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Extraction and Identification of Dothiepin, Paroxetine, Thioridazine and Trifluoperazine in Blood by Thin Layer Chromatography using Different Solvent Systems

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Abstract

An attempt has been made to develop a new thin layer chromatographic method for analysis of 'Dothiepin, Paroxetine, Thioridazine and Trifluoperazine' in blood using different solvent system as mobile phase. 'These antidepressant and antipsychotic drugs' were extracted from blood samples using liquid-liquid extraction method and analysed by Thin Layer Chromatography. 15 different solvent systems with different concentration were introduced and various TLC plates were run in these solvent systems. The Developed plates were viewed under UV light 254 nm followed by spray of chromogenic reagent i.e., Dragendorff's Reagent which efficaciously amplified the sensitivity without upsetting simplicity of the method. The observations in each case were thoroughly analysed and reported. The developed method is *a simple, rapid, low-cost, non-destructive and reproducible* which can be performed in any laboratory easily.

Keywords: Dothiepin, Paroxetine, Thioridazine, Trifluoperazine, Liquid-Liquid Extraction, Thin Layer Chromatography, Solvent System.

Introduction

Depression is a common mental illness prevalent in society which has grasped approximately 280 million people worldwide. It inculcates suicidal tendencies in people and has detrimental effects if it lasts long and proper psychological and pharmacological treatments are not given. Apart from psychological treatments like behavioural, cognitive and interpersonal therapy, anti-depressants medication forms an effective tool to deal with the clinical effects of depression.[1] Selective serotonin reuptake inhibitors (SSRIs) and Tricyclic antidepressants (TCA) are common medications to treat depression. Serotonin-norepinephrine reuptake inhibitor (SNRIs), monoamine oxidase inhibitors (MAOIs), atypical antidepressants etc are also in the list.[2] Dothiepin belongs to the class of tri-cyclic antidepressants[3] and Paroxetine is labelled as selective-serotonin reuptake inhibitors.[4]

Along with anti-depressants, antipsychotics too are often employed to treat depressive disorders. Anti-psychotics are derivatives of large chemical class named phenothiazines.[5] There are two categories of antipsychotics: 1. First generation or conventional or typical antipsychotic and 2. Second generation or atypical antipsychotics.[6] Thioridazine and Trifluoperazine are first

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generation antipsychotics used for the treatment of anxiety, schizophrenia and other depressive episodes.[5,6]

Few authors are of the view that concurrent treatment with antidepressant and antipsychotics are more effective in comparison to monotherapy with antidepressants. This is based on the fact that when antidepressants and antipsychotics are employed parallelly, they will act on multiple receptor systems, thus leading to a more pronounced effect.[6] Tri-cyclic Antidepressants show therapeutic effect by inhibiting monoamine reuptake while the detrimental effects are due to antagonism of the M1, H1, alpha 2 receptors. On the other hand, SSRI inhibits serotonin reuptake leading to its accumulation in synaptic cleft. The typical anti-psychotics discussed in this paper show therapeutic effect through antagonism of D2 receptors and the same antagonism is the cause of many adverse effects linked with these medications as an outcome of D2 receptor antagonism in other locations throughout the brain.[7]

Anti-depressants and Anti-psychotics are prescribed to regulate signals in brain that improves mood. The chemicals associated are serotonin, dopamine and norepinephrine. Over-dosing or taking it with alcohol, other prescription or illicit drugs can be life threatening at times. Over-dosing is treated by doctors by giving emergency treatments like activated charcoal to absorb the medication, stomach pump to eliminate medication, benzodiazepines to reduce agitation etc. but that too does not work always.[2]

According to WHO, India tops the list of most depressed countries in the world followed by China and U.S.A. 6.5% of India's population suffer from some form of the serious mental disorder with the average suicide rate being 10.9 for every lakh people. Majority of people who commit suicide are below 44 years of age.[8]

