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RESEARCH ARTICLE

A Study on Synthesis and Characterization of Various Polymorphic Forms of Trimipramine Maleate and Clomipramine Hydrochloride

Patel Keyurkumar Arunkumar[1], M D Karvekar[1,*]

[1]*Department of Pharmaceutical Chemistry, Krupanidhi College of Pharmacy, Bangalore, Karnataka, India*

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* *Corresponding author.*
M D Karvekar
drmdkarvekar@gamil.com

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ABSTRACT

This study aimed to synthesize and characterize the different polymorphs of Trimipramine Maleate and Clomipramine Hydrochloride. Polymorphism is highly significant in pharmacies because it controls the physical and thermal properties of the compounds, and hence, drug effectiveness and stability. Polymorphs were synthesized using recrystallization with different solvent combinations, such as ethyl acetate, methanol, and acetonitrile. The polymorphs were analyzed by various methods: Fourier transform infrared (FTIR) spectroscopy for identification of functional groups, nuclear magnetic resonance (NMR) spectroscopy for the examination of molecular structure, differential scanning calorimetry (DSC) for examination of thermal behavior, and powder X-ray diffraction (PXRD) for determining crystal structure. All chemicals and reagents were obtained from authentic suppliers, and the synthesis was performed in research laboratories equipped with specialized facilities. Unique polymorphs of Trimipramine Maleate (Polymorphs I-V) and Clomipramine Hydrochloride (Polymorphs IA-VC) were detected and evaluated. FTIR analysis demonstrated variations in the spectral attributes for every polymorph, referring to structural differences. DSC indicated variations in the melting points as well as heat of fusion, whereas PXRD gave unique diffraction patterns, indicating different crystalline structures. Several polymorphs exhibited comparable thermal behavior, indicating closely linked molecular arrangements. The study results reveal information regarding the polymorphic structures of Trimipramine Maleate and Clomipramine Hydrochloride, which are significant for optimizing drug formulations.

Keywords: Polymorphs; Differential Scanning Calorimetry (DSC); Powder X-ray Diffraction (PXRD)

INTRODUCTION

Polymorphisms in pharmaceutical substances are a foremost subject in drug development and formulation because differences in physicochemical properties among polymorphic forms can affect drug stability, bioavailability, and efficacy. Polymorphism is the condition in which the same substance exists in various crystalline structures, although they are chemically identical.[1] In this respect, the present work deals with the synthesis and characterization of different polymorphs of two antidepressant medicines: trimipramine maleate and clomipramine hydrochloride. Medicines are generally used to treat a range of psychiatric illnesses such as depression. These polymorphs can have a serious impact on their therapeutic effects, making it even more critical to study drug variations during development.

Earlier research on similar drugs has shown how crucial polymorphisms control drug characteristics. Ranitidine hydrochloride, a drug used in the treatment of stomach ulcers, occurs in two polymorphic forms distinguishable by sophisticated methods, such as terahertz pulsed spectroscopy (TPS).[1] In the case of venlafaxine hydrochloride, another antidepressant drug, more than one polymorph has been reported; five different forms with different characteristics and stability profiles have been detected.[2] These reports emphasize the necessity of a full study of polymorphisms in drugs used in medication, especially antidepressants such as trimipramine maleate and clomipramine hydrochloride, for optimal formulation and function.

Polymorphic forms are generally characterized using a combination of sophisticated analytical methods, including differential scanning calorimetry (DSC), thermogravimetric analysis (TGA), Fourier transform infrared (FT-IR) spec-

troscopy, and X-ray diffraction (XRD).[2,3] These techniques enable an in-depth analysis of the thermal characteristics, physical properties, and crystallinity of drug substances and offer useful information regarding the potential behavior of different polymorphs under different conditions. By knowing the physicochemical characteristics of these various forms, scientists can more accurately predict their stability, solubility, and bioavailability, all of which are critical to the therapeutic effect of the drug.

