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Polymorph And Salts Of Active Pharmaceutical Ingredients

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Abstract: ***The objective of present study was to synthesize various novel salts of Cetirizine and to search polymorphs present in novel salts. Remarkably two inorganic salts i.e. Cetirizine calcium and cetirizine lithium and two organic salts i.e. Cetirizine oxalate and Cetirizine salicylate were discovered in this study. Along with these new routes were searched to prepare already existing Cetirizine hydrochloride and Cetirizine nitrate salts. Novel salts were prepared with aim of enhancing their dissolution rates and their bioavailability. Melting point, DSC, IR and PXRD were used to characterize the novel salts to confirm the novel salt formation and polymorph present in prepared novel salts. Novel salts with distinct melting. DSC, FTIR and PXRD data was obtained. The novel salts prepared and new process for existing salt may have good aqueous solubility of the novel salts leads to improved dissolution of Cetirizine, bioavailability Thus; the new salts are a viable alternative solid form that can improve the dissolution rate and bioavailability of the drug.***

Keywords: Cetirizine salts; organic base; DSC; IR and PRXD;

I. INTRODUCTION

POLYMORPHISM IN PHARMACEUTICALS

Polymorphism means existence of substance in more than one form. Many pharmaceutical solids can exist in different physical forms. Polymorphism is often characterized as the ability of a drug substance to exist as two or more crystalline phases that have different arrangements and/or conformations of the molecules in the crystal lattice. However, they share one common form once they are in solution form.

The phenomenon of molecule existing in more than one solid-state structure is a result of differences in packing arrangement and/or molecular Conformation. Different polymorphs of the same compound exhibit different physical and chemical properties. One example of a compound showing such behavior is ritonavir, a protease inhibitor, developed by Abbott Laboratories. The appearance of a less-soluble second polymorph of ritonavir resulted in the need to reformulate the drug two years after it was launched. In the case of acetaminophen, a well-known analgesic drug, form I of the compound lacks slip planes in its crystal structure, which make it unsuitable for direct compression in to tablets. On the other hand, form II of the compound has well-developed slip planes which give it processing advantages over form I.

The importance of discovering all polymorphs of an active pharmaceutical ingredient cannot be overstated. The late discovery of polymorphs can lead to a delay in the time to market for a drug. Once a drug is launched, discovery of new polymorphs can lead to patent protection issues. The U.S. Food and Drug Administration (FDA) also require characterization of all possible polymorphs and identification of the stable form of a drug. Thus, polymorph screening is needed in the early stages of drug development. The discovery of polymorphs requires extensive experimentation. Typically, a variety of factors such as supersaturation, agitation rate, cooling rate, solvent composition, temperature, seed crystals, additives, impurities, etc. are varied as they are known to affect crystallization. Increasing the number of experiments leads to a higher possibility of identifying the majority of different polymorphs. In a high throughput polymorphism study on acetaminophen, Peterson et al. obtained Form II in only 29 out of 7776 trials.

The crystal form produced from solution is the result of competing thermodynamic and kinetic factors that govern crystallization of polymorphs. The polymorph with lower free energy is the thermodynamic stable form, whereas the other

polymorphs are known as metastable forms. According to Ostwald's rule of stages, the metastable form is the first to crystallize, followed by transformation to the more stable form [10]. This transformation proceeds in many cases through a Dissolution-recrystallization mechanism. Under certain conditions, the transformation process can be hindered or suppressed, leading to the generation of a metastable polymorph as the final crystal form.

The main controlling factors in the crystallization of polymorphs include temperature, supersaturation, and type of solvent, as well as the addition of seed crystals, stirring rate, and interfaces. It is well-known that in enantiotropic systems, the thermodynamic stability order among polymorphs can be inverted by shifting temperature above and below the transition temperature. Moreover, the temperature can change the dissolution rate, and the kinetics of nucleation and growth of each polymorph retarding the appearance of certain polymorphs and promoting others. Also, it has been shown that a rapid generation of supersaturation provides crystals of different polymorphic forms when compared with those obtained with a slow increase in supersaturation[13]. In the case of the effect of solvents, the interactions between solute and solvent molecules result in solute molecules assembling in particular conformation structure and/or packing mode.

