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RESEARCH ARTICLE

A Study on the Synthesis and Characterization of Various Polymorphic Forms of Carbinoxamine Maleate and Orphenadrine Citrate

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ABSTRACT

Pharmaceutical polymorphisms can affect the solubility, stability, and bioavailability of compounds. The objective of this study was to synthesise and characterise different polymorphic forms of carbinoxamine maleate and orphenadrine citrate, which are antihistaminic drugs, to assess their physicochemical variations. This study was conducted at the Krupanidhi College of Pharmacy, Bangalore. Recrystallisation with various solvent systems and cooling methods was used to synthesise polymorphs of carbinoxamine maleate and orphenadrine citrate. Characterisation was carried out using Fourier Transform Infrared Spectroscopy, Differential Scanning Calorimetry, and Powder X-ray Diffraction, assisted by melting point, ^{1}H NMR, and mass spectrometry. Different polymorphic forms were successfully synthesised and characterised. Carbinoxamine maleate polymorphs showed melting point peaks ranging from 119.98°C to 122.54°C with enthalpies from -3.63 to -105.93 J/g, while orphenadrine citrate showed a peak at 139.27°C with an enthalpy of -129.51 J/g. PXRD confirmed structural variation, with major peaks for polymorphs ranging from 4.26 Å to 4.49 Å, indicating differences in crystallinity and stability. Fourier Transform Infrared Spectroscopic analysis showed functional group uniformity among polymorphs, whereas Differential Scanning Calorimetry indicated large melting point and enthalpy variations, suggesting thermodynamic differences. Powder X-ray Diffraction characterisation differentiated polymorphs through characteristic diffraction patterns, allowing them to be grouped according to their interplanar spacing and intensity. This study presents the first comparative polymorphic profile of carbinoxamine maleate and orphenadrine citrate, highlighting their structural variability and stability, which can be utilised to maximise formulation strategies for pharmaceutical development.

Keywords: Polymorphism; Carbinoxamine maleate; Orphenadrine citrate; Antihistamine; Bioavailable

INTRODUCTION

Formulators aim to make products stable, producible, and bioavailable. Several drugs are found in more than one polymorphic form, and the choice of the most stable form guarantees a consistent bioavailability. Less stable forms can be tolerated if they provide fast absorption or increased concentrations, which is necessary for their effectiveness. If there is no therapeutic benefit, the risks associated with the less stable forms are eliminated. Huge laboratory effort goes into testing for form changes and guaranteeing the quality of the product and bioavailability[1]. Polymorphs, which are various crystalline forms of the same substance, influence physical properties such as solubility, dissolution rate, stability, bioavailability, and formulation technology[2]. Polymorphism is the capacity of a substance to crystallise in more than one arrangement, in crystalline, amorphous, solvate, and hydrate forms[3]. Polymorphs may transform from one form to another, reversibly (enantiotropic) or irreversibly (monotropic), with transition temperatures being important for determining stable forms[4]. These types influence the dissolution, bioavailability, and stability of the drug, which may affect its therapeutic action[5].

The differences in solubility between polymorphs have a major influence on bioavailability, especially in drugs with restricted dissolution. Production processes, environmental factors, and stress induce polymorphic transformation. Techniques such as X-ray diffraction, microscopy, spectroscopy, and thermal analysis identify these forms[6]. Carbinoxamine maleate, a first-generation antihistamine, is used to treat allergic and extrapyramidal symptoms of

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Parkinson's disease. It has a molecular weight of 406.87 and melting point of 117-119°C[7,8]. Orphenadrine citrate, with a molecular weight of 461.50, is used for relief from musculoskeletal pain and treatment of Parkinson's disease. It has a melting point of 136-139°C[9]. The identification and characterisation of polymorphs of drugs are imperative to guarantee their safety, stability, and efficacy during development and production. This research emphasises the synthesis of carbinoxamine maleate and orphenadrine citrate polymorphs using various solvents and ratios.

MATERIALS AND METHODS

This study was conducted in association with the R&D Laboratory of R. L. Fine Chemicals Private Limited, Yelahanka, Bangalore and in the research laboratory of the Department of Pharmaceutical Chemistry of Krupanidhi College of Pharmacy, Bangalore. DSC and 1H NMR spectral data of the synthesised compounds were recorded using an advanced analytical instrumentation facility at the Indian Institute of Science (IISc), Bangalore. All reagents and chemicals used for the project were of analytical reagent (AR) and laboratory reagent (LR) quality, and were obtained from well-known sources such as Lancaster, Sigma, NR Chem, Rolex, S.D. Fine Chem Ltd., and Merck.