The Covid-19 pandemic has given a surge to depression cases and reported suicides. Financial losses, loss of livelihood due to lockdown, death of dear ones, fear of contracting disease etc has significantly affected the mental health of people. Social isolation makes a person way more vulnerable to manic depression and suicidal thoughts.[9]

Anti-depressants are employed in treatment of depression and many psychiatric illnesses. Studies revealed that there exist close association between usage of anti-depressants and development of suicidal tendencies however the reason behind this trigger in suicidal tendency occurs on account of drug usage or progressing disease, still lies undeciphered.[10] A study conducted during the initial phase of pandemic claimed that the Corona virus pandemic would make lot more people to get dependent on anti-depressants to cope-up. And the same happened as the sale of anti-depressants in pandemic went up by 23% from April 2020 to April 2021 in India.[11] According to data gathered by market research firm AIOCD-AWAC, sales of antidepressants went up 15% y-o-y to 632 crores while that of anti-psychotics went up by 13% y-o-y to 270 crores.[12]

Psychological distress is one of the inevitable ramifications of Covid-19 that will continue being a serious implication of this global pandemic.[13]

Analysis of viscera and body fluids forms the essence of a toxicological laboratory. Often, we encounter cases that require qualitative and quantitative assessment of mischievous component(s) if present, in the sample sent. Analysis of drugs (extraction, identification, qualitative assessment and quantification) is a routine activity carried out in almost all toxicological laboratories.

The recent advancements in analytical techniques like GC-HS, MS, HPLC, HP-TLC, are no-doubt a blessing to all toxicological experts but at the same time the set-up of these techniques demands huge capital right from installation to their regular maintenance and are complex to handle as well. There are huge number of cases reported in forensic laboratories with limited resources and manpower which keeps on adding to the case pendency.[14,15]

Sliding to the traditional mode of analysis, if efficient results are obtained, if efficient results are obtained, is not only cost-effective but at the same time is simple to perform, rapid, non-destructive and can very easily be performed by ay laboratory without the need of sophisticated high-end instruments.

The paper focusses on 2 anti-depressant and 2 anti-psychotic drugs, 'Dothiepin, Paroxetine, Thioridazine and Trifluoperazine', their extraction & identification using different solvent system of varying concentration and calculation pf Rf in each case.

Dotheipin

a. IUPAC[16] :3-Dibenzo[b,e] thiepin–11(6H)-ylidene-N,N-dimethyl–1–propanamine
b. Molecular Mass[16] : C19H21NS=295.4
c. M.p.[16] : 55° to 57°.
d. Half Life[16]

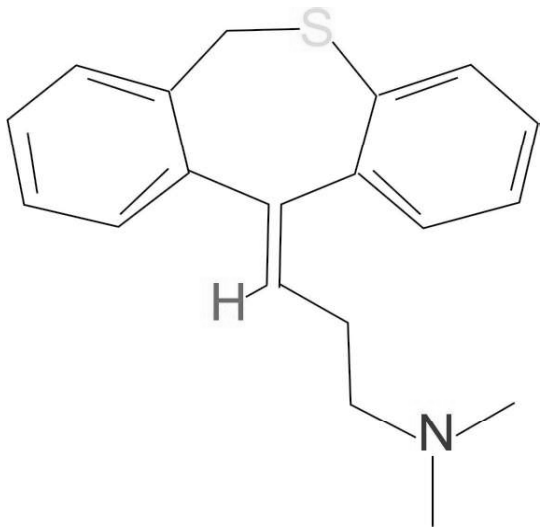

Fig. 1: Structure of Dothepin[17]