Cetirizine hydrochloride is a second generation, nonsedating, selective H1-receptor antagonist that is used to treat atopic dermatitis, asthma, allergic rhinitis, and idiopathic urticaria in humans. It has also been reported to be effective for the prevention of the development of asthma in atopic children. Cetirizine lacks the anticholinergic effects of first-generation antihistamines at therapeutic doses in humans, and its long half-life allows once-daily dosing. It has also been used as a treatment for canine atopic dermatitis, and has been associated with rare and mild adverse side effects in this species.

Cetirizine acts as an inverse agonist and stabilizes the inactive conformation of H1 receptors. It also has non-H1-dependent activities such as inhibition of preformed mediators of inflammation such as histamine, tryptase, and leu-kotrienes from basophils and mast cells; inhibition of eosinophil chemotaxis; reduction of eosinophil survival; and alteration of adhesion molecule expression. All of these elements are involved in the pathogenesis of allergic inflammation. Cetirizine is nonsedating at therapeutic doses in humans due to efflux from the central nervous system via the P-glycoprotein pump system.

It is therefore an objective of the present invention to provide new polymorphic forms of acceptable salts of cetirizine and polymorphic forms thereof. In particular, the provided salts and polymorphs of cetirizine will show at least one of the following advantages compared to prior art forms of cetirizine salt: improved bioavailability, reduced inter-patient variability, improved overall therapeutic efficacy, good mechanical, polymorphic and/or chemical stability, excellent flow properties, good compressibility and improved dissolution problems. The new forms are preferably non-hygroscopic and/or do not electrostatically charge. It has been found that the forms of cetirizine and cetirizine salts according to this invention are advantageous in at least one aspect of the above-mentioned properties.

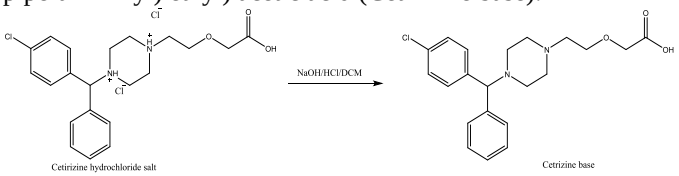
II. MATERIAL AND METHODS

MATERIAL

Cetirizine hydrochloride salt was a gift sample from Aarti Drugs., they were of pharmaceutical grade. Calcium carbonate, calcium hydroxide, salicylic acid, Hydrochloride, sodium hydroxide, lithium hydroxide monohydrate, oxalic acid dihydrate.

METHODS

Preparation of 2-(2-(4-((4-chlorophenyl) (phenyl) methyl) piperazin-1-yl) ethyl) acetic acid (Cetirizine base):

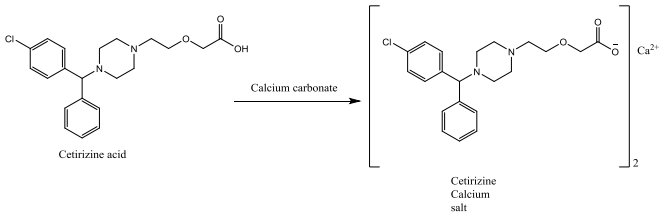


2-(2-(4-((4-chlorophenyl)(phenyl)methyl)piperazin-1-yl)ethoxy)acetic acid hydrochloride (50 g) in 500 water was basified with aqueous sodium hydroxide to have pH between 13-14. Then the reaction mixture pH adjusted to around 9 with 15% dilute hydrochloric acid, washed the resulted reaction mass with two times ethyl acetate. The pH of the separated aqueous layer was further adjusted to 4.0 with 15% hydrochloric acid and extracted with two times with 200 ml dichloromethane. Then the combined dichloromethane layer was evaporated under vacuum to get the required Cetirizine base solid (40.5 g).

NOVEL INORGANIC SALT WERE ATTEMPTED AS PER BELOW

EXAMPLE 1

Preparation of Cetirizine calcium salt



In 100 ml two necks round bottom flask cetirizine base (0.50 g, 1.29 mmol) was dissolved in 3 ml isopropanol on magnetic stirrer. The reaction was stirred on a magnetic stirrer to give a light yellow colour clear solution. A solution of calcium carbonate (0.13 g, 1.29 mmol) in 3 ml (2:1) 2-propanol: water was added over the course of 2 min in cetirizine free base solution. It gave a clear solution and the reaction mixture was stirred for 1 h. Reaction mass was distilled under vacuum at 45 °C to give semi solid mass. Given stripping of 10 ml mixture of 2:9 2-propanol: cyclohexane to give free solid. Again added 10 ml mixture of 2:9 2-propanol: cyclohexane cooled to room temperature and stirred for 1h. The solids were filtered off and washed with 2 ml mixture of 2:9 2-propanol: cyclohexane and dried under vacuum at 50° for 6 h to give 0.49 g (82.15%) of a white solid.

