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STUDIES ON SYNTHESIS, METHOD DEVELOPMENT, CHARACTERIZATION AND ANTIMICROBIAL ACTIVITIES OF IBUPROFEN LYSINATE

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ABSTRACT

The aim of the study is to Synthesis, Method Development, Characterisation and Antimicrobial activities of Ibuprofen lysinate. The following some of the important findings in the present study.Ibuprofen lysinate were synthesized in good yield.Compound exhibited good antimicrobial activity. Percentage recovery of Ibuprofen Lysinate is 99.2% by HPLC .The compound exhibited good antibacterial activity against Bacillus subtilis, Staphyloccus aureous, Escherrichia coli, Pseudomonas aeruginosa, and good antifungal activity against candida albicans.

KEY WORDS

Ibuprofen lysinate, antimicrobial activity, HPLC.

INTRODUCTION

Drug discovery involves the identification of new active compounds often called “hits” which are typically found by screening many compounds for the desired biological properties. These hits can come from natural sources, such as plants animals or fungi. More often, the hits can come from synthetic sources, such as historical compound collection and combinatorial chemistry. This thesis deals with the investigation carried out by the writer in this laboratory on the synthesis, characterization and Analgesic and Anti-inflammatory, Anti-pyretic activity of Ibuprofen Lysinate. The Ibuprofen can be applied orally and topically as an alternative to a corticosteriodal therapy in inflammation treatment. For pain relief different Ibuprofen salts, especially the lysine salt are used. The elevated water solubility of Ibuprofen lysinate is also advantageous. As Ibuprofen itself is surface active its application is connected with local tissue irritation and ocular discomfort. Further ibuprofen amino acids compound Ibuprofen Lysinate were synthesized and examined as well. Topical formulations may be a reduction of surface tension, haemolysis and influence on porcive cornea tissue integrity.The

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lysine salt increases water solubility, allowing the medication to be administered intravenously. Ibuprofen lysine has been shown to have a more rapid onset of action compared to acid ibuprofen.

MATERIALS AND METHODS

Isobutyl benzene, Acetyl Chloride, Methylene Chloride, Water (HPLC grade) Monochloro acetate, Potassium bromide are procured by Rankam, Mumbai. Isopropyl alcohol is procured by Shasun Ltd., Acetonitrile (HPLC grade) Sodium metal, Sodium hydroxide, Methanol are procured by Merck Specialty Pvt., Mumbai. Phosphoric acid (AR) is procured by S.D. Fine Chem. Ltd., Mumbai.

SYNTHESIS

Dissolve 78.8ml of pure isobutyl benzene in 35.5ml of acetyl chloride in presence of 13.3g of aluminium chloride and ethylene chloride 11.8ml which was taken in a separate beaker and these solution was added to the mixture of Isobutyl benzene and acetyl chloride. These react together and forms isobutyl acetophenone (I).In an separate beaker 7.7ml isopropyl alcohol was taken and this can be treated with 4.9g monochloro acetate reacts to form isopropyl chloroacetate (II).In an separate beaker (should be free from water moisture) 7.7ml of Isopropyl alcohol and 1.1gm of sodium metal was added. Ant it was heated upto 80ºc using heating mandle to get the sodium isoproxide (III).The above formed sodium isoproxide (III) was added dropwise in the mixture of isobutyl acetophenone (I) with isopropyl chloroacetate (II) by vigrous stirring lead to the formation of epoxy ester. To this added 20ml of 1M sodium hydroxide solution. Hydrolysation reaction occured and there was a formation of 4 (Iso butyl phenyl propan-2-al) Aldehyde, carbondioxide and Isopropyl alcohol. The above formed 4 (Iso butyl phenyl propan – 2 – al) aldehyde, on oxidation by adding John's reagent (4ml of sulphuric acid + 12g of sodium dichromatic) with 15ml of acetone stirred for 2 hours by using magnetic stirrer for 2 hours at 28ºc. Ibuprofen crystallized out. Filter the solution through a buchner funnel with suction.Recrystalyse the product from 25ml hexane cool it over night. Ibuprofen was separate in hexane layer, cooled and dried then the product Ibuprofen was collected. Then this Ibuprofen 10.3g was taken and dissolved in 25ml of methanol and 7.3g lysine stirr well at 10°c by kept in a ice bath. The ibuprofen lysinate was separated. The yield of ibuprofen lysinate was found to be l7.5gm

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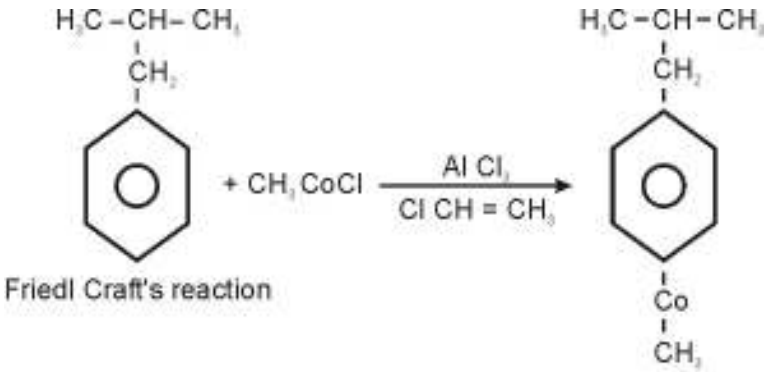
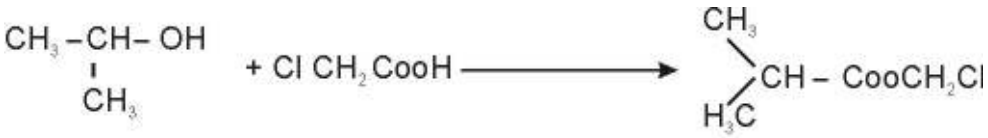
SYNTHESIS

