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POLYMORPH AND SALTS OF ACTIVE PHARMACEUTICAL INGREDIENT DICLOFENAC ACID

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Keywords:

diclofenac salts; organic base; DSC and IR; X-ray diffractogram

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ABSTRACT

The objectives of this study were to prepare and characterize the novel salts diclofenac and to study the polymorph present in novel salts of diclofenac. Remarkably two new salts i.e. Diclofenac hemi Ethylene diamine and Diclofenac hemi piperazine were discovered in this study.Along with these new routes were searched to prepare already existing Diclofenac Piperidine and Diclofenac N-methylmorpholine salts.Novel salts were prepared with aim of enhancing their dissolution rates and their bioavailability. DSC, IR and PXRD were used to characterize the novel salts form. Novel salts with distinct melting. DSC, FTIR and XRPD data was obtained. The study indicates that the improved aqueous solubility of the novel salts leads to improved dissolution of DiclofenacThus; the new salts are a viable alternative solid form that can improve the dissolution rate and bioavailability of poorly soluble drugs. SubsequentlyDiclofenac salts containing the organic amines have been prepared and characterized by Infrared spectroscopy and differential scanning calorimetry. Crystallinity of the Diclofenac salts was characterized by using X-ray diffraction.

INTRODUCTION

Diclofenac is a potent anti-inflammatory drug,marketed since 1970, which wasproposed as amodel compound, comprehensive of the best performancesof the few drugs of the same class,developed after the introduction of acetyl salicylic acid in 1898.[1] After this proposal it was soonevident that, besides its favorable properties relatedto absorption, therapeutic efficacy andlimited side effects, solubility of the drug originatedproblems; this way it was suggested theutilization of diclofenac as a salt;[2] and, to supporthow the solubility of diclofenac still remains anintriguing problem, it must be rememberedthat this drug is present on the pharmaceuticalmarket as four different salt forms and theresearch concerning salts of diclofenac is stillcontinuing, examining a large variety of saltforming agents, such as aliphatic amines,[3–13] and heavy metal ions.[14–17] The studies revealedinteresting behavior of some of these salts, both inthe solid state[7,8] and as solute,[10,18–23] and stimulatea systematic investigation on this topic.In previous studies, we largely examined theproperties of the diclofenac salt with the baseN-(2-hydroxyethyl) pyrimidine,[7,8] used for preparingtopical formulations (gel and patch), and thethermal behavior of sodium and potassium diclofenacsalts;[24] following this last study, in this studywe examined the nature of the salts formed bydiclofenac with organic bases such as amines (primary, secondary and tertiary)cationsusing differential scanning calorimetry (DSC) and X-ray diffractometricanalysis (XRD).Also the thermal behavior of diclofenac ammoniumsalt is discussed, as an example of the saltsformed with volatile bases.Pharmaceutical salts are often formulated forpoorly solubleionisable drugs, but the selection ofa suitable salt forming agent is often left to theexperience of the researcher; actually each saltform of a given drug displays peculiar behavior,both in the solid state and in solution, difficult topreview and describe without experimental evidences.

MATERIAL AND METHODS:

Material:

Diclofenac sodium salt was a gift sample from Aarti Drugs., they were of pharmaceutical grade. Ethylene diamine, Piperidine, N-methylmorpholine and Piperazine base were commercial samples (Merck India).

Methods: Example 1

Preparation of [2-[(2, 6-dichlorophenyl) amino]phenyl]acetic acid (Diclofenac acid)

2-(2-(4-((4-chlorophenyl)(phenyl)methyl)piperazin-1-yl)ethoxy)acetic acid hydrochloride (50 g) in 6.5% w/v aqueous sodium hydroxide (200 ml) was stirred at room temperature to have clear solution. Then the reaction mixture was further diluted with water (300 ml) accompanied by adjusting the pH of the reaction solution around 9.0 with concentrated hydrochloric acid, washed the resulted reaction mass with ethyl acetate. The pH of the separated aqueous layer was further adjusted to 4.0 with concentrated hydrochloric acid and extracted with dichloromethane. Then the combined dichloromethane layer was evaporated under vacuum to get the required Diclofenacacid solid (40.5 g).

Example 2

Preparation of Diclofenac Piperidine salt

Acetone (20.0 ml) was added to 2.0 g (6.8 mmol) diclofenac acid and the mixture was stirred at room temperature to obtain a light yellow coloured solution. A solution of 0.58 g (6.8 mmol) Piperidine in 10.0 ml acetone was added over the course of 2 min in diclofenac acid solution. It gave a clear solution and the reaction mixture was stirred. Solid was precipitated and it was further stirred for 2 h then filtered, washed with 20 ml acetone to give white colour solid. Wet

solid was dried on a rotary evaporator at 45-50° C./3 mbar for 6 h to give 1.92 g (74.60% yield) of a white solid.

Example 3

Preparation of Diclofenac Piperidine salt

Acetonitrile (40.0 ml) was added to 2.0 g (6.8 mmol) diclofenac acid and the mixture was stirred at room temperature to obtain a light yellow coloured solution. A solution of 0.58 g (6.8 mmol) Piperidine in 10.0 ml acetonitrile was added over the course of 2 min in diclofenac acid solution. It gave a clear solution and the reaction mixture was stirred. Solid was precipitated and it was further stirred for 2 h then filtered, washed with 30 ml acetonitrile to give white colour solid. Wet solid was dried on a rotary evaporator at 45-50° C./3 mbar for 6 h to give 1.96 g (76.11% yield) of a white solid.