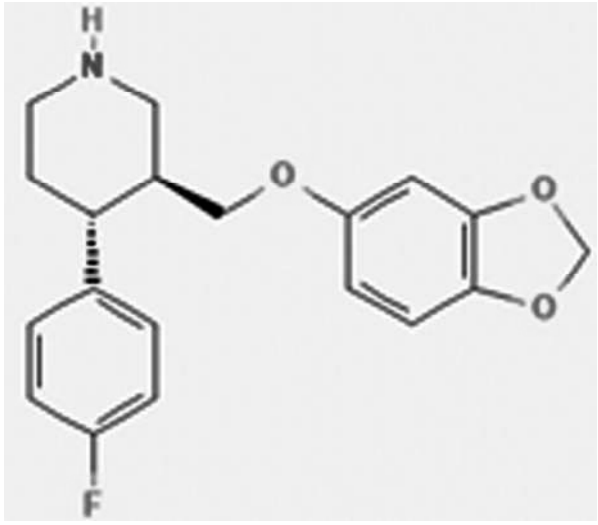

Fig. 2: Structure of Paroxetine[19]

Dothiepin: 20 hours (Yu et al. 1996). Active metabolites: 24-40 hours (Yu et al. 1996)

Dosulepin Hydrochloride[16]

Proprietary names. Dopin; Dopress; Dothapax; Dothep; Jardin; Prepadine; Prothiaden; Protiaden(e); Thaden; Xerenal.

C19H21NS, HCl=331.9

Properties: A white to faintly yellow crystalline powder with M.P. 218° to 221°.[16] It's a tricyclic antidepressant drug used to treat major depressive disorders. It causes potentiation of adrenergic synapses and blocks the reuptake of norepinephrine and serotonin at nerve endings.[18]

Therapeutic Dosage[3]***:*** Adults: 50 mg - 150 mg daily in either divided doses or as a single dose at night. In severely depressed patients, doses of up to 225 mg daily have been used. Child: Not recommended.

Adverse effects[3]***:*** Antimuscarinic effects, sedation, arrhythmias, postural hypotension, tachycardia, sweating, tremor, rashes, hypomania or mania, confusion, interference with sexual function, weight gain, convulsions, hepatic and haematological reactions.

Paroxetine

a. IUPAC[16]: (3S-trans)-3-[(1,3-Benzodioxol–5–yloxy) methyl]-4-(4–fluorophenyl)-piperidine

b. Molecular Mass:[16] C19H20FNO3=329.4

Paroxetine Hydrochloride Hemihydrate[16]

Proprietary names. Aropax; Deroxat; Frosinor; Motivan; Paxil; Sereupin; Seroxat; Tagonis.

C19H20FNO3, HCl.1/2H2O=374.8

c. Crystals:[16] M.P. 129° to 131°.

d. Therapeutic concentration:[16] The serum therapeutic concentration range is 10 to 75 µg/L.

e. Toxicity[16]:Toxic effects may occur with conc. greater than 400 µg/L.

f. Half–life[16]: 12 to 40 h

Paroxetine (also known as Selective serotonin re-uptake inhibitor) is used as a medication to treat depression, panic attacks, obsessive compulsive disorder (OCD), anxiety disorders, and posttraumatic stress disorder. The clinical effect is due to restoration of neurotransmitter Serotonin in brain that improve mood, sleep, appetite, and energy level and restores interest in routine life. It may decrease fear, anxiety, unwanted thoughts, and the number of panic attacks, etc.[4] The most common side effects are:Nausea, Headache,Somnolence,Dry mouth, sweating, weight gain, All SSRIs can cause sexual dysfunction.[20]

Thioridazine

a. *IUPAC*[16]: 10-[2-(1-Methyl–2–piperidinyl)ethyl]-2-(methylthio)-10H-phenothiazine

b. Molar mass[16] = C21H26N2S2=370.6

c. *Proprietary names*[16]: Mellaril-S; Melleretten; Melleril; Rideril

d. *Properties*[16]: A white or slightly yellow crystalline powder which darkens on exposure to light and M.P. 72° to 74°.Toxicity: The estimated minimum lethal dose is 1 g. Blood concentrations greater than about 2 mg/L may produce toxic effects and can be lethal; and with sulforidazine, a total concentration of 3 mg/L drug and metabolite is toxic. Half–life:

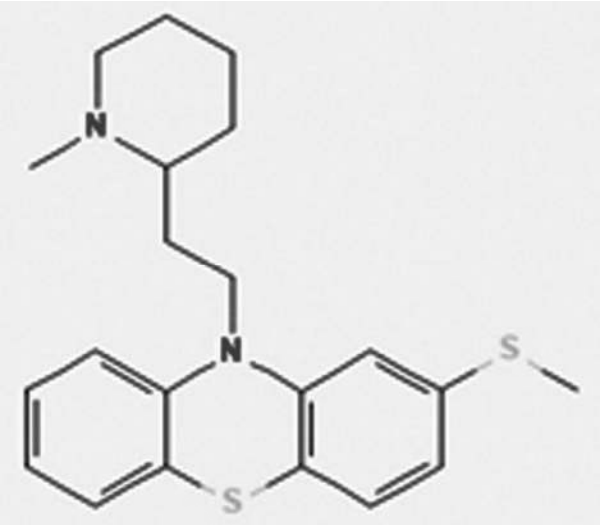

Fig. 3: Structure of Thioridazine[21]

Plasma half–life, 10 to 36 h.Dose.50 to 300 mg of thioridazine hydrochloride daily; maximum of 600 mg daily.

Thioridazine Hydrochloride[16]

Proprietary names. Aldazine; Mallorol; Mellaril; Melleretten (tablets); Melleril (tablets); Melzine; Novoridazine; Orsanil; Thioril; Thiozine.

C21H26N2S2, HCl=407.0

A white or slightly yellow crystalline powder. M.p. 158° to 160° (from acetone). Soluble 1 in 9 of water, 1 in 10 of ethanol and 1 in 1.5 of chloroform; freely soluble in methanol; practically insoluble in ether

Thioridazine is a phenothiazine antipsychotic used in the management of Phycoses, including Schizophrenia and used to control disturbed and agitated behaviour.[21]

Trifluoperazine

a. I.U.P.A.C[16]: 10-[3-(4-Methyl–1–piperazinyl)propyl]-2-(trifluoromethyl)-10H-phenothiazine

b. Molar mass[16]: C21H24F3N3S=407.5

c. Half–life[16]: Plasma half–life, 7 to 18 h (mean 12).

d. Dose[16]: For psychoses, the equivalent of 10 to 20 mg of trifluoperazine daily; more than 40 mg daily has been given.

e. Trifluoperazine Hydrochloride[16]: Synonym. Triph-thazinum

Proprietary names. Eskazine; Flupazine; Jatroneural; Modalina; Novoflurazine; Stelazine; Terfluzine; Triplex. It is an ingredient of Parstelin, and Stelabid.

C21H24F3N3S,2HCl=480.4

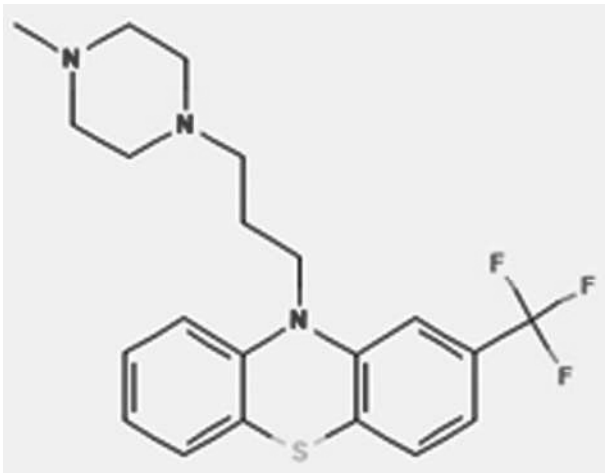

Fig. 4: Structure of Trifluoperazine[22]

A white to pale yellow, hygroscopic, crystalline powder. M.p. 242° to 243°.Soluble 1 in 2 of water, 1 in 11 of ethanol, and 1 in 100 of chloroform; practically insoluble in ether.[16]