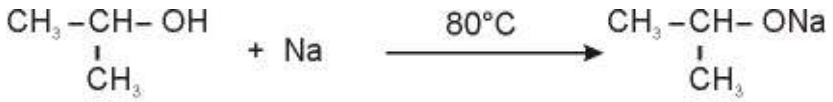


Friedl Craft's reaction

Isobutyl benzene + Acetyl Chloride → Isobutyl aceto phenone



Isopropyl alcohol + Monochloro acetate → Isopropyl chloro acetate



Isopropyl alcohol + Sodium Metal → Sodium Isoproxide

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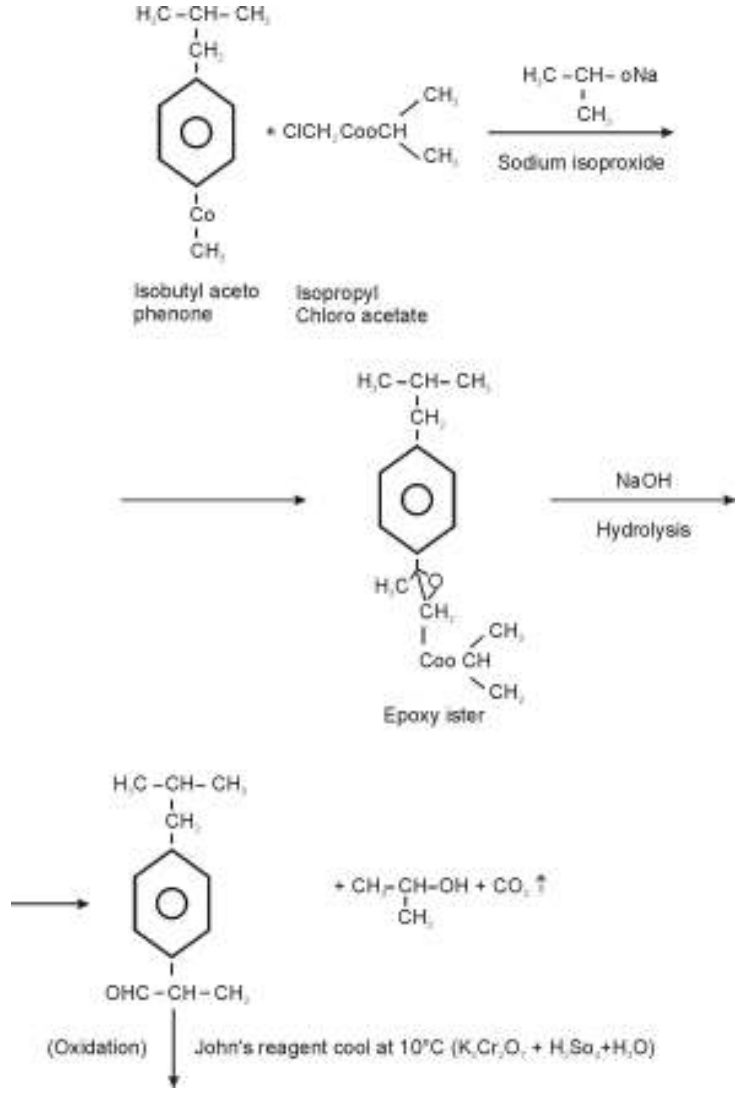
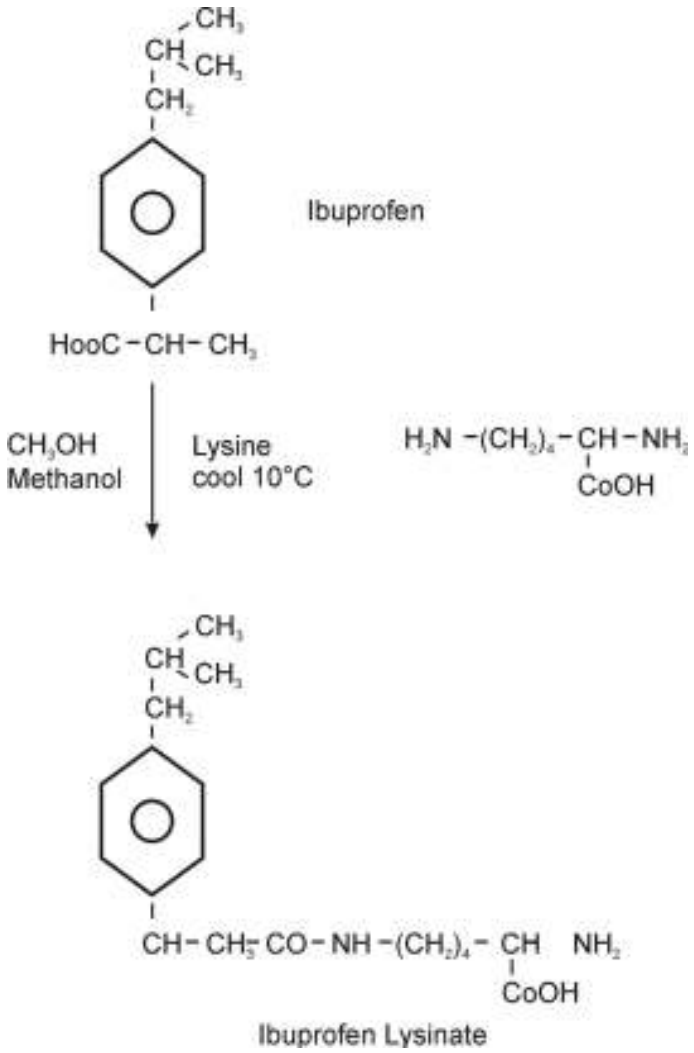


STUDIES ON SYNTHESIS, METHOD DEVELOPMENT, CHARACTERIZATION AND ANTIMICROBIAL ACTIVITIES OF IBUPROFEN LYSINATE



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METHOD DEVELOPMENT TRIALS

Trial – 1

From the above discussion the trial was performed by using water P^H 5.5 was adjusted with phosphoric acid and acetonitaile in the ratio (30:70); KROMASIL column C_8 with flow rate 2.0ml/min. The retention time was found at 40mins for Ibuprofen 18min for Lysine.