Example 4

Preparation of Diclofenac N- methyl morpholine salt

Acetone (20.0 ml) was added to 2.0 g (6.8 mmol) diclofenac acid and the mixture was stirred at room temperature to obtain a light yellow coloured solution. A solution of 0.68 g (6.8 mmol) N-methyl morpholine in 10.0 ml acetone was added over the course of 2 min in diclofenac acid solution. It gave a clear solution and the reaction mixture was stirred. Solid was not precipitated so further cooled to 2-4 °C and kept for 48 h. Solid was precipitated out, filtered, washed with 20 ml acetone to give white colour solid. Wet solid was dried on a rotary evaporator at 45-50° C./3 mbar for 5 h to give 1.87 g (69.69% yield) of a white solid.

Example 5

Preparation of Diclofenac N- methyl morpholine salt

Acetonitrile (20.0 ml) was added to 2.0 g (6.8 mmol) diclofenac acid and the mixture was stirred at room temperature to obtain a light yellow coloured solution. A solution of 0.68 g (6.8 mmol) N-methyl morpholine in 10.0 ml acetonitrile was added over the course of 2 min in diclofenac acid solution. It gave a clear solution and the reaction mixture was stirred. Solid was not precipitated so further cooled to 2-4 °C and kept for 48 h. Solid was precipitated out, filtered, washed with 20 ml acetonitrile to give white colour solid. Wet solid was dried on a rotary evaporator at 45-50° C./3 mbar for 5 h to give 1.7 g (63.36% yield) of a white solid.

Example 6

Preparation of Diclofenac N- methyl morpholine salt

Ethyl acetate (40.0 ml) was added to 2.0 g (6.8 mmol) diclofenac acid and the mixture was stirred at room temperature to obtain a light yellow coloured solution. A solution of 0.68 g (6.8 mmol) N-methyl morpholine in 10.0 ml ethyl acetate was added over the course of 2 min in diclofenac acid solution. It gave a clear solution and the reaction mixture was stirred. Solid was not precipitated so further cooled to 2-4 °C and kept for 48 h. Solid was precipitated out, filtered, washed with 20 ml ethyl acetate to give white colour solid. Wet solid was dried on a rotary evaporator at 45-50° C./3 mbar for 5 h to give 1.83 g (68.20% yield) of a white solid.

Example 7

Preparation of Diclofenac hemi ethylene diamine salt

Acetonitrile (40.0 ml) was added to 2.0 g (6.8 mmol) diclofenac acid and the mixture was stirred at room temperature to obtain a light yellow coloured solution. A solution of 0.21 g (3.4 mmol) ethylene diamine in 10.0 ml acetonitrile was added over the course of 2 min in diclofenac acid solution. It gave a clear solution and the reaction mixture was stirred. Solid was precipitated and it was further stirred for 2 h then filtered, washed with 30 ml acetonitrile to give white colour solid. Wet solid was dried on a rotary evaporator at 45-50° C./3 mbar for 6 h to give 1.97 g (89.37% yield) of a white solid.

Example 8

Preparation of Diclofenac hemi ethylene diamine salt

Ethyl acetate (40.0 ml) was added to 2.0 g (6.8 mmol) diclofenac acid and the mixture was stirred at room temperature to obtain a light yellow coloured solution. A solution of 0.21 g (3.4 mmol) ethylene diamine in 10.0 ml ethyl acetate was added over the course of 2 min in diclofenac acid solution. It gave a clear solution and the reaction mixture was stirred. Solid was precipitated and it was further stirred for 2 h then filtered, washed with 30 ml ethyl acetate to give white colour solid. Wet solid was dried on a rotary evaporator at 45-50° C./3 mbar for 6 h to give 2.03 g (92.07% yield) of a white solid.

Example 9

Preparation of Diclofenac hemi Piperazine salt

Acetone (20.0 ml) was added to 2.0 g (6.8 mmol) diclofenac acid and the mixture was stirred at room temperature to obtain a light yellow coloured solution. A solution of 0.29 g (3.4 mmol) Piperazine in 10.0 ml acetone was added over the course of 2 min in diclofenac acid solution. It gave a clear solution and the reaction mixture was stirred. Solid was precipitated and it was further stirred for 2 h then filtered, washed with 20 ml acetone to give white colour solid. Wet solid was dried on a rotary evaporator at 45-50° C./3 mbar for 6 h to give 1.50 g (65.41% yield) of a white solid.

Example 10

Preparation of Diclofenac hemi Piperazine salt

Acetonitrile (40.0 ml) was added to 2.0 g (6.8 mmol) diclofenac acid and the mixture was stirred at room temperature to obtain a light yellow coloured solution. A solution of 0.29 g (3.4 mmol) Piperazine in 10.0 ml acetonitrile was added over the course of 2 min in diclofenac acid solution. It gave a clear solution and the reaction mixture was stirred. Solid was precipitated and it was

further stirred for 2 h then filtered, washed with 30 ml acetonitrile to give white colour solid. Wet solid was dried on a rotary evaporator at 45-50° C./3 mbar for 6 h to give 1.90 g (83.03% yield) of a white solid.

Example 11

Preparation of Diclofenac hemi Piperazine salt

Ethyl acetate (40.0 ml) was added to 2.0 g (6.8 mmol) diclofenac acid and the mixture was stirred at room temperature to obtain a light yellow coloured solution. A solution of 0.29 g (0.34 mmol) Piperazine in 10.0 ml ethyl acetate was added over the course of 2 min in diclofenac acid solution. It gave a clear solution and the reaction mixture was stirred. Solid was precipitated and it was further stirred for 2 h then filtered, washed with 30 ml ethyl acetate to give white colour solid. Wet solid was dried on a rotary evaporator at 45-50° C./3 mbar for 6 h to give 2.0 g (88.53% yield) of a white solid.