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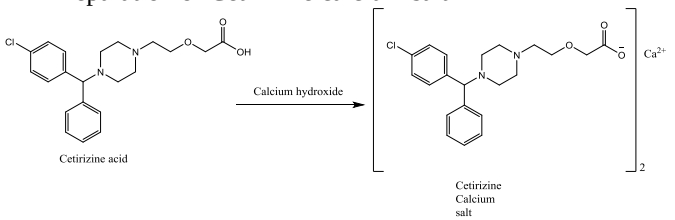
EXAMPLE 2

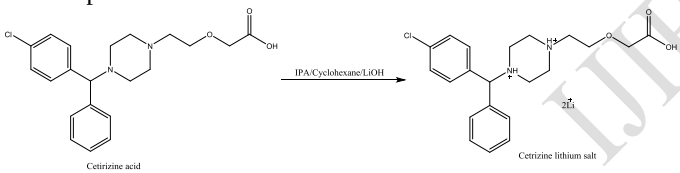
Preparation of Cetirizine calcium salt



In 100 ml two necks round bottom flask cetirizine base (0.50 g, 1.29 mmol) was dissolved in 3 ml isopropanol on magnetic stirrer. The reaction was stirred on a magnetic stirrer to give a light yellow colour clear solution. A solution of calcium hydroxide (0.13 g, 1.29 mmol) in 3 ml (2:1) 2-propanol: water was added over the course of 2 min in cetirizine free base solution. It gave a clear solution and the reaction mixture was stirred for 1 h. Reaction mass was distilled under vacuum at 45 °C to give semi solid mass. Given stripping of 10 ml mixture of 2:9 2-propanol: cyclohexane to give free solid. Again added 10 ml mixture of 2:9 2-propanol: cyclohexane cooled to room temperature and stirred for 1h. The solids were filtered off and washed with 2 ml mixture of 2:9 2-propanol: cyclohexane and dried under vacuum at 50° for 6 h to give 0.48 g (79.80 %) of a white solid.

EXAMPLE 3

Preparation of Cetirizine lithium salt

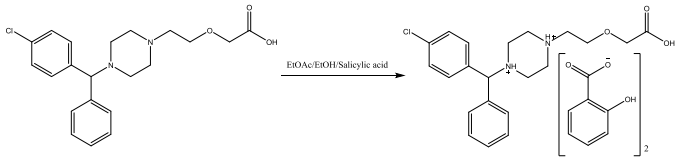


In 100 ml two necks round bottom flask cetirizine base (0.50 g, 1.29 mmol) was dissolved in 3 ml isopropanol on magnetic stirrer. The reaction was stirred on a magnetic stirrer to give a light yellow colour clear solution. A solution of lithium hydroxide monohydrate (0.13 g, 1.29 mmol) in 3 ml (2:1) 2-propanol: water was added over the course of 2 min in cetirizine free base solution. It gave a clear solution and the reaction mixture was stirred for 1 h. Reaction mass was distilled under vacuum at 45 °C to give semi solid mass. Given stripping of 10 ml mixture of 2:9 2-propanol: cyclohexane to give free solid. Again added 10 ml mixture of 2:9 2-propanol: cyclohexane cooled to room temperature and stirred for 1h. The solids were filtered off and washed with 2 ml mixture of 2:9 2-propanol: cyclohexane and dried under vacuum at 50° for 6 h to give 0.48 g (95.47 %) of a white solid.

NOVEL ORGANIC SALT WERE ATTEMPTED AS PER BELOW.