Trial – 2

The trail–2 was performed by using water P^H 6.0 adjusted with phosphoric acid and acetonitrile in the ratio of (55:45) KROMASIL column C_8, with flow rate 1.0 ml/min. The retention time was found at 30 mins for Ibuprofen, 12mins for Lysine.

Trial – 3

The trial-3 was performed by using water P^H 6.2 adjusted with phosphoric acid and acetonitrile in the ratio of (50:50) KROMASIL column C_8 with flow rate 1.0ml/min. The retention time was found at 20mins for Ibuprofen, 7 mins for Lysine.

Trial – 4

The trial-4 was performed by using water P^H 6.6 adjusted with phosphoric acid and acetonitrile in the ratio of (45:55) KROMASIL column C_8 with flow rate 1.0ml/min. The retention time was found at 13.7 mins for Ibuprofen and 1.9 mins for Lysine was confirmed.

Chromatographic parameters

Instrument	:	Shimadzu LC – 2010 A
Column	:	KROMASIL C8, 250mm x 4.6mm, 5µ
Flow rate	:	1ml/min.
Injection volume	:	20µL
Wave length	:	220nm
Column temperature	:	Ambient
Run time	:	30 minutes

Mobile phase preparation

450ml of HPLC grade water, 0.45ml of phosphoric acid and 550ml of HPLC grade acetonitrile was added and made upto 1000ml, shaken well, filtered (through 0.45µm membrance filter) and degassed for 10 mins.

Standard preparations

Solution A – 10%

Accurately weighed 0.050 gm of ibuprofen was taken in a 50ml standard volumetric flask, dissolved and diluted to 50ml with sample solvent.

Solution B – 0.01%

Transferred ml of solution A into a 10ml standard volumetric flask diluted to volume with sample solvent.

Sample preparation

Solution A – 0.1%

Accurately weighed 0.050g of ibuprofen lysinate was taken in 50ml standard volumetric flask, dissolved and diluted to 50ml with sample solvent.

Solution B – 0.01%

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Transferred 1ml of solution A_1 into a 10ml standard volumetric flask diluted to the volume with sample solvent.

ANTIMICROBIAL SCREENING

Evaluation of antimicrobial activity

The antimicrobial activity can be evaluated by disc diffusion test. Diffusion test used to determine the sensitivity of organism by measuring zone of inhibition.

Initially the zone of inhibition carried out to evaluate the sensitivity of the organism towards the compounds. From the zone of inhibition data the organisms were selected for determination of Minimum Inhibitory Concentration (MIC).

Disc diffusion test

Modified Kirby-Bauer method was used for the evaluation of microbial sensitivity of the synthesized compounds. Circular paper disks were impregnated with the specific amount of test compounds and were placed on suitable agar medium (Muller Hinton agar), which was inoculated with the test organism. After incubation, the petri dishes were observed for growth of inhibition zone around the disk. A "halo" or Zone of inhibition forms, where concentration of the diffused molecule is sufficient to inhibit microbial growth. The diameter of zone of inhibition is directly proportional to antimicrobial activity of the compound. The diameter of zone of inhibition was compared with that of standard antibiotics.

The size of zone of inhibition depends on rate of antibiotic diffusion, rate of bacterial growth and incubation condition, concentration of organism.

The following bacterial cultures were used for the study.

1. *Bacillus subtilis* – Gram positive bacteria
2. *Staphylococcus aureous* – Gram positive bacteria
3. *Escherichia coli* – Gram negative bacteria
4. *Pseudomonas aeruginosa* – Gram negative bacteria

The following fungal culture were used for the study.

1. *Candida albicans*

Drugs Control

1. Ciprofloxacin (antibacterial)
2. Tobramycin (antifungal)

Concentration : All the test compounds were tested at 100µg/ml

Solvent : Dimethylformamide (DMF)

Preparation of paper discs[58,59]

Paper disk of 6mm diameter and 2mm thickness was used for the test. These disks were found to absorb 0.02ml of the solvent (DMF). These disks were sterilized by autoclaving at 121°C (15lbs psig) for 15 minutes.

Preparation of culture medium

Its provides all essential nutrients for the growth of microorganism. Muller Hinton agar medium was used to inoculate bacterial strains and Sabourands medium used for fungal strains.

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Composition of Muller Hinton agar medium

Beef infusion	300ml
Casein hydrolysate	16gm
Starch	1.5gm
Agar	15gm
Distilled water	1000ml
pH	7.2 ± 0.2

Composition of Sabouraud's dextrose agar medium

Dextrose	40gm
Peptone	10gm
Agar	20gm
Distilled water	1000ml
pH	5.6 ± 0.2

The medium was prepared by dissolving the specified quantity of the dehydrated medium in purified water and was dispersed in 20ml volumes in to test tubes. The test tubes were closed with cotton plugs and were sterilized by autoclaving at 121°c (15 lb psig) for 15 minutes. The contents of tubes were pound aseptically into sterile petri plates (90mm diameter) and allowed to solidify.

PROCEDURE

Petri dishes were filled to depth of 3-4mm with a nutrient agar medium which had previously been inoculated with suitable inoculums of a susceptible test organism. The dishes should be selected with flat bottom and should be placed on a level surface to ensure that the layer of the medium will be of a uniform thickness. Each plate was divided into six equal positions along the diameter. Each portion was used to place one disk. Four disk of each sample was placed on four portions, two disks were placed one each with ciprofloxacin disk and a disk impregnated with the solvent.