1) Figures:

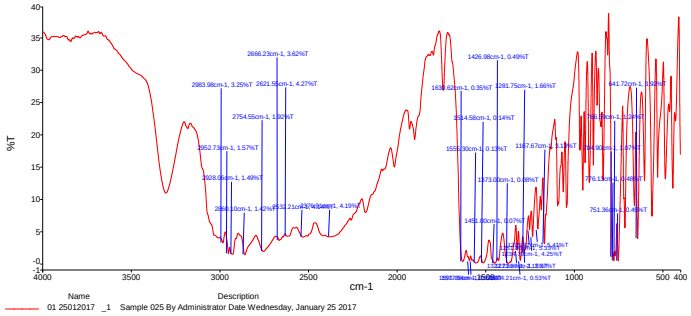

Fig. 1: IR spectra Example 2

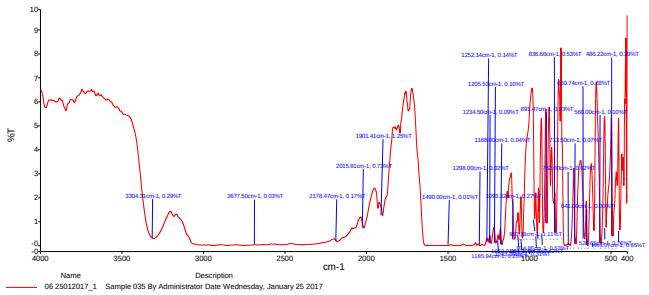

Fig. 2: IR spectra Example 3

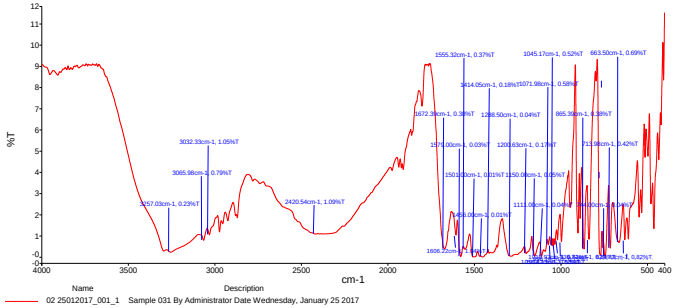

Fig. 3: IR spectra Example 4

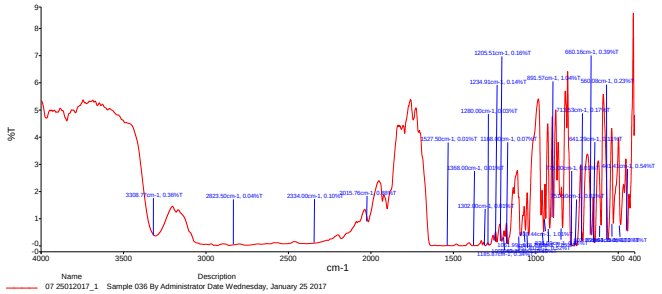

Fig. 4: IR spectra Example 5

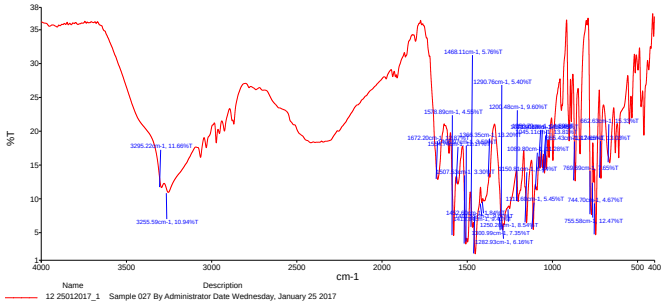

Fig. 5: IR spectra Example 6

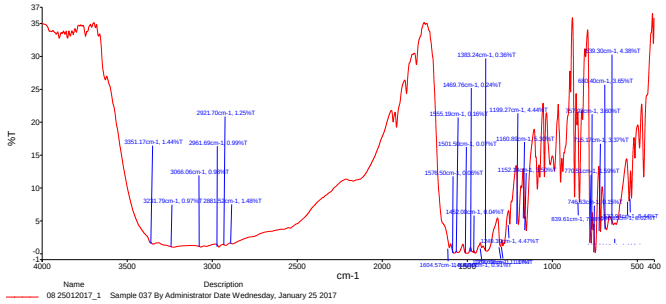

Fig. 6: IR spectra Example 7