EXAMPLE 4

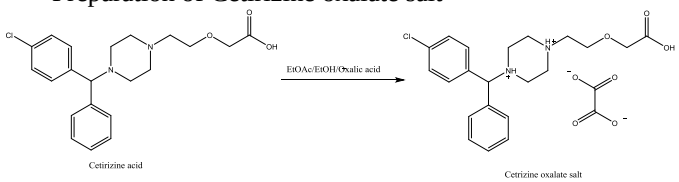
Preparation of Cetirizine salicylate salt



In 100 ml two necks round bottom flask cetirizine base (0.50 g, 1.29 mmol) was dissolved in 5 ml ethyl acetate on magnetic stirrer. The reaction was stirred on a magnetic stirrer to give a light yellow colour clear solution. A solution of salicylic acid (0.07 g, 2.57 mmol) in 5 ml ethanol was added over the course of 2 min in cetirizine free base solution. It gave a clear solution and after 24 h solid was precipitated out. Precipitated solid was filtered off and washed with 3 ml ethyl acetate and dried under vacuum at 50° for 6 h to give 0.35 g (40.92 %) of a white solid.

EXAMPLE 5

Preparation of Cetirizine oxalate salt

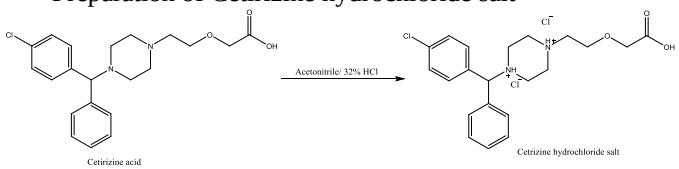


In 100 ml two necks round bottom flask cetirizine base (0.50 g, 1.29 mmol) was dissolved in 5 ml ethyl acetate on magnetic stirrer. The reaction was stirred on a magnetic stirrer to give a light yellow colour clear solution. A solution of oxalic acid dihydrate (0.193 g, 2.57 mmol) in 5 ml ethanol was added over the course of 2 min in cetirizine free base solution. It gave a clear solution and after 10 mins solid was precipitated out. Precipitated solid was filtered off and washed with 3 ml ethyl acetate and dried under vacuum at 50° for 6 h to give 0.55 g (83.07 %) of a white solid.

NEW ROUTES FOR EXISTING SALTS WERE ATTEMPTED AS PER BELOW

EXAMPLE 6

Preparation of Cetirizine hydrochloride salt



In 100 ml two necks round bottom flask cetirizine base (0.50 g, 1.29 mmol) was dissolved in 5 ml acetonitrile on magnetic stirrer. The reaction was stirred on a magnetic stirrer to give a light yellow colour clear solution. A solution of 32.0% HCl (0.29 g, 2.57 mmol) in 3 ml acetonitrile was added over the course of 2 min in cetirizine free base solution. It gave a clear solution and after 30 mins solid was precipitated out. Precipitated solid was filtered off and washed with 3 acetonitrile and dried under vacuum at 50° for 6 h to give 0.47 g (80.00 %) of a white solid.

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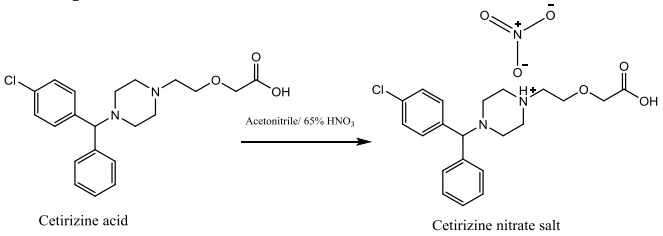
EXAMPLE 7

Preparation of Cetirizine nitrate salt



Cetirizine acid — Cetirizine nitrate salt

In 100 ml two necks round bottom flask cetirizine base (0.50 g, 1.29 mmol) was dissolved in 5 ml acetonitrile on magnetic stirrer. The reaction was stirred on a magnetic stirrer to give a light yellow colour clear solution. A solution of 65.0% nitric acid (0.29 g, 2.57 mmol) in 3 ml acetonitrile was added over the course of 2 min in cetirizine free base solution. It gave a clear solution and after 30 mins solid was precipitated out. Precipitated solid was filtered off and washed with 3 acetonitrile and dried under vacuum at 50° for 6 h to give 0.65 g (97.88 %) of a white solid.