All plates were kept in the refrigerator for 30 min to allow the diffusion of sample to the surrounding agar medium. The petri dishes were incubated at 30°c for 18 h. Diameter of the zone of inhibition was measured and the average diameter for each sample was calculated. The diameter obtained for the test samples were compared with that produced by standard ciprofloxacin.

Similar procedure was carried out for the evaluation of antifungal activity of using Sabourauds dextrose agar medium and Tobramycin, 10µg disc as standard drug. Antifungal activity was tested against *candida albicans*.

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RESULT AND DISCUSSION

1. Ibuprofen Lysinate was synthesized and yield was found to be 17.5gms. Synthesized compound characterized by the IR-Spectro photometer and the reported peak values were found as given below.

Ibuprofen wave number (cm^{-1})

2960.11	1379.52	1121.09	865.807
1719.49	1322.16	1070.62	779.415
1507.59	1268.51	1008.36	746.165
1460.88	1229.88	969.296	668.281
1420.24	1183.05	934.869	

Ibuprofen Lysinate wave number (cm^{-1})

2960.81	1554.74	1291.01	882.929
2370.84	1522.79	1216.44	839.81
2190.92	1453.78	1127.31	800.769
1627.23	1393.88	1080.71	724.063
1593.79	1319.05	912.991	

2. Prepared compound was analysed by RP HPLC method development and the assay value was found to be 99.2%.
3. The prepared compound was tested for the antimicrobial activity by using Petri dishes inoculated with the test organism. The diameter of zone of inhibition was compared with that of standard antibiotics were listed in table no. 1 & 2.

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Shimadzu CLASS-VP V6.14 SP2 Area % Report Page 1 of 1

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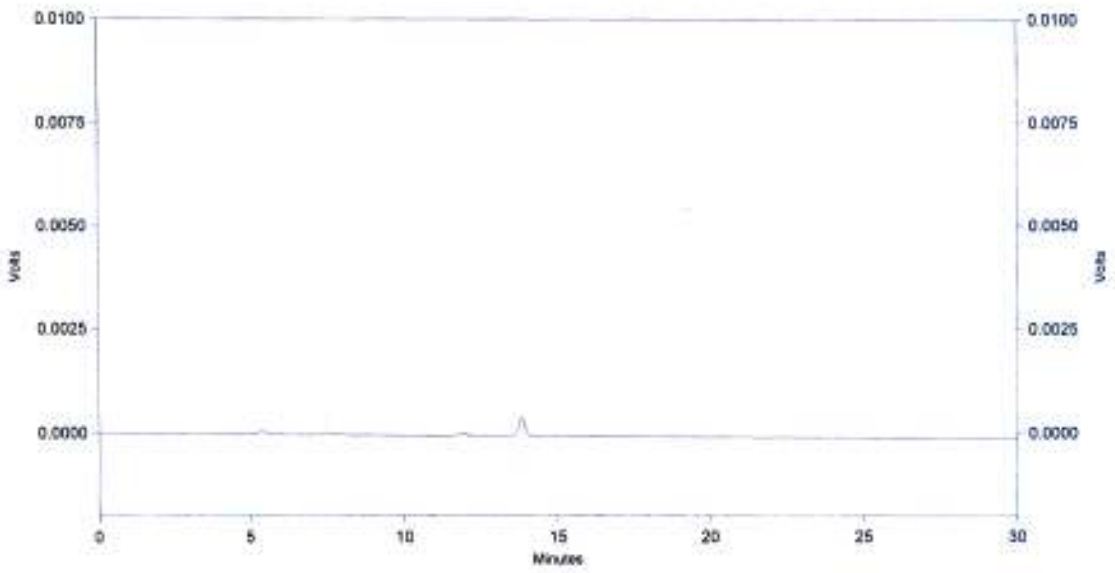
Instrument	:	SHIMADZU LC-2010A HT SERIES CODE: P04CHP009 (Offline)
Column	:	KROMASIL C8,5 Micron(250 mm x 4.6mm) Inhouse ID Number:LCPY039
Wave length	:	220 nm
Sensitivity	:	Auxillary range: 3 Range : 1 Response : 4
Mobile phase	:	Water(0.1% V/V OF H3PO4 IN WATER 450V) : Acetonitrile(550V)
Flow rate	:	1ml/min
Vol injection	:	20 micro litre



Detector A
(220nm)

Pk #	Retention Time	Area	Height	Area %	Name

Fig. No. 1 : Blank Run

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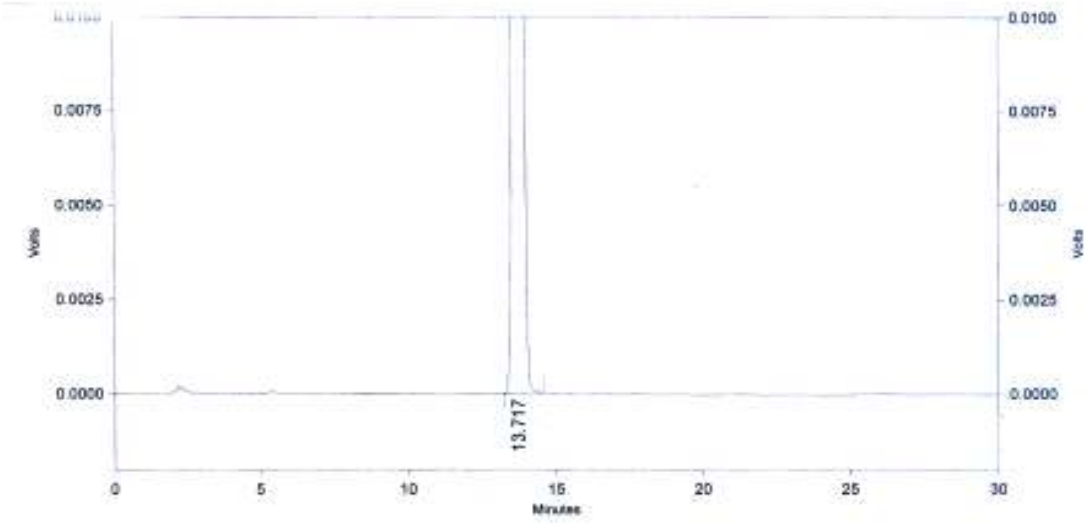
Wave length	:	220 nm
Sensitivity	:	Auxillary range: 3 Range : 1 Response : 4
Mobile phase	:	Water(0.1% V/V OF H3PO4 IN WATER 450V) : Acetonitrile(550V)
Flow rate	:	1ml/min
Vol injection	:	20 micro litre