The preparation of various polymorphs of carbinoxamine maleate and orphenadrine citrate requires multiple recrystallisation processes. The drug (10 g) was weighed and transferred to a conical flask, and a small amount of solvent was added, which was heated in a water bath. More solvent was gradually added until the drug was completely dissolved in the solution, producing a supersaturated solution. The solution was then filtered to remove the particulate matter. If the solution was coloured, a pinch of charcoal was added and boiled for 30 min before filtration using a high-flow filtration bed under suction. If any precipitation occurred, the solution was further boiled until clear, and then concentrated by evaporating half of the solvent.

Different pure solvents and mixtures of solvents, such as IPA, methanol, acetone, acetonitrile, and blends, such as IPA: $CHCl_3$, MEK: methanol, and acetone: ethyl acetate, were employed for recrystallisation. Two cooling procedures were used: slow cooling, in which the flask was cooled slowly to room temperature and subsequently cooled to 0°C in an ice-salt bath, which was rapidly cooled by immersion in an ice-salt bath or with dry ice in methanol. Stirring was continued during the process to obtain uniform crystallisation, and the crystallised material was filtered at cold temperatures and washed using the mother liquor or fresh solvent at temperatures less than 0°C.

Several analytical methods have been used to ascertain the purity and identity of polymorphs. Melting points were determined by Fourier Transform Infrared Spectroscopy (FTIR) using a SHIMADZU FTIR Affinity 1 spectrometer using the KBr pellet method. Thermal analysis was conducted with Pyris Differential Scanning Calorimetry (DSC), and Powder X-ray Diffraction (PXRD) patterns were used to detect distinct polymorphic forms. Additional verification of molecular weight, formula, and composition was obtained from credible sources, such as the Merck Index and Fluka.

To prepare carbinoxamine maleate, the reaction entailed the preparation of parachlorophenylmagnesium bromide was prepared by adding para-bromochlorobenzene to a magnesium suspension in anhydrous ether and then adding 2-pyridinealdehyde. Following the reaction and workup, the product was treated with sodium and 2-dimethyl-aminoethyl chloride to obtain the final compound. Carbinoxamine maleate was prepared with a yield of 64.81% and characterised by melting point, IR, NMR, and mass spectrometry. Likewise, Orphenadrine citrate was prepared by reacting 2-methyl benzhydrylbromide with beta-dimethyl aminoethanol, and then subjecting the resulting product to distillation and crystallisation with citric acid to give a white crystalline solid with a melting point of 137-139°C.

RESULTS

The polymorphs of carbinoxamine maleate and the crystalline forms of orphenadrine citrate are shown in Table 1 .

Polymorphs of carbinoxamine maleate and orphenadrine citrate were identified using three distinct and complementary analytical techniques: Fourier Transform Infrared Spectroscopy (FTIR), Differential Scanning Calorimetry (DSC), and Powder X-ray Diffraction (PXRD). Table 2 compares the IR absorption bands of carbinoxamine maleate and orphenadrine citrate for the functional groups in different polymorphs and samples. For Carbinoxamine maleate, key functional groups like the carbonyl group (C=O) of the acid (-COOH) have persistent absorption at around 1701 cm^{-1} in all polymorphs, whereas O-H stretching vibration occurs at about 3428-3429 cm^{-1}. Aromatic ring vibrations (C=C) are slightly different, with the C=N stretch always at 1578-1580 cm^{-1} for all polymorphs. In Orphenadrine citrate, the carbonyl stretch (C=O) is at 1728-1730 cm^{-1}, and the O-H stretching is seen in a higher range of 3300-2750 cm^{-1}. The aromatic ring and alkyl ether vibrations were the same in all samples, with C-H stretches at 3028-3048 cm^{-1}, signifying consistent functional group features in both molecules.