Trifluoperazine is a trifluoro-methyl phenothiazine derivative intended for the management of schizophrenia and otherpsychotic disorders. It works by restoring the balance of certain natural substances in the brain. The medication is also used to treat short term anxiety.[23]

Drowsiness, dizziness, anxiety, dry mouth, stuffy nose, headache, tiredness, constipation, weight gain, insomnia, breast swelling or discharge, irregular menstrual cycle, impotence, swelling in hands or feet, tremors, seizures, slow heart rate, weak pulse, fatigue or slow breathing etc are some of the side effects of Trifluoperazine.[23]

Material and Methods

Standard: 10 mg of dothiepin, paroxetine, thioridazine, trifluoperazine procured from Sigma-Aldrich. 1000µg/ml solution was prepared.

Chemicals: Sodium Tungstate, Conc. Sulphuric Acid, Di ethyl ether, Dichloromethane, Anhydrous Sodium Sulphate, Methanol, Ammonia, Toluene, Carbon tetra chloride, Ethyl Methyl ketone, Chloroform, Ethanol, Acetone, Iso-propyl alcohol, Acetic acid, Ethyl acetate of analytical grade and procured from Merck India.

Glassware and others

Pre-coated Thin layer chromatographic plates

(silica gel G 60 F254 DC Kiesel gel 60 F254 CCM Gel silica gel 60 F254) procured from Merck Germany. Chromatographic Chamber, Beaker, Conical flask, separating funnel, evaporating bowl and pipettes, capillary tubes were from Borosil. Saturation paper to be used during TLC chamber saturation and paraffin sheet to cover and protect evaporating samples from contamination were also employed.

Extraction of dothiepin, paroxetine, thioridazine, trifluoperazine from Blood

Spiking of sample

5 ml of blood was spiked with 1 ml of working standard of each of Dothiepin, Paroxetine, Thioridazine, Trifluoperazine respectively and then kept overnight in incubator.

Deproteinization

100 mg of sodium tungstate and 3ml of conc. Sulphuric acid was added to 5 ml of spiked blood and subjected to heat at 60 C for 2-3 min then cool it down and filtered.

Liquid-liquid extraction

Filtrate was subjected to liquid–liquid extraction with 20 ml of di ethyl ether and di-chloromethane. Separate the two aqueous and organic layers. Repeat the same for three times with aqueous layer. Separated organic layer was allowed to pass through anhydrous ammonium sulfate and was air dried and concentrated up to 1 ml.

Activation of Thin layer chromatographic plates/ Saturation of TLC developing chamber:

TLC plates were placed at 105 degrees Celsius for 30 min for activation. The developing chamber was saturated for 30min with different reagent as per Table-1

Spotting of Samples and Standards:

Extracted samples were loaded on the TLC plates along with the standard using fine capillaries with appropriate marking. Loaded plates were developed in 15 solvent systems as per Table -1given below

Solvent System Preparation:

15 different solvent systems were prepared by hit and trial method keeping in consideration the drug being analysed whose composition and ratio are mentioned in table-1.

Preparation Of Spray Reagent:

Dragendroff reagent is the solution made by mixing of two solutions A and B.

Solution A- 0.5g of bismuth nitrate into beaker and 10 ml of concentrated HCl was added.Solution B-4g of potassium iodide into another beaker and water was added until KI is completely dissolved. The two solutions were mixed in equal amount and used as spray reagent

Table 1: Various solvent system

S.No.	Solvent System			
1	Hexane: Acetone	80	20	
2	Methanol: NH_3	100	0.5	
3	Ethanol: NH_3	100	0.5	
4	Ethyl acetate: Toluene	50	50	
5	Ethyl acetate: Toluene	80	20	
6	Ethyl acetate: Toluene	20	80	
7	Butanol: NH_3			
8	Chloroform: Methanol	50	50	
9	Ether: Methanol	50	50	
10	Amyl alcohol: Dichlor-omethane: Methanol	10	5	5
11	Chloroform: Acetone	50	50	
12	Cyclohexane: CCl4: Methanol	10	5	5
13	Methanol: EMK: NH_3	15	5	0.5
14	Methanol: EMK: NH_3	10	10	0.5
15	Ethyl Acetate: NH_3	100	0.5	