The present research will contribute to the increasing amount of information regarding pharmaceutical polymorphisms, and more specifically, to trimipramine maleate and clomipramine hydrochloride. Through the synthesis and characterization of different polymorphic forms of these antidepressants, this study hopes to shed light on their physicochemical properties and stability profiles, thereby contributing to the development of better formulations. Knowledge of the polymorphic nature of these compounds will provide useful information that can have a direct influence on drug formulation, resulting in enhanced drug stability and efficacy, and ultimately better patient outcomes. The results of this research will be an important contribution to the scientific knowledge of pharmaceutical polymorphisms, assisting in the optimization of the design and delivery of these critical drugs.

MATERIALS AND METHODS

Different polymorphic forms of Trimipramine Maleate and Clomipramine Hydrochloride were prepared and characterized at the R&D Laboratories of the Department of Pharmaceutical Chemistry, Krupanidhi College of Pharmacy, Bangalore, and the R & D Laboratory of R L Fine Chemicals Pvt. Ltd., Yelahanka, Bangalore. The reagents and chemicals employed in this research were of AR and LR grade and were obtained from recognized dealers such as Lancaster, Sigma, NR Chem, Rolex, and S.D.-Fine Chem. Ltd., and Merck.

The analytical methods used for the identification and characterization of the synthesized compounds and polymorphs were melting point determination, infrared (IR) spectroscopy, nuclear magnetic resonance (NMR) spectroscopy ((^{1}H NMR and ^{13}C NMR), differential scanning calorimetry (DSC), and powder X-ray diffraction (PXRD). Melting points were measured using a Scientific MP digital instrument and IR spectra were obtained using a Fourier Transform IR Spectrophotometer. NMR spectra were obtained at the Sophisticated Analytical Instrumentation Facility, IISc, Bangalore, in deuterated chloroform for ^{1}H NMR and DMSO for ^{13}C NMR. DSC measurements were carried out at the Society for Innovation and Development, IISc, Bangalore, on a Mettler Toledo Star System, while PXRD patterns were obtained from both IISc, Bangalore, and the STIC, Cochin University of Science & Technology, Cochin, Kerala, using Philips and Bruker AXS X-ray generators.

To synthesize Trimipramine Maleate, 10,11-dihydro-5H-dibenz[b,f]azepine was treated with sodium amide in xylene under a nitrogen atmosphere and then with N,N-dimethylamino isopropyl chloride, and the reaction was refluxed for 16 hours. The maleic acid solution was added after filtration and concentration, which led to the deposition of Trimipramine Maleate crystals. The same synthetic procedure was adopted for Clomipramine Hydrochloride with 3-chloro-10,11-dihydro-5H-dibenz[b,f]azepine and sodium amide, followed by treatment with N, N-dimethylaminopropyl chloride and refluxing.

Preparation of various polymorphs of Trimipramine Maleate (polymorphs I, II, IIIA, IIIB, IV, and V) and clomipramine hydrochloride (polymorphs IA, IB, IIA, IIB III, IV, VA, VB, and VC) was accomplished using a range of recrystallization methods. These are slow cooling, rapid cooling, and anti-solvent methods using a range of solvent combinations that are optimized according to the solubility characteristics of the compounds. The various polymorphs were recrystallized from solvents such as ethyl acetate, methanol, acetonitrile, chloroform, and IPA. Each polymorph was thoroughly characterized in terms of its melting point, IR spectra, and DSC data. The polymorphs exhibited unique thermal behaviors, as reflected by their DSC thermograms, and also had varying crystal structures and yields, with certain polymorphs yielding higher amounts than the others.

RESULTS

The results obtained for various polymorphs of Trimipramine Maleate are as follows.

Polymorphs of Trimipramine Maleate

The Trimipramine Maleate polymorphs were characterized using FTIR, DSC, and PXRD. Five different polymorphs (I, II, IIIA, IIIB, IV, and V) with different melting points and solubility properties were characterized (Tables 1 and 2).

- **Identification of Trimipramine Maleate Polymorphs:**

The Polymorphs were identified using FTIR, DSC, and PXRD techniques. These methods allow for the differentiation and characterization of polymorphs, owing to their different spectral and thermal properties.

- **IR Spectroscopy:**

IR spectra were obtained for every polymorph of Trimipramine Maleate. This information provided variations in the bond stretch wave numbers, especially for the O-H (maleate) stretch, C-H (aromatic) and (aliphatic), C=C, and C-N stretches, showing unique structural differences among the polymorphs.