The DSC results in Table 3 show the thermodynamics of the different polymorphs of carbinoxamine maleate and orphenadrine citrate. In the case of carbinoxamine maleate, the base polymorph initiates at 116.81°C, peaks at 119.98°C, and has an enthalpy of fusion of -102.37 J/g. Polymorph I has values that are slightly greater, with a peak at 122.54°C and an enthalpy of -103.01 J/g. Polymorphs II A and II B showed various transitions with enthalpies from -3.63 to 105.93 J/g. Orphenadrine citrate shows a greater onset (137.54°C), peak (139.27°C), and enthalpy of -129.51 J/g. S-2 and S-7

Table 1: Carbinoxamine maleate and orphenadrine citrate

Polymorphs of Carbinoxamine maleate						
Type of poly-morph	**Recrystallized from**	**Quantity of solvent needed (ml)**	**Drug consumed (gm)**	**Yield (%)**	**Melting point (°C)**	**% of polymorph**
I	IPA: CHC13	11	10	75	116-119	100
II A	MIBK: MEK	22	8	87.5	117-119	397
II B	MEK: Methanol	11	10	83	116-119	595
III A	IPA: Water	5	10	70	116-119	100
III B	MIBK: DCM	27	8	81.25	117-119	100
III C	Acetone: E.A	24	7	78.57	116-119	100

Different crystalline forms of Orphenadrine citrate					
Compound code	**Recrystallized from**	**Quantity of solvent needed (ml)**	**Drug consumed (gm)**	**Yield (%)**	**Melting point (°C)**
S-1	Acetonitrile	120	7.2	87.5	136-139
S-2	Methanol	20	7.8	65.38	136-138
S-3	Methanol: Acetonitrile	20	13.6	43.38	136-138
S-4	Methanol: E.A.	35	13.2	49.24	136-139
S-5	Methanol: MEK	28	12	49.16	136-139
S-6	Methanol: MIBK	20	10	57	136-138
S-7	Toluene: Methanol	30	11.6	71.41	136-138
S-8	Methanol	45	15	48.66	136-139

displayed comparable thermal behaviours, with enthalpies of approximately -129.7 J/g. These variations correspond to the differences in the crystallinity and stability of each polymorph.

X-ray Powder Diffraction analyses of carbinoxamine maleate and its polymorphs revealed characteristic diffraction patterns, enabling differentiation between the polymorphs according to their interplanar spacings (d) and relative intensities (I/T). Polymorph I had a strong peak at 4.49 Å, whereas Polymorph II A possessed a broad peak at 4.38 Å, and Polymorph II B possessed peaks at 4.40 Å. Polymorphs III A, III B, and III C show characteristic diffraction patterns with significant peaks at 4.26 Å, 4.28 Å, and 4.26 Å, respectively. Such variations in the peak positions and intensities facilitate the identification and differentiation of the different polymorphic forms of carbinoxamine maleate. (Table 4)

DISCUSSION

The findings of the current study on the carbinoxamine maleate and orphenadrine citrate polymorphs were identified and characterised using FTIR, DSC, and PXRD. In the present study, FTIR was used to identify the functional groups in the polymorphs, such as the residual absorption bands for carbonyl (C=O) and O-H stretches for carbinoxamine maleate and orphenadrine citrate. The characteristics of the aromatic and alkyl ether regions, with variations in these regions, were used to differentiate between polymorphs.

Thermal analysis using differential scanning calorimetry (DSC) has been extensively applied to investigate the thermal behaviour of polymorphs, including enthalpy changes and melting points. PXRD analysis, a vital tool for polymorph differentiation, demonstrated distinctive diffraction patterns for the carbinoxamine maleate polymorphs. This supports the strength of PXRD as a tool for distinguishing polymorphs based on their crystallinity and stability. Park et al. described the use of Differential Scanning Calorimetry (DSC) to determine the solubilities of different polymorphs. This study shows that DSC is an effective technique for assessing the thermal behaviour of polymorphs, including their melting points and enthalpy of fusion. By analysing these properties, the authors established a relationship between the polymorphic form and its solubility, which is essential for optimising the drug formulation and bioavailability[10].

The findings of the present study highlight the necessity of polymorph characterisation in the development of medicines, as individual polymorphs may have varying solubility, stability, and bioavailability, thereby directly reflecting the efficacy and safety of the medicine. These outcomes are similar to those of Brittain, where the pivotal significance of polymorphism in pharmaceutical systems, especially of solubility and bioavailability, was

Table 2: Comparison of IR values of carbinoxamine maleate and orphenadrine citrate