Detector A (220nm)

Pk #	Retention Time	Area	Height	Area %	Name
1	13.717	2428925	171585	100.000	IBUPROFEN
Totals		2428925	171585	100.000	

Fig. No. 2: Run -1 Standard

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Method Name	:	D:\P04CHP009\Method\IBUPROFEN LYSINATE.met
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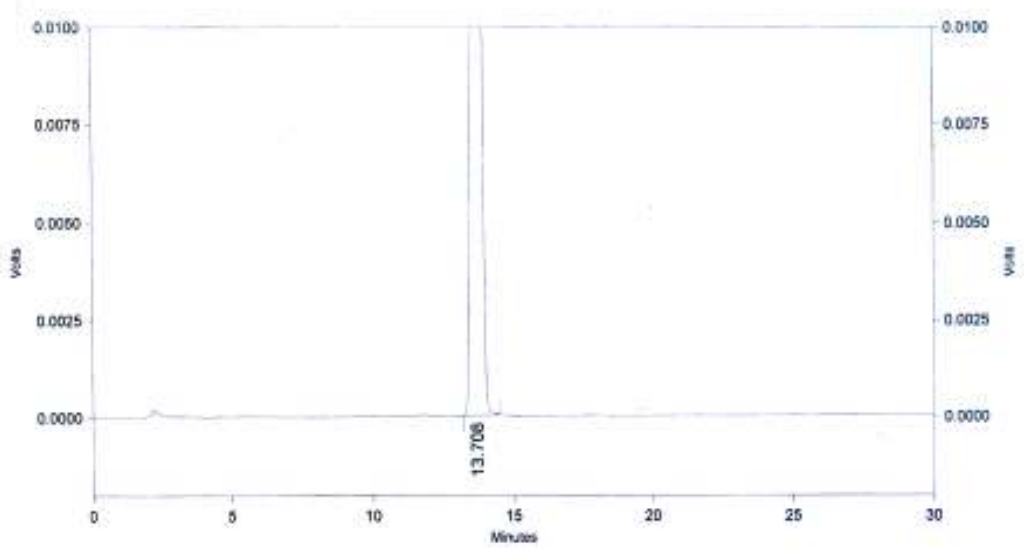
Wave length	:	220 nm
Sensitivity	:	Auxillary range: 3 Range : 1 Response : 4
Mobile phase	:	Water(0.1% V/V OF H3PO4 IN WATER 450V) : Acetonitrile(550V)
Flow rate	:	1ml/min
Vol injection	:	20 micro litre



Detector A (220nm)

Pk #	Retention Time	Area	Height	Area %	Name
1	13.708	2427164	171819	100.000	IBUPROFEN
Totals		2427164	171819	100.000	

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Method Name	:	D:\P04CHP009\Method\IBUPROFEN LYSINATE.met
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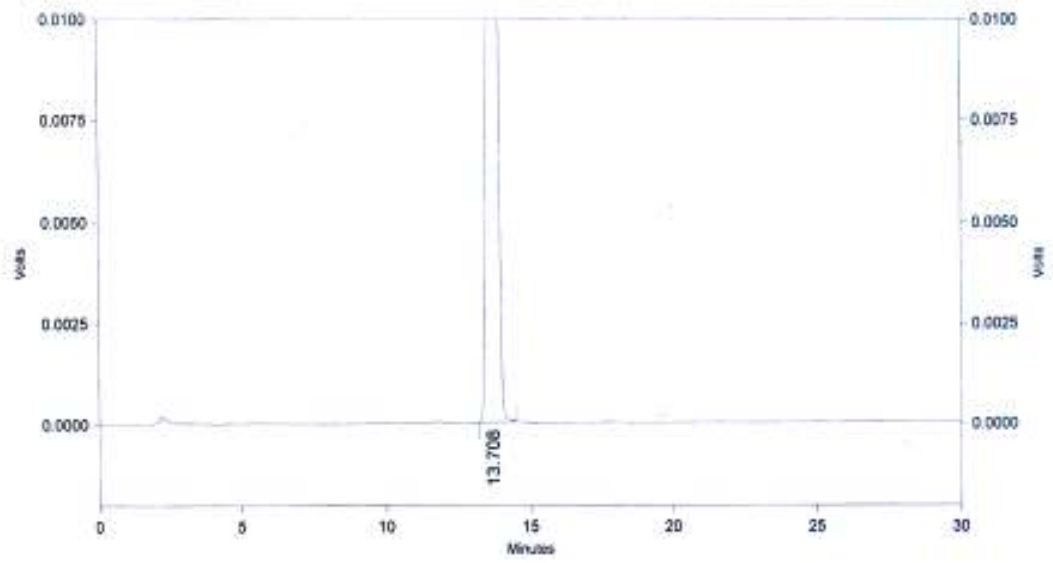
Wave length	:	220 nm
Sensitivity	:	Auxillary range: 3 Range : 1 Response : 4
Mobile phase	:	Water(0.1% V/V OF H3PO4 IN WATER 450V) : Acetonitrile(550V)
Flow rate	:	1ml/min
Vol injection	:	20 micro litre



Detector A (220nm)

Pk #	Retention Time	Area	Height	Area %	Name
1	13.708	2427164	171819	100.000	IBUPROFEN
Totals		2427164	171819	100.000	