III. FIGURES

A. FIGURES OF INFRA-RED SPECTROSCOPY SPECTRA

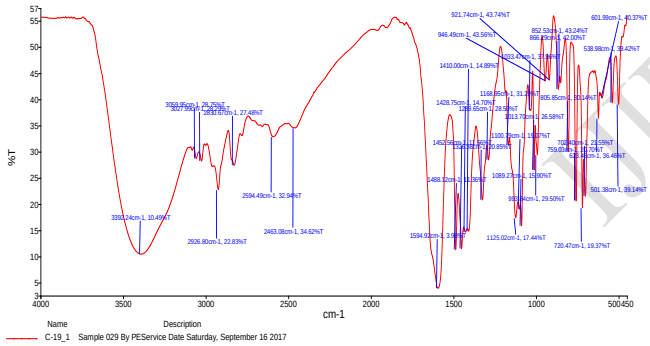


Figure 1: IR spectra Example 1

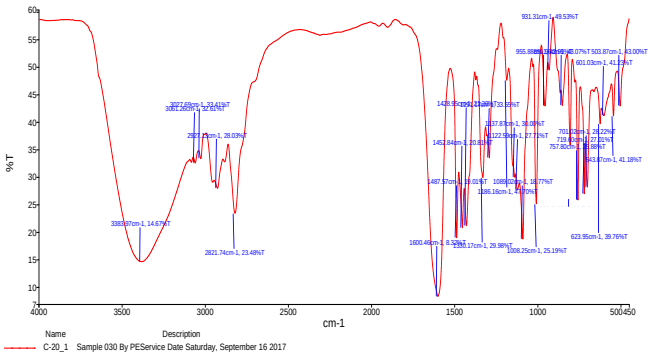


Figure 2: IR spectra Example 2

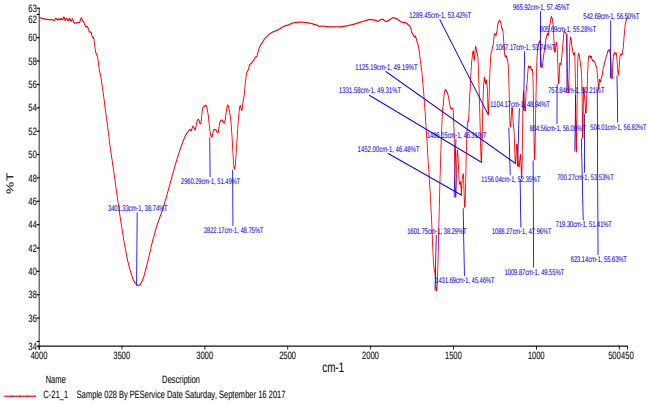


Figure 3: IR spectra Example 3

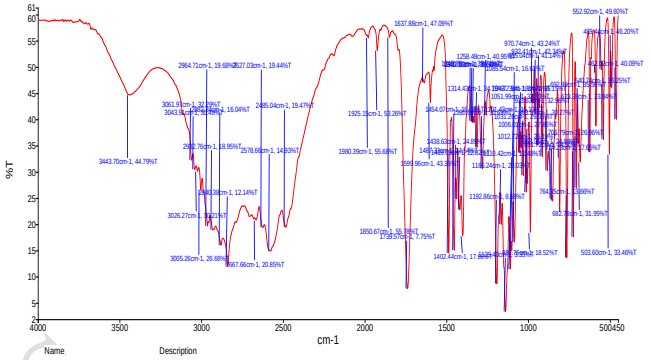


Figure 4: IR spectra Example 4

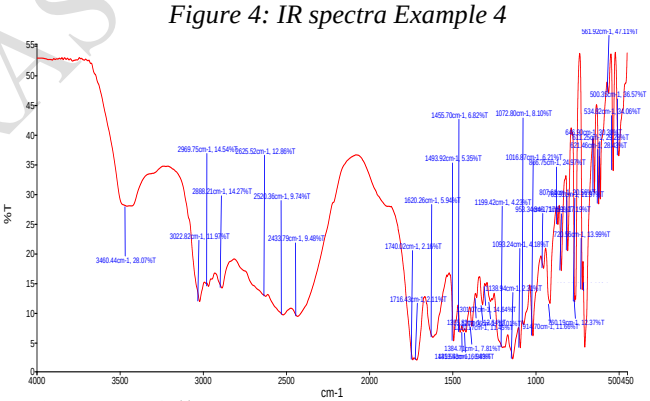


Figure 5: IR spectra Example 5

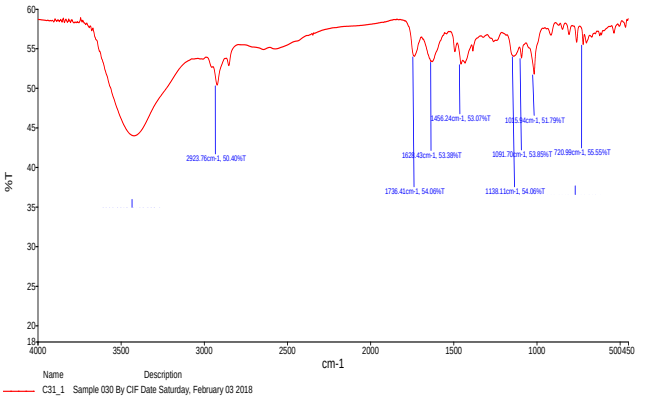


Figure 6: IR spectra Example 6

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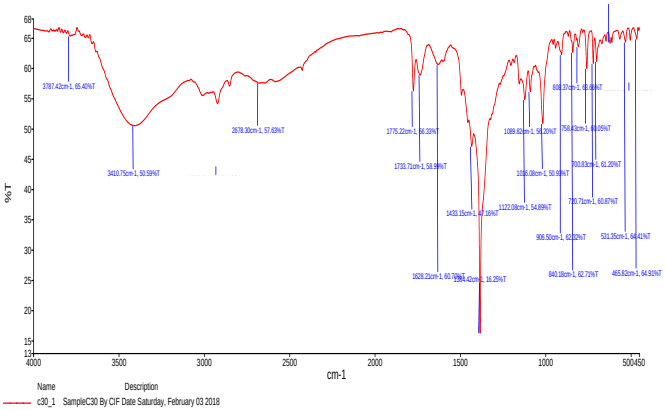