Table 1: Polymorphs of Trimipramine Maleate: Comparison of IR Spectral and Thermal Data

Type Of Polymorph	Recrystallized From	Solvent Needed (ml)	Drug Consumed (g)	Yield (%)	Melting Point (° C)
I	Water	40	5.5	94.64	139-142
II	IPA	21	5.5	98.18	139-142
IIIA	Acetone	35	5.5	72.72	139-142
IIIB	MEK	20	5.5	83.64	139-142
IV	Acetonitrile	16	5.5	61.82	139-142
V	Acetonitrile: Methanol (1:1)	8	7	71.42	140-142

Bond (Stretch)	Wave Number (cm^{-1})						
	Trimipramine Maleate	Type of Polymorph					
		I	II	IIIA	IIIB	IV	V
O-H (Maleate)	3446.79	3442.94	3439.08	3444.87	3444.87	3442.94	3441.01
C-H (Aromatic)	3028.24	3028.24	3030.17	3028.24	3030.17	3028.24	3028.24
C-H (Aliphatic)	2962.66, 2926.01	2962.66, 2926.01	2962.66, 2926.01	2962.66, 2926.01	2962.66, 2926.01	2962.66, 2926.01	2960.73, 2926.01
C=C	1577.77-1444.68	1579.70-1483.26	1579.70-1483.26	1579.70-1483.26	1579.70-1483.26	1579.70- 1483.26	1579.70-1481.33
C-O	1381.03, 1352.10	1381.03, 1354.03	1379.01, 1352.10	1381.03, 1354.03	1381.03, 1354.03	1381.03, 1354.03	1379.01, 1352.10
C-N	1234.44	1234.44	1234.44	1234.44	1234.44	1234.44	1234.44

Polymorphs	Onset (° C)	Peak (° C)	End set (° C)	Enthalpy of Fusion (J/g)
Trimipramine Maleate	142.33	143.51	145.18	106.17
I	143.93	146.70	148.93	68.06
II	142.22	144.67	150.02	93.78
IIIA	142.04	144.41	147.15	106.37
IIIB	142.22	144.67	150.02	106.80
IV	146.95	149.82	152.47	55.03
V	142.22	146.71	149.48	105.46

Table 2: Comparisons of relative intensities and interplanar spacing derived from the powder pattern of Trimipramine Maleate and its different polymorphs

	Type of Polymorph											
Trimipramie Maleate		I		II		IIIA		IIIB		IV		V	
d-spacing [Å]	Rel. Int. [%]	d-spacing [Å]	Rel. Int. [%]	d-spacing [Å]	Rel. Int. [%]	d-spacing [Å]	Rel. Int. [%]	d-spacing [Å]	Rel. Int. [%]	d-spacing [Å]	Rel. Int. [%]	d-spacing [Å]	Rel. Int. [%]
4.53	100	10.092	100	4.076	100	10.107	100	10.137	100	4.214	100	10.156	100
10.2	69.2	4.513	73.1	10.106	90	4.067	46.9	4.085	40.9	4.53	79.1	4.051	58.8
4.206	65.6	4.085	60.8	4.525	75.4	4.523	27	4.53	33	10.172	42.1	6.421	39.4
4.089	51.7	4.189	56.1	5.589	51.2	4.196	20.3	4.204	32.8	3.763	34.9	3.6	28.4
4.817	48.9	3.46	37.5	4.197	46.6	5.088	17.3	5.095	23.3	5.588	31.8	5.051	27.8
5.599	46	3.754	32	5.109	34.5	4.792	11.6	4.809	10.9	4.804	30.7	4.749	22.1
6.476	40.9	4.977	24.5	4.764	18.5	3.937	7.69	3.925	3.48	4.085	29.7	3.504	19

- **Differential Scanning Calorimetry (DSC):**

Thermal analysis of the polymorphs showed their melting points and enthalpies of fusion. All polymorphs had comparable melting points between 139°C and 142°C, with the enthalpy of fusion differing among polymorphs, reflecting variations in thermal behavior.

Polymorphs of Clomipramine Hydrochloride

The polymorphs of clomipramine Hydrochloride were also investigated and characterized using a procedure similar to that used for Trimipramine Maleate (Tables 3 and 4).