Result and Discussion

After development of chromatogram, the TLC plates were exposed to UV light of 254nm wavelength to determine the separation. Then the TLC plates were sprayed with Dragendroff solution, orange colour spots were observed with yellow background. The Rf value of samples and standard were calculated and values obtained has been reported in observation tables respectively.

Out of 15 solvent systems {prepared by self-analysis}, positive results were obtained in only 9 solvent system which showed clear spot. table-2, 3, 4 & 5

- UV-light examination is a preliminary analysis to check the developed spots before spraying reagent. The developed TLC plate is exposed to ***short wave UV-light of 254 nm so that the UV active compounds present in sample undergo fluorescence quenching and appear as dark spots on a bright background.***[25] Visualisation of developed TLC plates were done as a preliminary spot analysis.

- Dragendr off Reagent is a colourless reagent that helps in detection of alkaloids present in the test sample by producing an orange and orange-red precipitate. It's a solution of potassium bismuth iodide prepared from basic bismuth nitrate {Bi $(NO_3)_3$}, tartaric acid and potassium iodide {KI}. Selective and specific alkaloids reagents are various modifications of Dragendroff's reagent and potassium iodoplatinate which react with ***tertiary and quaternary Nitrogen atoms.***[26] The nitrogen atoms present in Dothiepin, Paroxetine, Thioridazine, Trifluoperazine (on developed TLC plate) reacted with Dragendroff reagent and showed Bright orange spots with yellow background confirming their presence. (Image 5-8)

Table 2: Retention Factor of DOTHEIPIN in various solvent systems:

S.NO.	Solvent System				RF {Dothiepin in blood}	RF {Std. Dothiepin}
1.	Hexane : Acetone	80	20		-	-
2.	Methanol: NH_3	100	0.5		0.49	0.48
3.	Ethanol: NH_3				0.49	0.5
4.	Ethyl acetate: Toluene	50	50		-	-
5.	Ethyl acetate: Toluene	80	20		-	-
6.	Ethyl acetate: Toluene	20	80		-	-
7.	Butanol: NH_3	-			-	-
8.	Chloroform: Methanol	50	50		0.529	0.54
9.	Ether: Methanol	50	50		0.31	0.30
10.	Amyl alcohol: Dichlorome-thane: Methanol	10	5	5	0.22	0.23
11.	Chloroform: Acetone	50	50		0.12	0.12
12.	Cyclohexane: CCl_4: Methanol	10	5	5	0.41	0.40
13.	Methanol: EMK: NH_3	15	5	0.5	0.40	0.40
14.	Methanol: EMK: NH_3	10	10	0.5	0.35	0.36
15.	Ethyl Acetate: NH_3		100	0.5	-	Tailing

Table 3: Retention factor of Paroxetine in various solvent system

S.No.	Solvent System				RF {Paroxetine in blood}	RF {Std. Paroxetine}
1.	Hexane : Acetone	80	20		-	-
2.	Methanol: NH_3	100	0.5		0.21	0.22
3.	Ethanol: NH_3				0.21	0.21
4.	Ethyl acetate: Toluene	50	50		-	-
5.	Ethyl acetate: Toluene	80	20		-	-
6.	Ethyl acetate: Toluene	20	80		-	-
7.	Butanol: NH_3	-			-	-
8.	Chloroform: Methanol	50	50		0.21	0.21
9.	Ether: Methanol	50	50		0.12	0.13
10.	Amyl alcohol: Dichlorome-thane: Methanol	10	5	5	0.12	0.11
11.	Chloroform: Acetone	50	50		-	-
12.	Cyclohexane: CCl_4: Methanol	10	5	5	0.41	0.40
13.	Methanol: EMK: NH_3	15	5	0.5	0.49	0.50
14.	Methanol: EMK: NH_3	10	10	0.5	0.44	0.43
15.	Ethyl Acetate: NH_3		100	0.5	-	Tailing