Figure 7: IR spectra Example 7

B. FIGURES OF INFRA-RED SPECTROSCOPY GRAPH

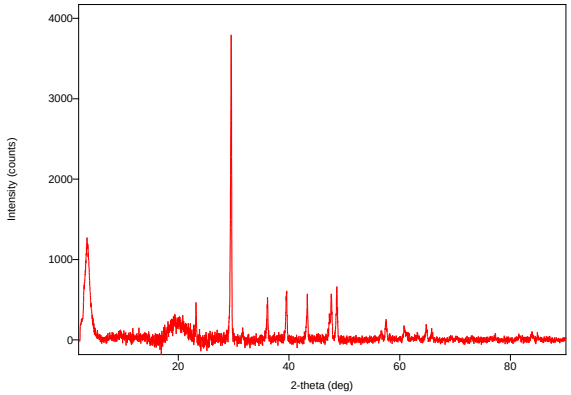

Figure 8: XRPD spectra Example 1

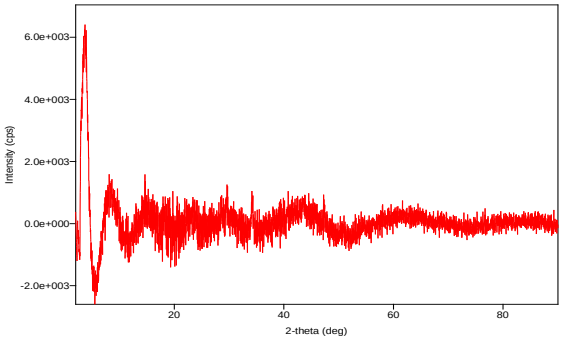

Figure 9: XRPD spectra Example 2

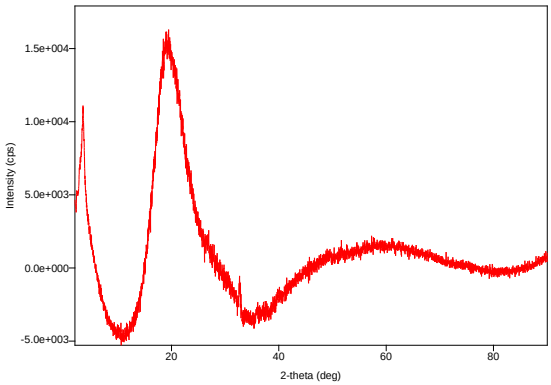

Figure 10: XRPD spectra Example 3

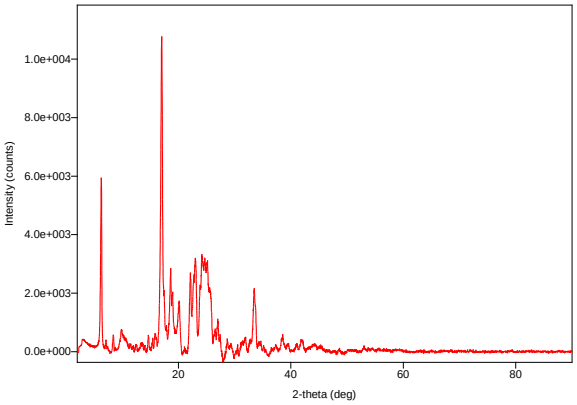

Figure 11: XRPD spectra Example 5

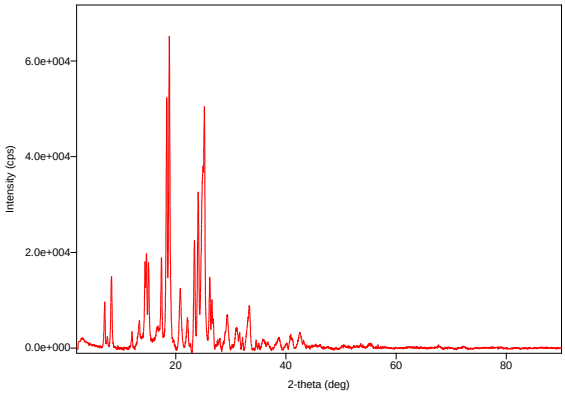

Figure 12: XRPD spectra Example 6

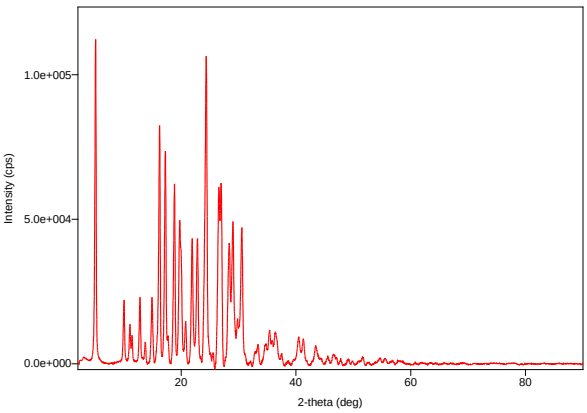

Figure 13: XRPD spectra Example 7

IV. ANALYSIS AND CHARACTERIZATION

Preliminary Characterization:
Melting points:

Example	Salt Name	Melting Point (°C)
1	Cetirizine Calcium (From $CaCO_3$)	195-198
2	Cetirizine Calcium	185-189

	(From $(CaOH)_2$)	
3	Cetirizine Lithium	133-135
4	Cetirizine salicylate	180-182
5	Cetirizine Oxalate	172-175
7	Cetirizine nitrate	146-148
6	Cetirizine Hydrochloride	241-243

Table 1

Fourier transforms infrared spectroscopy:

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

Powder X-ray diffraction:

The Cetirizine 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.

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 °C The instrument was equipped with a refrigerated cooling system.

V. RESULTS AND DISCUSSION

Cetirizine is an acidic drug. Cetirizine solubility increases only when this structure is destroyed by the ionization of the carboxyl groups, as a consequence of an increase of pH or the formation of a salt. Cetirizine salts can be easily crystallized from organic solvents.

Based on DSC (Differential scanning chromatography) thermograms, Powder X-ray diffraction and Fourier transforms infrared spectroscopy following salts were prepared.

Cetirizine calcium and Cetirizine lithium inorganic salts were prepared.

Cetirizine salicylate and Cetirizine oxalate organic salts were prepared.

New route for Cetirizine HCl and Cetirizine Nitrate salts prepared.

VI. CONCLUSIONS

Following conclusions were drawn from the above experimental work.

- ✓ Novel Cetirizine Calcium salt was prepared using inorganic calcium carbonate and calcium hydroxide. This salt was having crystalline nature (prepared from $CaCO_3$) and amorphous (prepared using $Ca(OH)_2$).
- ✓ Novel Cetirizine oxalate salt was prepared which was crystalline in nature
- ✓ Novel Cetirizine salicylate salt was prepared which was crystalline in nature.
- ✓ Cetirizine hydrochloride and Cetirizine nitrate were prepared using new route.

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