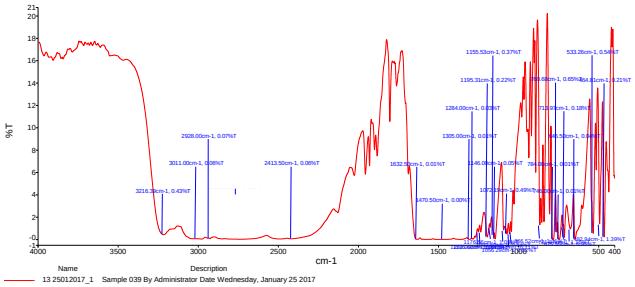

Fig. 7: IR spectra Example 8

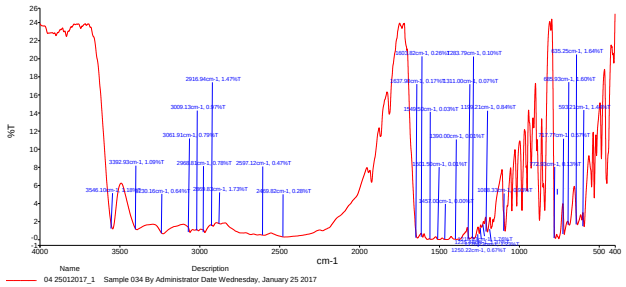

Fig. 8: IR spectra Example 9

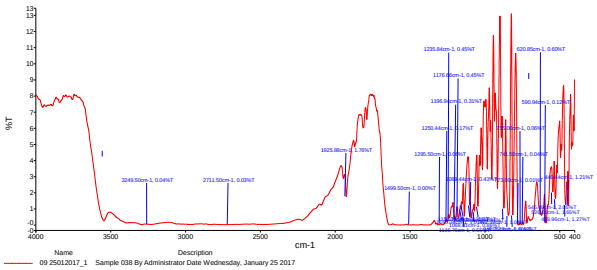

Fig. 9: IR spectra Example 10

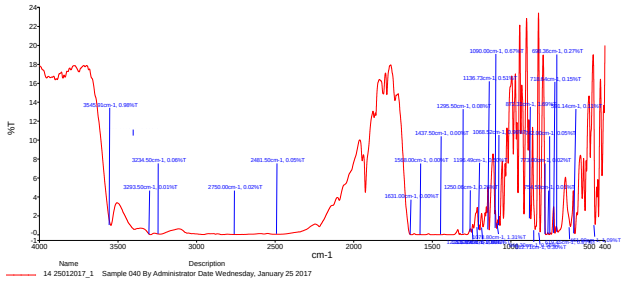

Fig. 10: IR spectra Example 11

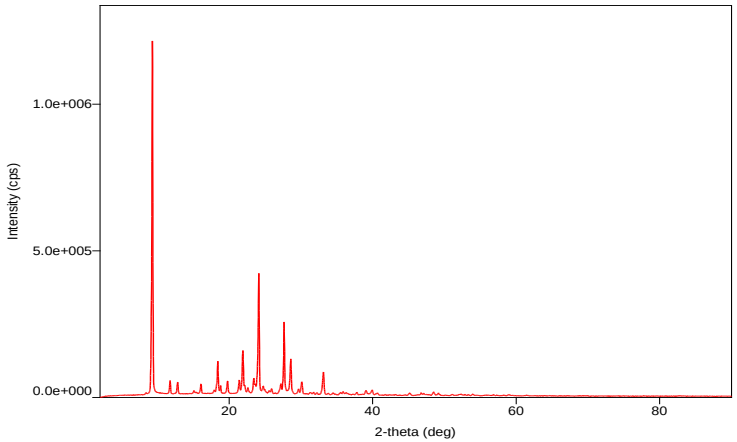

Fig. 11:XRPD spectra Example 2

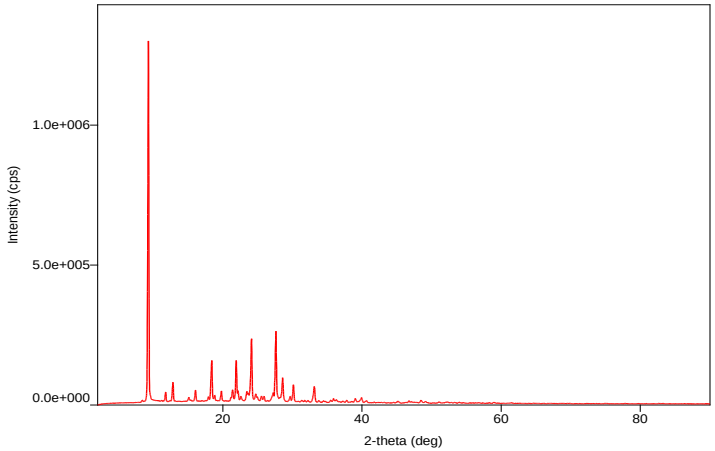

Fig. 12:XRPD spectra Example 3