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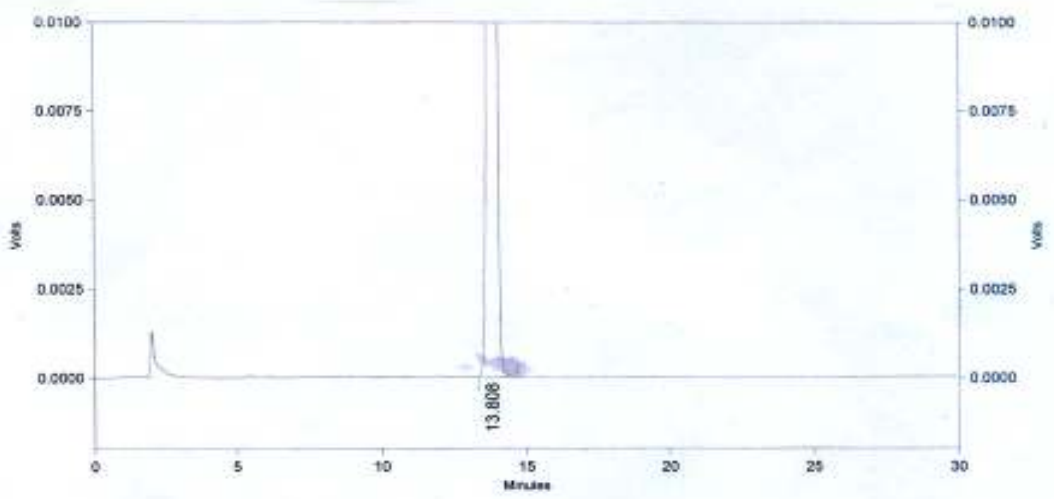
Wave length	:	220 nm
Sensitivity	:	Auxillary range: 3 Range : 1 Response : 4
Mobile phase	:	Water(0.1% V/V OF H3PO4 IN WATER 450V) : Acetonitrile(550V)
Flow rate	:	1ml/min
Vol injection	:	20 micro litre



Detector A (220nm)

Pk #	Retention Time	Area	Height	Area %	Name
1	13.808	1388132	98376	100.000	IBUPROFEN LYSINATE
Totals		1388132	98376	100.000	

Fig. No. 3: Run - 1 Sample

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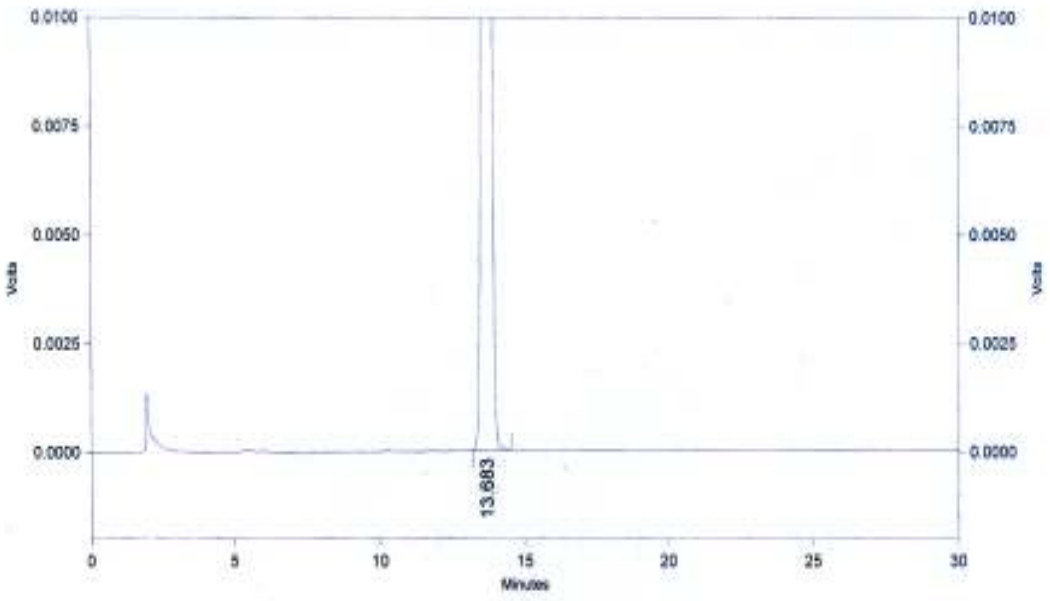
Wave length	:	220 nm
Sensitivity	:	Auxiliary range: 3 Range : 1 Response : 4
Mobile phase	:	Water(0.1% V/V OF H3PO4 IN WATER 450V) : Acetonitrile(550V)
Flow rate	:	1ml/min
Vol injection	:	20 micro litre



Detector A (220nm)

Pk #	Retention Time	Area	Height	Area %	Name
1	13.683	1400885	98325	100.000	IBUPROFEN LYSINATE
Totals		1400885	98325	100.000	