Table 4 : Retention Factor of Thioridazine in various solvent system

S.No.	Solvent System				RF {Thioridazine in blood}	RF {Std. Thioridazine}
1.	Hexane : Acetone	80	20		-	-
2.	Methanol: NH_3	100	0.5		0.39	0.38
3.	Ethanol: NH_3				0.41	0.42
4.	Ethyl acetate: Toluene	50	50		-	-
5.	Ethyl acetate: Toluene	80	20		-	-
6.	Ethyl acetate: Toluene	20	80		-	-
7.	Butanol: NH_3				-	-
8.	Chloroform: Methanol	50	50		0.589	0.6
9.	Ether: Methanol	50	50		0.22	0.22
10.	Amyl alcohol: Dichlorome-thane: Methanol	10	5	5	0.15	0.14
11.	Chloroform: Acetone	50	50		0.078-	0.08
12.	Cyclohexane: CCl_4: Methanol	10	5	5	0.349	0.35
13.	Methanol: EMK: NH_3	15	5	0.5	0.35	0.36
14.	Methanol: EMK: NH_3	10	10	0.5	0.28	0.27
15.	Ethyl Acetate: NH_3	100	0.5		-	Tailing

Table 5 : Retention Factor of Trifluoperazine in various solvent systems

S.No.	Solvent System				RF {Trifluoperazine in blood}	RF {Std. Trifluoperazine}
1.	Hexane : Acetone	80	20		-	-
2.	Methanol: NH_3				0.48	0.49
3.	Ethanol: NH_3				0.42	0.41
4.	Ethyl acetate: Toluene	50	50		-	-
5.	Ethyl acetate: Toluene	80	20		-	-
6.	Ethyl acetate: Toluene	20	80		-	-
7.	Butanol: NH_3				-	-
8.	Chloroform: Methanol	50	50		0.48	0.48
9.	Ether: Methanol	50	50		0.28	0.27
10.	Amyl alcohol: Dichlorome-thane: Methanol	10	5	5	0.28	0.29
11.	Chloroform: Acetone	50	50		0.07	0.06
12.	Cyclohexane: CCl_4: Methanol	10	5	5	0.368	0.37
13.	Methanol: EMK: NH_3	15	5	0.5	0.41	0.42
14.	Methanol: EMK: NH_3	10	10	0.5	0.32	0.31
15.	Ethyl Acetate: NH_3	100	0.5		-	Tailing

Conclusion

New solvent systems were developed for Extraction and identification of Dothiepin, Paroxetine, Thioridazine, Trifluoperazine from blood. The performed method is economic and easy to perform with all chemical and apparatus readily available in the laboratory. The solvent system used in the study showed clear spot of active constituent target analyte in blood samples which are matched with the standards.

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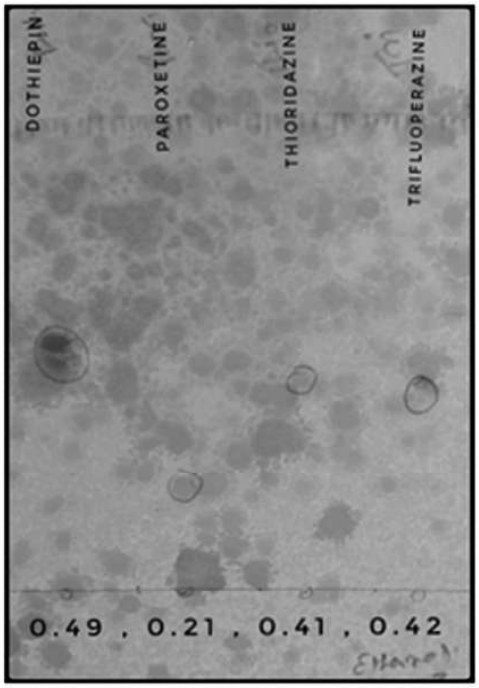