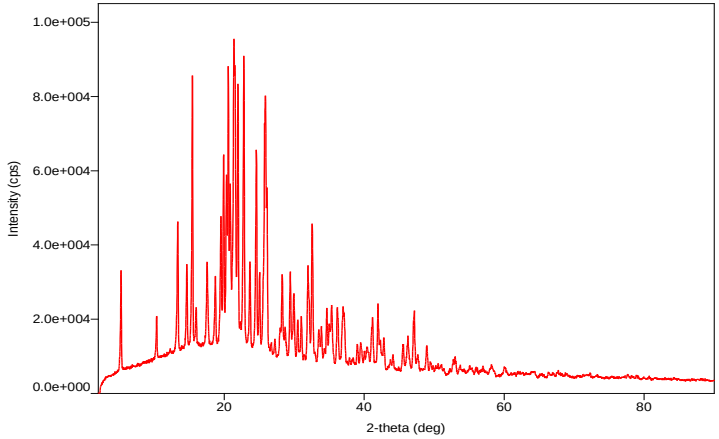

Fig. 13: XRPD spectra Example 4

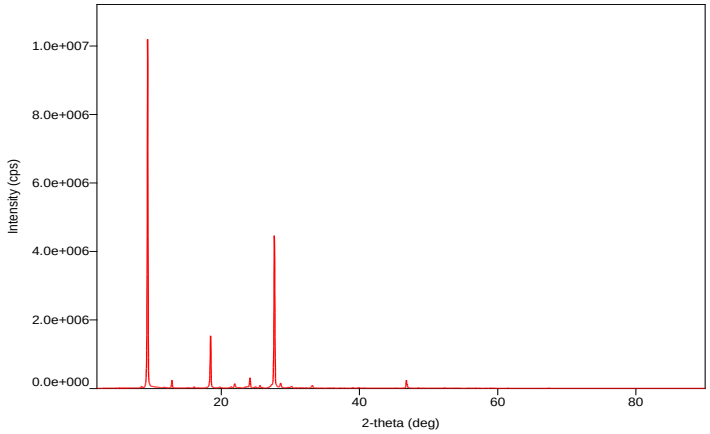

Fig. 14: XRPD spectra Example 5

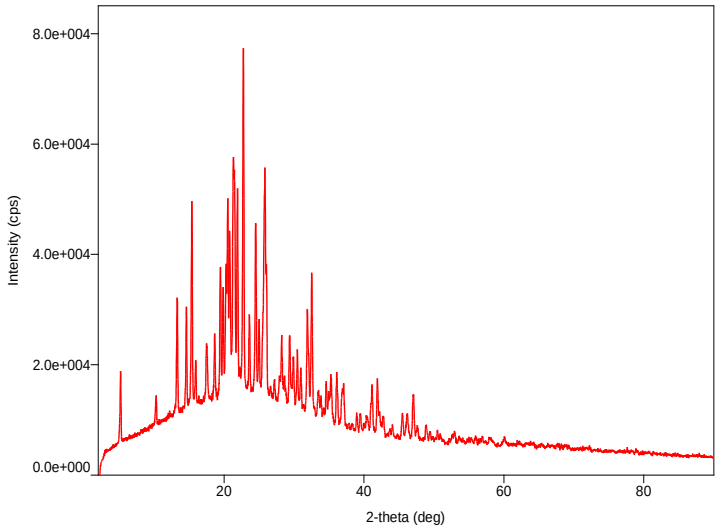

Fig. 15: XRPD spectra Example 6

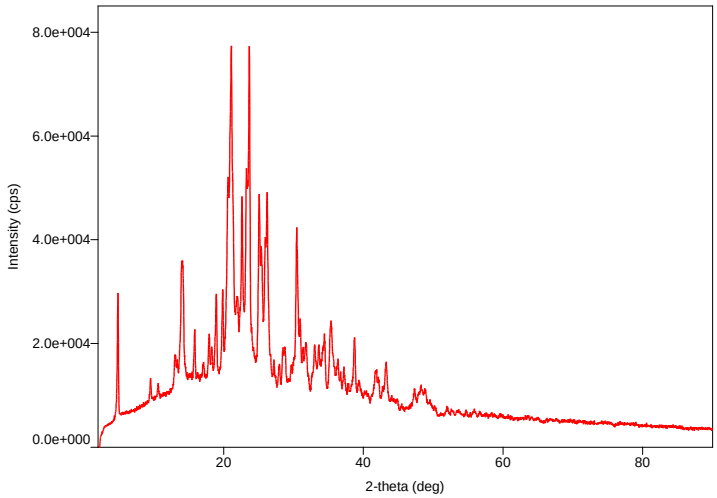

Fig. 16: XRPD spectra Example 7

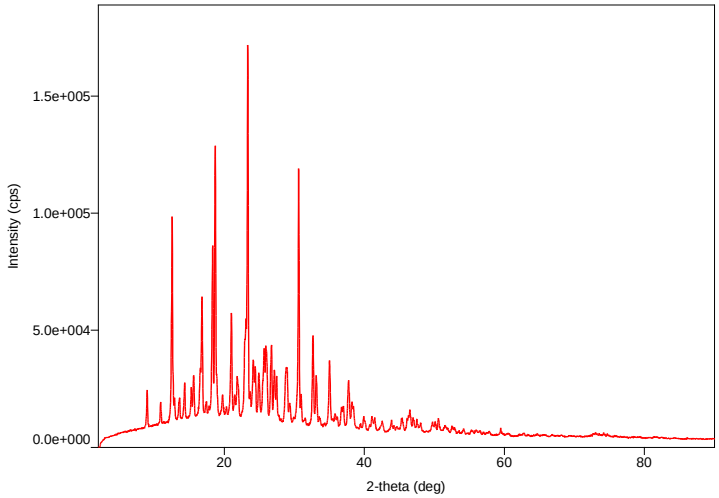

Fig. 17: XRPD spectra Example 8

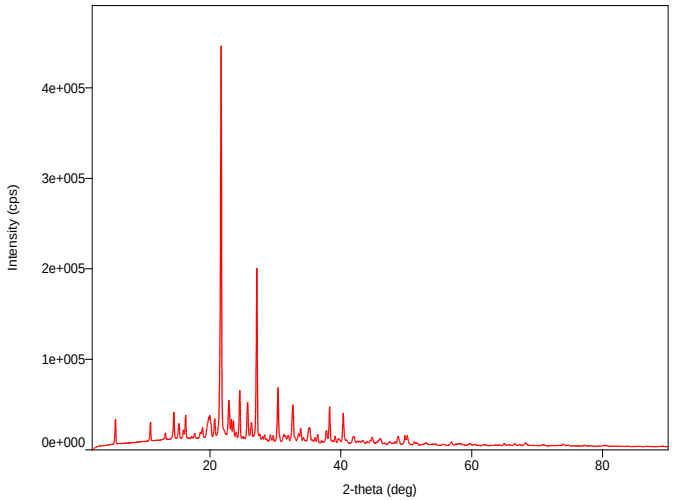

Fig. 18: XRPD spectra Example 9