Carbinoxamine maleate								
Group	Polymorph Range	STD	I	II A	II B	III A	III B	III C
Acid (-COOH)								
C=O	1710-1700	1701	1701	1701	1701	1701	1701	1701
O-H	3500-3400	3429	3428	3429	3428	3428	3428	3429
Aromatic ring								
C=C	1600-1400	1570 1467	1489 1473	1543 1473	- 1473	1543 1473	1543 1473	1543 1473
C=N	1600-1550	1580	1582	1578	1580	1578	1578	1578
C-H	3200-3050	3130 3051	3051 -	3051 -	3051 -	3088 3051	3051 -	3051
C-Cl	1100-1090	1107 1096	1107 1094	1107 1096	1107 1094	1107 1096	1107 1096	1107 1096
Alkyl ether								
Alkyl-O	1300-1200	1360	1362	1358	1360	1358	1358	1358
Aliphatic								
C-H	3000-2900	2961 2924	2963 2920	2963 2920	2963 2920	2963 2918	2963 2918	2963 2920
C-N	1200-1100	1196	1194	1196	1196	1196	1196	1196
C=C	1400-1600	1620	1618	1620	1620	1620	1620	1620

Orphenadrine citrate										
Group	Sample Range	STD	S-1	S-2	S-3	S-4	S-5	S-6	S-7	S-8
Acid (-COOH)										
C=O	1710-1700	1728	1730	1728	1730	1730	1730	1728	1728	1730
O-H	3300-2700	3300-2750	3300-2750	3300-2750	3300-2750	3300-2750	3300-2750	3300-2750	3300-2750	3300-2750
Aromatic ring										
C=C	1600-1400	1429	1431	1429	1429	1429	1431	1429	1429	1429
C-H	3200-3050	3048 3028	3048 3028	3048 3028	3048 3028	3048 3028	3048 3028	3048 3030	3048 3028	3048 3028
Alkyl ether										
Alkyl-O	1300-1200	1221	1223	1221	1223	1221	1221	1221	1221	1223
Aliphatic										
C-H	3000-2800	2970 2891	2976 2891	2974 2893	2974 2893	2976 2893	2976 2891	2974 2893	2974 2893	2974 2893
C-N	1200-1100	1288	1288	1288	1288	1288	1288	1288	1288	1288

Table 3: Thermal data carbinoxamine maleate and orphenadrine citrate

Polymorphs	Onset (°C)	Peak (°C)	End set (°C)	Enthalpy of fusion (J/g)
Carbinoxamine maleate	116.81	119.98	122.87	-102.37
Polymorph I	120.54	122.54	123.75	-103.01
Polymorph IIA	118.92	120.18/121.57	121.02/123.17	-3.63/105.93
Polymorph IIB	119.30/120.56	120.86/122.79	121.58/124.20	-5.75/104.04
Polymorph IIIA	117.35	121.14	123.40	-107.06
Polymorph IIIB	116.46	121.41	123.64	-106.31
Polymorph IIIC	118.65	121.83	124.34	-107.91
Orphenadrine citrate	137.54	139.27	141.42	-129.51
S-2	134.73	138.39	141.19	-129.84
S-7	135.04	138.70	141.49	-129.70

Table 4: Comparisons of relative intensities and interplanar spacings derived from Powder pattern of carbinoxamine maleate and their different polymorphs

Type - 01		**Type - 02**				**Type - 03**					
I		IIA		IIB		IIIA		IIIB		IIIC	
I/T	d	I/T	d	I/T	d	I/T	d	I/T	d	I/T	d
100	4.49	100	4.38	100	4.40	100	4.26	100	4.28	100	4.26
15.6	4.39	26.9	4.05	19.5	4.05	23.5	3.90	24.2	3.90	42.5	3.88
23.8	4.29	34.3	3.80	54.4	3.81	34.2	3.49	36.6	3.49	21.6	3.51
7.4	3.82	19.2	3.42	18	3.42	18.9	3.42	10.4	3.42	20.7	3.41
13	3.00	18.9	3.19	16.8	3.20	13.5	3.12	6.4	3.12	12.2	3.11
4.5	3.56	10.6	2.98	21.3	2.98	13.9	2.89	7.2	2.81	14.7	2.81

accentuated[11]. As indicated by Tiwari et al., PXRD and DSC are critical analytical tools for polymorph quantitation and determining the implications of polymorphs in drug formulations. The authors explored the ability of this technique to accurately measure the proportions of various polymorphs in the drug samples[12].

CONCLUSION

In conclusion, the present study successfully synthesised and characterised several polymorphic forms of carbinoxamine maleate and orphenadrine citrate and identified distinct differences in their thermal and structural properties. These results highlight the significance of polymorphic screening during pharmaceutical development, because polymorphs affect drug performance, stability, and formulation outcomes.

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