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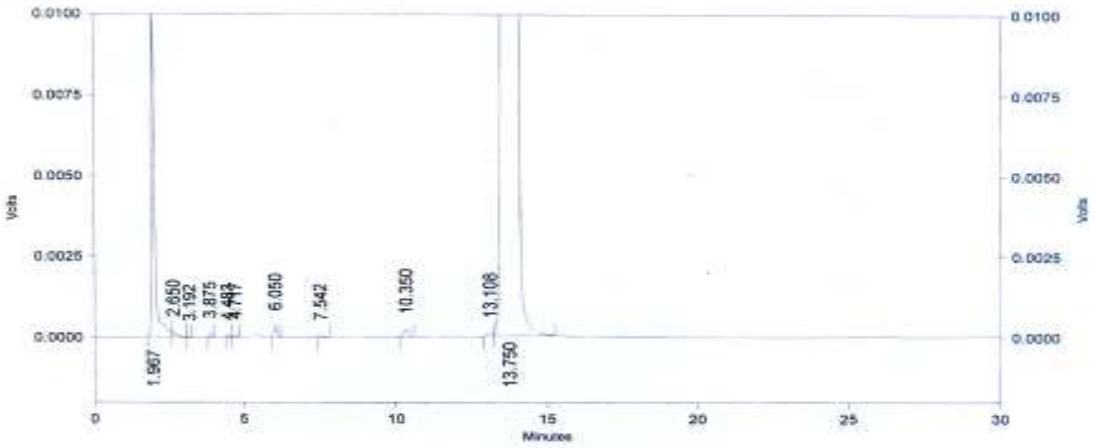
Wave length	:	220 nm
Sensitivity	:	Auxillary range: 3 Range : 1 Response : 4
Mobile phase	:	Water(0.1% V/V OF H3PO4 IN WATER 450V) : Acetonitrile(550V)
Flow rate	:	1ml/min
Vol Injection	:	20 micro litre



Detector A (220nm)

Pk #	Retention Time	Area	Height	Area %	Name
1	1.967	89991	13713	0.658	LYSINE
2	2.650	1611	162	0.012	
3	3.192	131	19	0.001	
4	3.875	762	129	0.006	
5	4.483	394	74	0.003	
6	4.717	656	109	0.005	
7	6.050	2588	372	0.019	2-(4-ISO BUTRYLPHENYL)PRO.ACID
8	7.542	611	67	0.004	
9	10.350	2630	252	0.019	
10	13.108	1240	108	0.009	
11	13.750	13583805	924995	99.265	IBUPROFEN LYSINATE
Totals		13684419	940000	100.000	

Fig. No. : 4 Ibuprofen Lysinate

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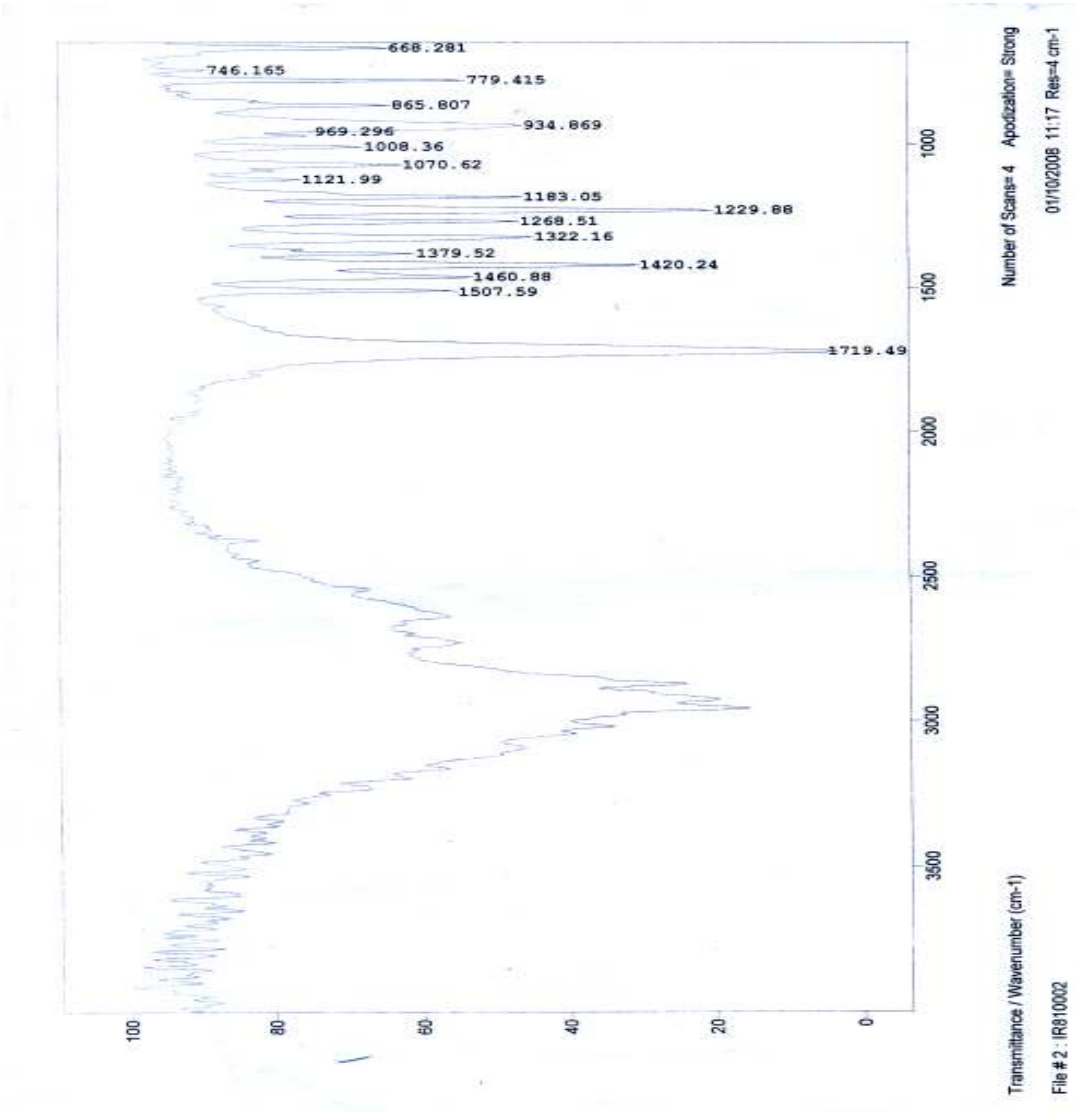