Fig. 5: Rf in Ethanol: AmmoniaImage

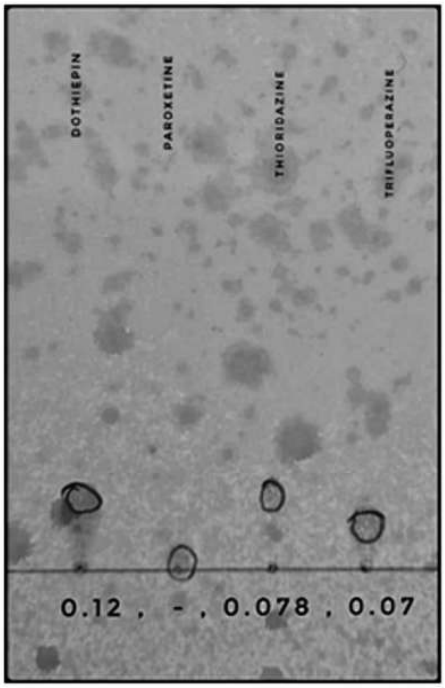

Fig. 6: Rf in Chloroform: Acetone

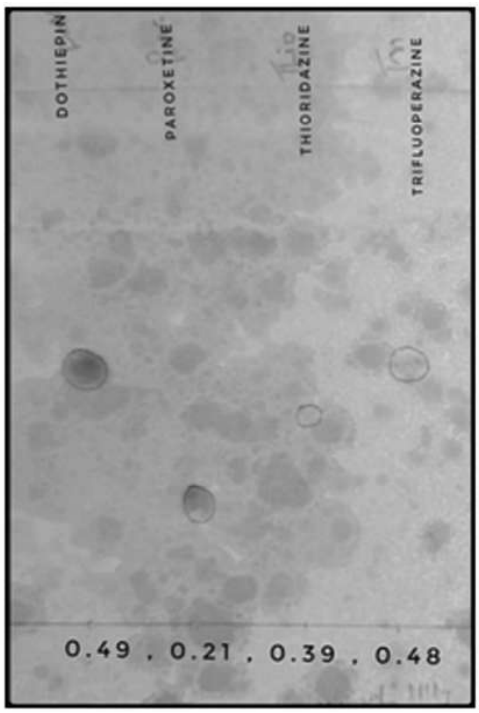

Fig. 7: Rf in Methanol: Ammonia

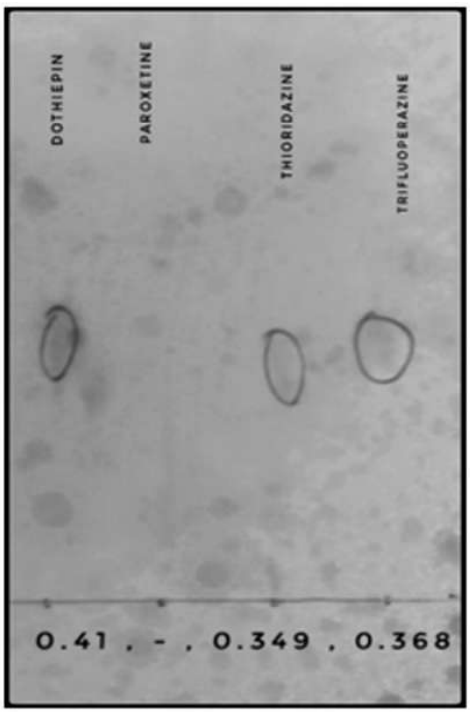

Fig. 8: Rf in Cyclohexane: CCl4: Methanol

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