- **Detection of Polymorphs of Clomipramine Hydrochloride:**

The polymorphs of Clomipramine Hydrochloride were detected using FTIR, DSC, and PXRD. These analyses enabled the discrimination and characterization of polymorphs through their distinct spectral and thermal properties.

- **IR Spectroscopy:**

The IR spectroscopy study provided clear information regarding the functional groups and bond vibrations of the Clomipramine Hydrochloride polymorphs, which allowed for the identification of individual polymorphic forms.

- **Differential Scanning Calorimetry (DSC):**

DSC analysis revealed differences in the melting points and heat of fusion of Clomipramine Hydrochloride polymorphs, which further established polymorphic variations.

Powder X-ray Diffraction Study

The polymorphic forms were also validated using PXRD through the identification of unique diffraction patterns for the unique polymorphs of Clomipramine Hydrochloride. These data provide broad insight into Trimipramine Maleate polymorphs, as well as the physical and thermal properties of those associated with Clomipramine Hydrochloride.

DISCUSSION

The objective of this study was to synthesize different polymorphs of Trimipramine Maleate and Clomipramine Hydrochloride. The synthesized compounds were characterized using FTIR, NMR, and mass spectrometry. Of the various solvents and solvent combinations used for the preparation of the polymorphs, only a few regularly produced pure polymorphs. These polymorphs were characterized by FTIR, DSC, and PXRD. FTIR spectroscopy is a common and simple method for investigating and determining polymorphs. Although most molecular characteristics remain unchanged in different polymorphs, the influence of the environment on certain bonds and their vibrational properties is not always considerable enough to be significant in the IR spectra. The IR spectra of Trimipramine Maleate and its polymorphs were also investigated and compared. Trimipramine Maleate and its polymorphs (Type I, Type II, Type IIIA-IIIB, Type IV, and Type V) were found to have different IR spectral features, such as significant peak position shifts and the disappearance of certain peaks. These variations were due to the differences in the molecular structures of the polymorphs. The IR spectra of Clomipramine Hydrochloride and its polymorphs were also examined and found to have unique spectral features. Polymorphs such as Type IA-IB, IIA-IIB, and VA-VB-VC exhibited varying IR spectral features, which were ascribed to molecular-level structural differences.

Nonetheless, FTIR analysis is not considered reliable for polymorph identification. The subtlety of spectral differences can render FTIR difficult in some cases, such as when the spectral differences between polymorphs are small, or when there is more than one polymorph in a mixture.[4,5] In these situations, other analytical methods may be required to support FTIR information for determining the identity and amount of the polymorph. Various strategies have been devised to enhance the reliability of FTIR spectroscopies. Attenuated total reflectance Fourier transform infrared spectroscopy (ATR-FTIR) coupled with second-derivative analysis and peak ratio computations has been successful in the precise quantification of polymorphic mixtures.[4] Moreover, principal component analysis (PCA) of Raman spectroscopic data, which is complementary to IR spectroscopy, has demonstrated high sensitivity in the quantitative analysis of polymorphic forms.[5]

DSC was also utilized to determine polymorphs, and thermodynamic information such as melting temperatures, heat of fusion, and polymorphic transformations were determined. The area of the DSC peaks was proportional to the heat absorbed or evolved during the thermal events, and the heat of fusion (enthalpy) was calculated by integrating the peak areas. For Trimipramine Maleate, DSC analysis indicated the following: Polymorph I showed a sharp endothermic peak with an onset temperature of 143.93°C, a peak at 146.70°C, and a heat of fusion of 68.06 J/g. Polymorph II showed a sharp endothermic peak at 142.22°C and a heat of fusion of 93.78 J/g. Polymorph IIIA produced a sharp endothermic peak with an onset temperature of 142.04°C and heat of fusion of 106.37 J/g, comparable to Polymorph IIIB, which produced a heat of fusion of 106.80 J/g. Polymorph IV had a greater onset temperature (146.95°C) and a heat of fusion of 55.03 J/g, whereas Polymorph V had a broad endothermic peak with an onset temperature of 142.22°C and a heat of fusion of 105.46 J/g. These differences in the melting points and heat of fusion indicate differences in the thermal behavior of the different polymorphs.