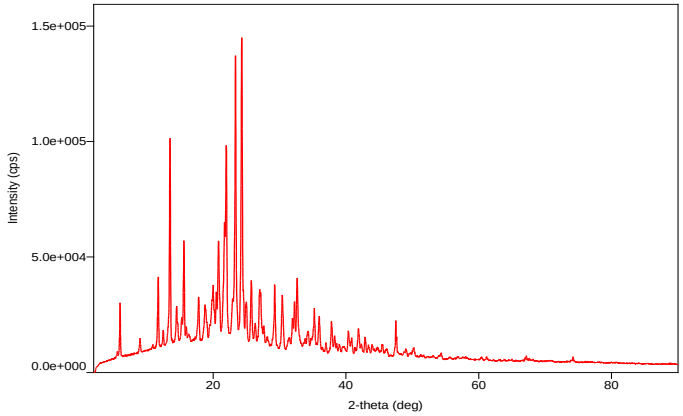

Fig. 19: XRPD spectra Example 10

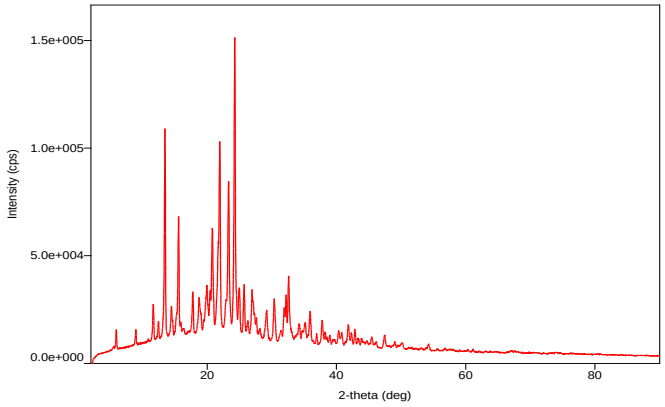

Fig. 20: XRPD spectra Example 11

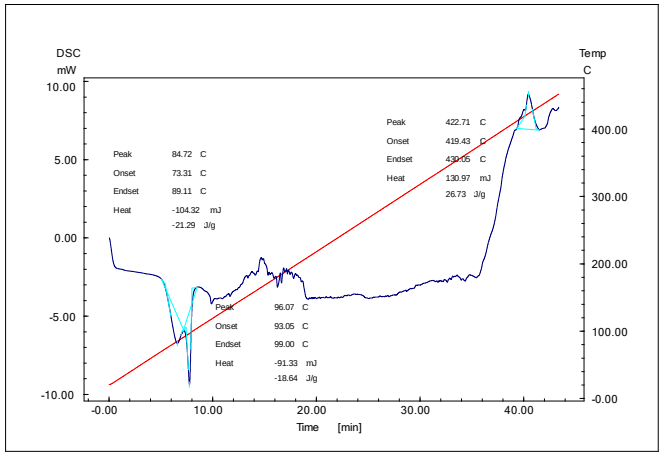

Fig. 21:DSC spectra Example 2

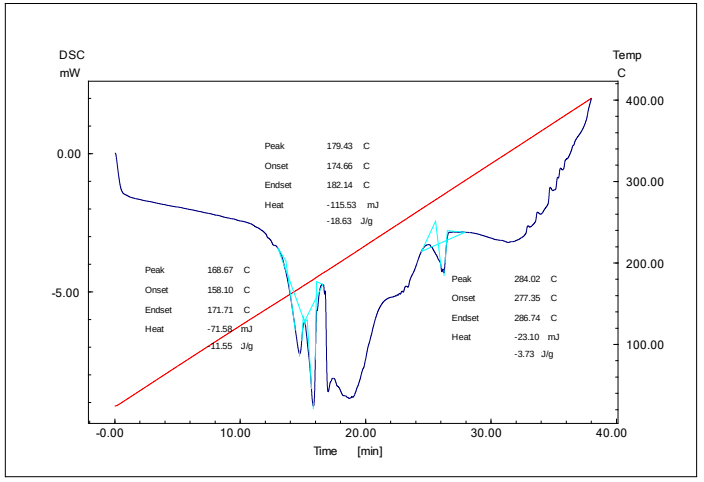

Fig. 22:DSC spectra Example 3

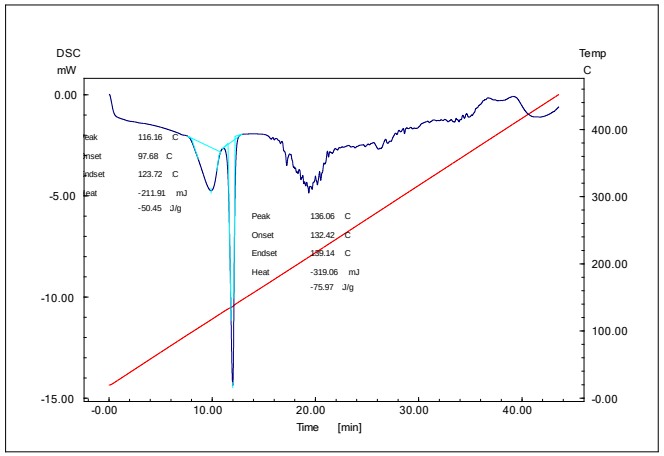

Fig. 23:DSC spectra Example 4

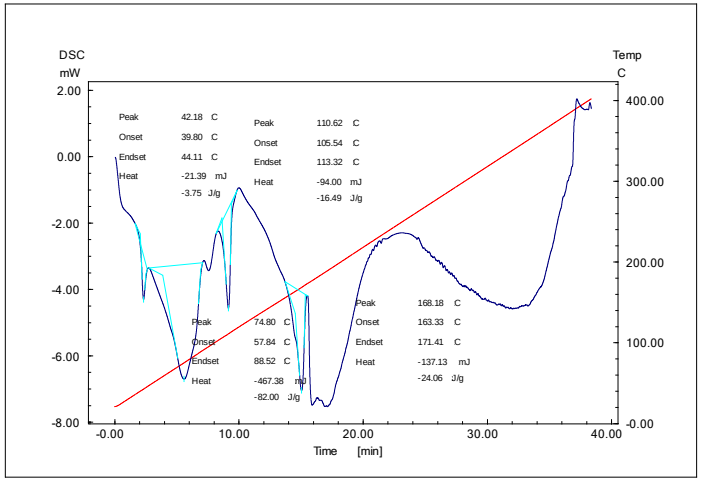

Fig. 24:DSC spectra Example 5

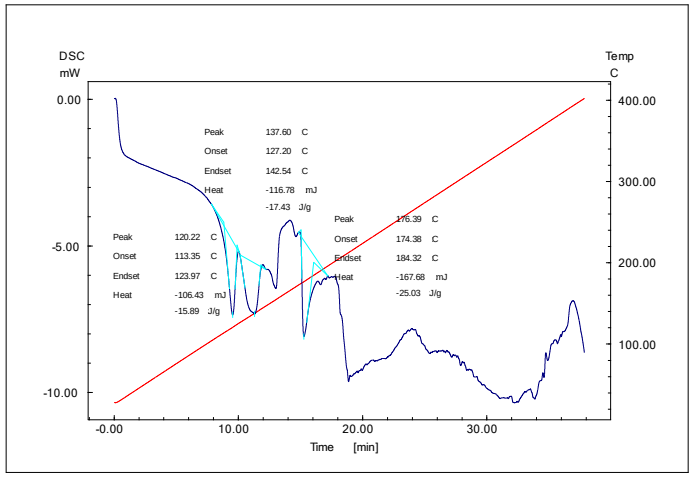

