicates good crystalline quality. FTIR spectra shows close match between the polymorphs. DSC measurements show enhanced thermal stability for the new polymorph. Higher purity is indicated by the HPLC studies.

ACKNOWLEDGEMENT

We are thankful to the Principal of CK T College, Mumbai for providing the support for this research work.

REFERENCES

- Abirami G., Logesh R., Vetrichelvan T., 2011, Spectrophotometric method for estimation of desvenlafaxine succinate in tablet dosage form, *Res. Pharm. Biol. Che. Sci.*, **2**, 721-729
- Archer, DF., Dupont, C.M., Constantine, GD., Pickar, JH., Oliver S., 2009, Desvenlafaxine for the treatment of vasomotor symptoms associated with menopause: a double-blind, randomized, placebo-controlled trial of efficacy and safety, *Am. J. Obstet. Gynecol.*, **200**, e1-238
- Brittain HG., 2009. Polymorphism and Solvtomorphism, *J. Pharm. Sc.*, **98**, 1617-1642
- De Martinis NA., Yeung PP., Entsuah R., Manley AL., 2007, A double-blind, placebo-controlled study of the efficacy and safety of desvenlafaxine succinate in the treatment of major depressive disorder, *J. Clin. Psychiatry.*, **68**, 677-88
- Giron D., 2002. Applications of thermal analysis and coupled techniques in pharmaceutical Industry, *J. Therm. Anal. Calorim.*, **68**, 335-357
- Kornstein SG., Jiang Q., Reddy S., Musgnung, JJ., Guico-Pabia CJ., 2010, Short-term efficacy and safety of desvenlafaxine in a randomized, placebo-controlled study of perimenopausal and postmenopausal women with major depressive disorder, *J. Clin. Psychiatry*, **71**, 1088-1096
- Liebowitz MR., Tourian KA., 2010, Efficacy, Safety, and Tolerability of Desvenlafaxine 50 mg/d for the Treatment of Major Depressive Disorder: A Systematic Review of Clinical Trials, *J. Clin. Psychiatry*, **12**, 3-4
- Lourenco MT., Kennedy SH., 2009, Desvenlafaxine in treatment of major depressive disorder, *Neuropsychiatr. Dis. Treat.*, 127-136
- Retrieved
<http://www.faqs.org/patents/app/20100121108>
- Umand, E. M., Falconieri, L., 2012, Treatment options for vasomotor symptoms in menopause: focus on desvenlafaxine, *Int.J. Womens. Health.*, 305-319
- Venu N., Sreekanth BR., Ram T., Devarakonda S., 2008. Desvenlafaxine succinate Monohydrate, *Acta. Crystallogr. C.*, **64**, 290-292