Table 3: Polymorphs of Clomipramine Hydrochloride: Comparison of IR Spectral and Thermal Data

Type Of Polymorph	Recrystallized From	Solvent Needed (ml)	Drug Consumed (g)	Yield (%)	Melting Point (° C)
IA	Chloroform	12	5.2	73.07	192-194
IB	Acetone: Chloroform (1:1)	68	8.1	40.74	192-194
IIA	MEK	40	1.8	66.66	192-194
IIB	Chloroform: Toluene (1:1)	114	7	74.28	192-194
III	Chloroform: MEK (1:1)	30	3.3	63.63	192-194
IV	Acetonitrile: Acetone (1:1)	80	6	60	192-194
VA	IPA	40	8	75	192-194
VB	Acetone	100	1.2	45.54	192-194
VC	IPA:Toluene(1:1)	22	7	70	192-194

Bond (Stretch)	Wave Number (cm^{-1})									
	Clomipramine Hydrochloride	Type of Polymorph								
		IA	IB	IIA	IIB	III	IV	VA	VB	VC
N-H (Quat. Ammo. Salt)	3442.94	3444.87	3442.94	3442.94	3444.87	3444.87	3442.94	3441.01	3444.87	3444.87
C-H	3072.60-	3074.53-	3072.60-	3072.60-	3072.60-	3072.60-	3072.60-	3072.60-	3074.53-	3072.60-
(Aromatic)	3007.02	3007.02	3007.02	3007.02	3007.02	3007.02	3007.02	3007.02	3007.02	3007.02
C-H	2956.87-	2958.80-	2956.87-	2956.87-	2956.87-	2956.87-	2956.87-	2956.87-	2958.80-	2956.87-
(Aliphatic)	2870.08	2870.08	2870.08	2868.15	2868.15	2868.15	2868.15	2868.15	2870.08	2868.15
C=C	1585.49-	1585.49-	1585.49-	1585.49-	1585.49-	1585.49-	1585.49-	1585.49-	1583.56-	1585.49-
	1409.96	1411.89	1409.01	1409.96	1409.96	1409.96	1409.96	1409.96	1411.89	1409.96
C-N	1232.51	1226.73	1232	1232.51	1232.51	1232.51	1232.51	1232.51	1226.73	1232.51
C-Cl	754.17	756.1	754.17	754.17	754.17	754.17	754.17	754.17	754.17	754.17

Polymorphs	Onset (° C)	Peak (° C)	End set (° C)	Enthalpy of fusion (J/g)
Clomipramine Hydrochloride	193.99	195.08	197.28	110.58
IA	193.82	194.87	197.08	112.12
IB	192.88	194.81	200.29	110.92
IIA	196.92	199.05	200.71	71.59
IIB	196.51	199.75	205.79	71.3
III	193.94	195.28	197.2	108.66
IV	194.16	195.15	197.05	116.54
VA	193.91	194.95	197.11	114.03
VB	194.17	195.04	196.64	112.52
VC	194.67	195.04	197.73	114.08

Table 4: Comparisons of relative intensities and interplanar spacing derived from the powder pattern of Clomipramine Hydrochloride and its different polymorphs

Type of Polymorph																			
Clomipramine HCl		IA		IB		IIA		IIB		III		IV		VA		Vb		VC	
d value	Rel. Int. [%]	d value	Rel. Int. [%]	d value	Rel. Int. [%]	d value	Rel. Int. [%]	d value	Rel. Int. [%]	d value	Rel. Int. [%]	d value	Rel. Int. [%]	d value	Rel. Int. [%]	d value	Rel. Int. [%]	d value	Rel. Int. [%]
oA	%	oA	%	oA	%	oA	%	oA	%	oA	%	oA	%	oA	%	oA	%	oA	%
15.13	37.7	15.69	20.1	15.34	23.2	15.11	26.4	15.53	3.7	3.721	100	4.4	100	15.19	43.5	15.17	53.3	15.18	52.4
5.48	14.6	5.11	35.4	5.11	21.1	5.1	17.3	5.1	6.9	4.38	76.7	3.84	91.5	5.11	34.8	5.12	62.5	5.12	50.9
4.49	100	4.39	100	4.39	100	4.36	100	4.36	100	3.82	31.5	15.2	84.3	4.39	100	4.41	100	4.38	100
3.76	41.7	3.9	42.5	3.89	19.5	3.9	26.8	3.9	12.9	5.08	19.5	3.07	58.7	3.91	63.9	3.98	22.6	3.92	27.7
3.85	38.1	3.74	51.4	3.74	19.9	3.83	29	3.83	13.6	3.06	19.2	5.12	42.1	3.84	72.9	3.89	79	3.86	69.7
3.08	24.7	3.48	29.1	3.48	18	3.77	20.8	3.77	11.5	3.9	17.8	3.75	23.5	3.84	72.9	3.87	77.8	3.84	74.3
3.3	14.8	3.22	14.5	3.22	16.6	3.48	11.3	3.47	4.9	3.75	17.5	3.91	21.7	3.08	44.3	3.09	36.1	3.08	54.1