Fig. 25: DSC spectra Example 6

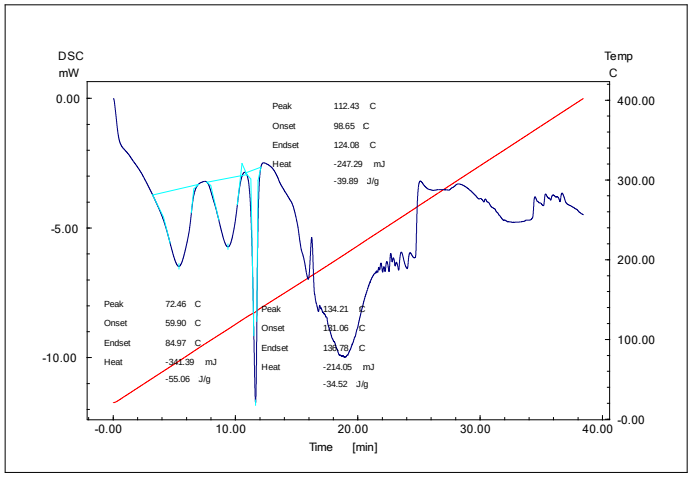

Fig. 26: DSC spectra Example 7

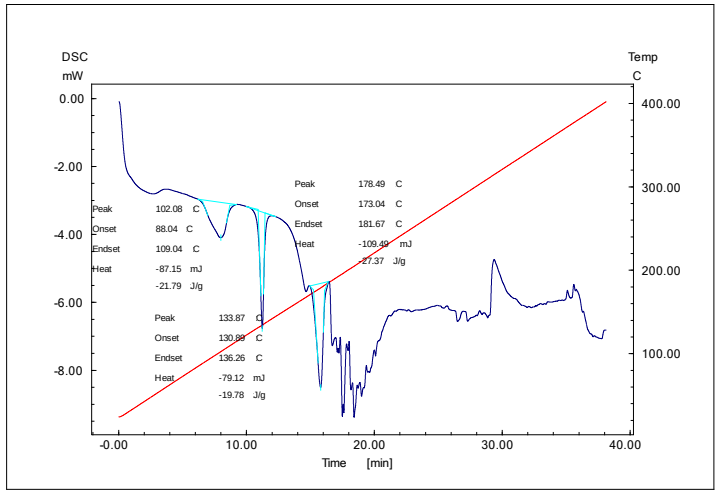

Fig. 27: DSC spectra Example 8

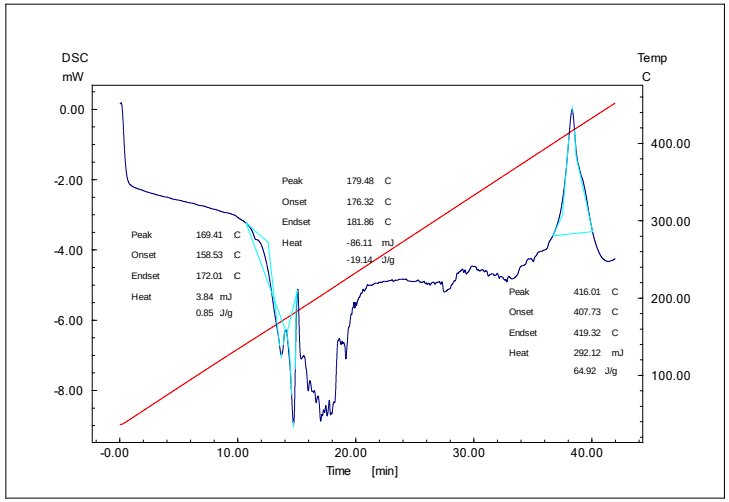

Fig. 28: DSC spectra Example 9

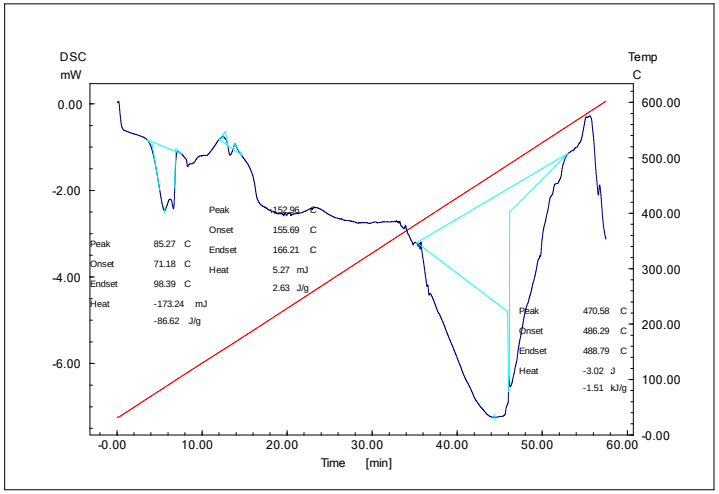

Fig. 29: DSC spectra Example 10

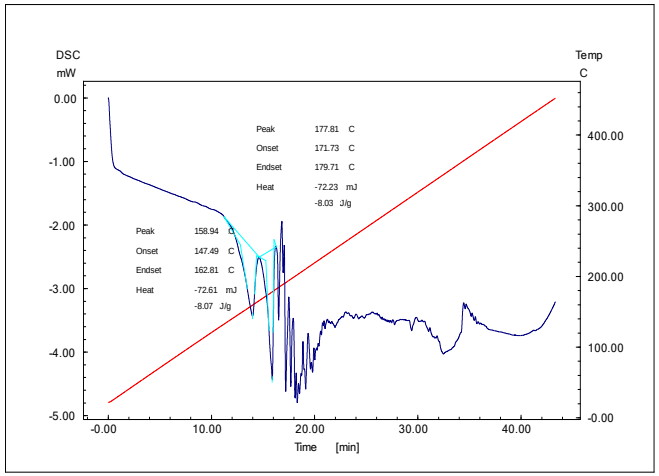

Fig. 30: DSC spectra Example 11

Analysis and characterization:

Preliminary Characterization:

Fourier transforms infrared spectroscopy:

Infrared spectra of the Diclofenac salts were recorded using a Perkin Elmer FT-IR C105627. In the range of 400- 4000cm-1with KBr pellets.

Differential scanning calorimetry:

Thermal analysis of the samples was performed on a DSC -60 Plus Shimadzu make was calibrated for temperature and enthalpy using indium. Samples (3-5 mg) were crimped in non-hermetic aluminum pans and scanned from 0 to 500 °CThe instrument was equipped with a refrigerated cooling system.

Powder X-ray diffraction:

The Diclofenac salts were analyzed by PXRD. The patterns were collected on a Miniflex 600 Chillex Mini powder diffractometer. The tube voltage and amperage were set at 40 kV and 15mA, respectively.

RESULTS AND DISCUSSION

Diclofenac, as most acidic drugs, forms a dimer in the solid state, through intermolecular hydrogen bonds of two carboxyl groups. Recently, it was also reported the existence of a polymorph of this drug, which differs only to a small extent with respect to the main structure and does not represent a form really useful for any technological purposes. The hydrophilic portion of the molecule is masked by the large hydrocarbon moieties of two phenyl groups, the mutual accommodation ofthese phenyl groups and the facing of the carboxylgroups,intermolecularly bonded, make the systemrigid and hydrophobic, moreover this closecontact of the molecules in the crystal lattice isreflected by a high melting point. All this can explainthe scarce solubility in water of acidicdiclofenac; its solubility increases only when thisstructure is destroyed by the ionization of thecarboxyl groups, as a consequence of an increaseof pH or the formation of a salt. Diclofenac canbe easily crystallized from organic solvents anddoes not appear to form solvates.

XRPD (X-Ray Powder Diffraction)

Table no.1

Sr. No.	Salts Name	Solvent used for salt preparation	Nature	Form	Fig No.
1	Diclofenac Piperidine	Acetone	Crystalline	Form - A	11
2		Acetonitrile	Crystalline	Form - B	12

3	Diclofenac N-methyl morpholine	Acetone	Crystalline	Form - A	13
4		Acetonitrile	Crystalline	Form - B	14
5		Ethyl acetate	Crystalline	Form - C	15
6	Diclofenac hemi ethylene diamine	Acetonitrile	Crystalline	Form - A	16
7		Ethyl acetate	Crystalline	Form - B	17
8	Diclofenac hemi Piperazine	Acetone	Crystalline	Form - A	18
9		Acetonitrile	Crystalline	Form - B	19
10		Ethyl acetate	Crystalline	Form - C	20

XRPD data shows that the salts formed are crystalline and in Diclofenac Piperidine two forms Form A and Form B observed. In Diclofenac N-methyl morpholine three forms, Form –A, Form-B and Form-C obtained. In Diclofenac hemi ethylene diamine two forms, form –A and Form-B obtained. In Diclofenac Piperazine three forms, Form-A, Form-B and Form-C obtained.

FTIR (Fourier-transform infrared spectroscopy)

FTIR data shows that the salts formed are crystalline and in Diclofenac Piperidine two forms Form A and Form B observed. In Diclofenac N-methyl morpholine three forms, Form –A, Form-B and Form-C obtained. In Diclofenac hemi ethylene diamine two forms, form –A and Form-B obtained. In Diclofenac Piperazine three forms, Form-A, Form-B and Form-C obtained.

DSC (Differential scanning chromatography) thermograms of salts prepared are given below.

Table no.2

Sr. No.	**Salts Name**	**Solvent used for salt preparation**	**Endotherm (°C)**			**Fig No.**
1	Diclofenac Piperidine	Acetone	84.72	96.07	--	21
2		Acetonitrile	168.67	179.43	--	22
3	Diclofenac N-methyl morpholine	Acetone	116.16	136.06	--	23
4		Acetonitrile	74.8	110.82	168.18	24
5		Ethyl acetate	74.8	110.82	168.18	25
6	Diclofenac hemi ethylene diamine	Acetonitrile	72.46	112.43	134.21	26
7		Ethyl acetate	102.08	133.87	178.49	27
8	Diclofenac hemi Piperazine	Acetone	169.41	179.48	--	28
9		Acetonitrile	85.27	152.96	--	29
10		Ethyl acetate	158.94	177.81	--	30

CONCLUSIONS

Following conclusions were drawn from the above experimental work.

1) Novel diclofenac hemi ethylene diamine salt was prepared. This salt was having crystalline nature. Two polymorphic forms i.e. Form-A and Form-B were found out.
2) Novel diclofenac hemi piperazine salt was prepared. This salt was having crystalline nature. Three polymorphic forms i.e. Form-A, Form-B and Form-C were found out.
3) Two crystalline polymorphic form of diclofenac piperidine salts i.e. Form-A and Form-B were found out.
4) Three crystalline polymorphic form of diclofenac N-methyl morpholine salts i.e. Form-A, Form-B and Form-C were found out.

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