Fig. No. 5 : Ibuprofen

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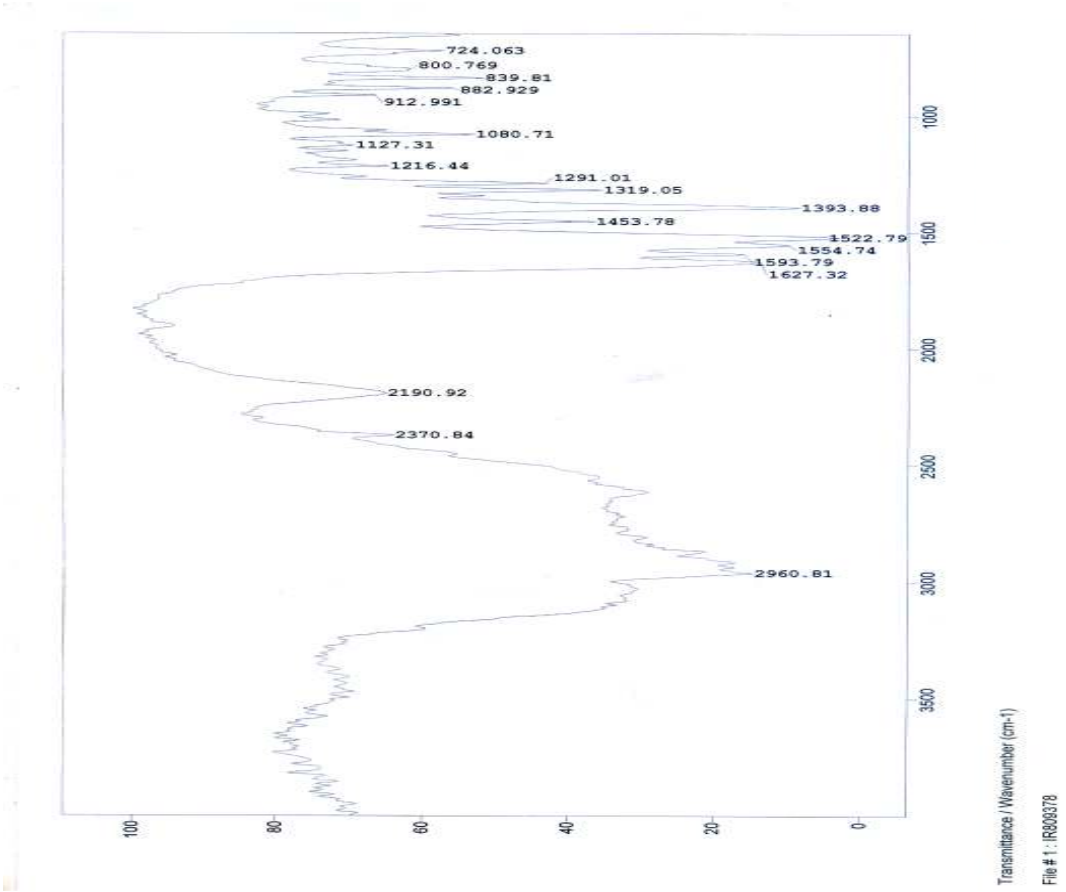

Fig. No. 6 : Ibuprofen

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Antimicrobial Screening

In vitro tests are used as screening procedure for new agents and for testing the susceptibility of individual isolates from infections to determine which of the available drugs might be useful therapeutically. Due to the development of sulphonamides and

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pencillins, in vitro measurement of susceptibility of microbes to chemotherapecutic agents has been used.

A drug is considered to have bacteriostatic or fungistatic activity when it inhibits the activity of bacteria or fungi respectively and bactericidal or funicidal activity and its kill bacteria and fungi. Important factors for antimicrobial activity for size of the incocluam, metabolic state of microbe, pH, temperature, duration of interaction, concentration of inhibitor and presence of interference substances.

The development of resistance among various pathogenic microbes towards the antibiotics has increased the impetus for investigating new antimicrobial agent. When a compound was found to have positive therapeutic index, a new series of related compounds are synthesized in the hope that one of them would be more effective than the existing one. A drug, which kills or inhibits the growth of microbes, is known as antmicrobial agent.

Antibacterial test was carried out on four bacterial strains, namely *Bacillus subtilis* (gram positive), *Staphylococcus aureus* (gram positive), *Eschertia coli* (gram negative), *Pseudomonas aeruginosa* and antifungal test was carried out on
Candida albicans.

Disc diffusion method

Antibacterial activity studies

The synthesized compound Ibuprofen Lysinate have shown potent to weak antibacterial activity. Compound showed potent activity against *Bacillus subtilis* and *Pseudomonas* and moderate activity against *Staphylococcus aureus* and *Escheritia coli* compared with the standard.

b. Antifungal activity studies

From the antifungal activities studies it is evident that the synthesized compound showed moderate activity against Canddida albicans compared to the standard.

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Table 1.
Data for antibacterial activities of synthesized compounds

S. No.	Compound	Diameter of zone of inhibition (mm)			
		B. Subtilis	S. Aurues	P.Aeruginosa	E.Coli
1.	Ibuprofen Lysinate	14	13	9	8
2.	Ciproflaxocin	25	19	22	23

Table 2.
Data for antifungal activities of synthesized compounds

S. No.	Compound	Diameter of zone of inhibition (mm) C. Albicans
1.	Ibuprofen Lysinate	5
2.	Tobramycin	15

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CONCLUSION

This thesis deals with the synthesis, method development, characterization, Antimicrobial screening of Ibuprofen Lysinate.Ibuprofen lysine is indicated for closure of a patent ductus arteriosus in premature infants weighing between 500 and 150 grams, who are no more than 32 weeks gestational age when usual medical management (e.g., fluid restriction, diuretics, respiratory support, etc.) is ineffective. With regard to this indication, ibuprofen lysine is an effective alternative to intravenous indomethacin and may be advantageous in terms of renal function. Hence it was concluded that the synthesized compound Ibuprofen Lysinate proved a better results by overcoming the above problems.

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