For Clomipramine Hydrochloride, DSC results were also consistent with similar trends: Polymorphs IA and IB had onset temperatures of approximately 193.82°C and 192.88°C, respectively, with heat of fusion of 112.12 J/g and 110.98 J/g. Polymorphs IIA and IIB also exhibited comparable melting points, with onset temperatures of 196.92°C and 195.51°C, respectively. Polymorph III had a slightly lower melting point (193.94°C) and heat of fusion of 108.66 J/g, whereas Polymorph IV possessed the highest heat of fusion (116.54 J/g) with an onset temperature of 194.16°C. Polymorphs VA, VB, and VC showed similar thermal characteristics, with onset temperatures of approximately 194°C and heat of fusion values of 112.52 J/g and 114.08 J/g. These differences in the melting points and heat of fusion between the polymorphs indicate differences in their molecular packing and lattice energy. The same has been observed for other drugs, such as salmeterol xinafoate, where two polymorphs (SX-I and SX-II) have different fusion enthalpies and melting behaviors[6], and for paracetamol polymorphs I and II, which have different thermal characteristics, with polymorph II converting to polymorph I before melting.[7] These thermal characteristics are important for the study of phase transitions and relative stabilities between polymorphs, as in the case of aprepitant polymorphs I and II, which show very minor differences in melting points and enthalpies of fusion.[8]

PXRD was performed to study the crystalline characteristics of the polymorphs. A sharp peak in the XRD patterns revealed a crystalline character, whereas a lack of peaks indicated an amorphous nature. The relative peak intensities were computed, and the interplanar spacing was calculated using the formula $n\lambda = 2d \sin\theta$. The interplanar spacings of the strongest reflections of a given polymorph were compared to those of another polymorph. The differences in the PXRD diffractograms were due to the differences in the crystalline structure and molecular arrangement in the crystal lattice. For Trimipramine Maleate, the PXRD spectra indicated that polymorphs I, II, III, IV, and V differed in crystalline patterns, with Polymorphs IIIA and IIB indicating similar patterns. Likewise, for Clomipramine Hydrochloride, the PXRD spectra revealed different crystalline patterns for polymorphs I, II, III, IV, and V, with Polymorphs IA-IB, IIA-IIB, and VA-VB-VC having identical crystalline patterns. This finding is in line with the belief that polymorphs with various crystalline forms of the same substance have different X-ray diffraction patterns because of their different crystal structures.[6,9]

Notably, certain polymorphs of the two compounds shared identical PXRD patterns (IIIA-IIB for Trimipramine Maleate; IA-IB, IIA-IIB, and VA-VB-VC for Clomipramine Hydrochloride). This indicates that these groups or pairs of polymorphs have either very closely related crystal forms or packing topologies, but they differ only trivially in forms that are impossible to discern simply by PXRD.[9]

CONCLUSION

This research effectively synthesized and characterized various polymorphs of Trimipramine Maleate and Clomipramine Hydrochloride employing different solvents, solvent blends, and recrystallization methods. FTIR, DSC, and PXRD analyses validated the presence of polymorphs, with IR peak shifts and heat of fusion differences observed for every polymorph. The PXRD analysis identified five polymorphs for each compound, further validating the presence of varying molecular arrangements in the crystal lattice.

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