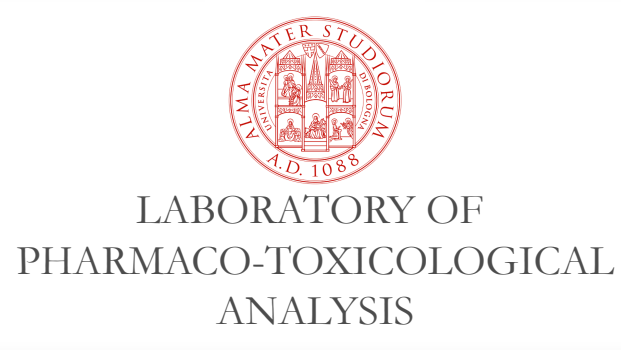


THERAPEUTIC DRUG MONITORING (TDM) BY MEANS OF NOVEL SAMPLING AND EXTRACTION PROCEDURES: A COMPARATIVE STUDY

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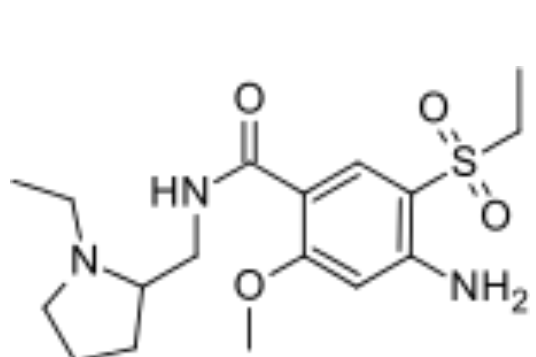
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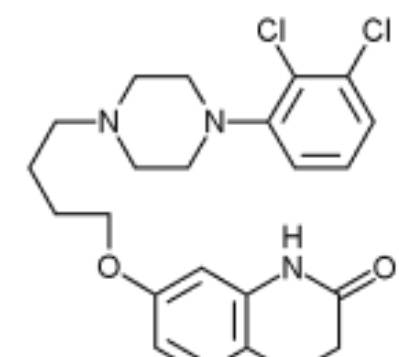


THERAPEUTIC DRUG MONITORING (TDM)

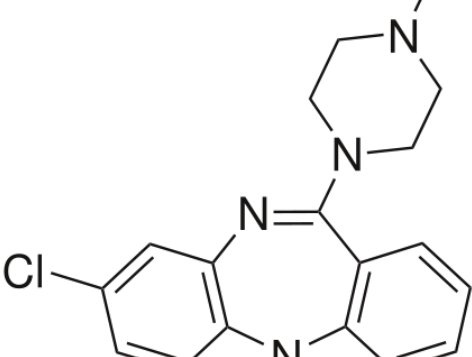
The therapeutic drug monitoring (TDM) is designed to study important correlations between the administered drug dosage and the related levels found in biological matrices, to better understand therapeutic effects, side effects and toxicity. In this work TDM is applied to psychiatric patients undergoing therapy with central nervous system drugs, particularly with atypical antipsychotics. The biological matrices most commonly used for TDM purpose are blood, plasma and serum but some crucial issues concerning their sampling and pretreatment are still present



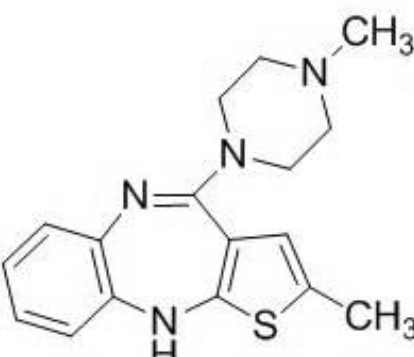
Amisulpride



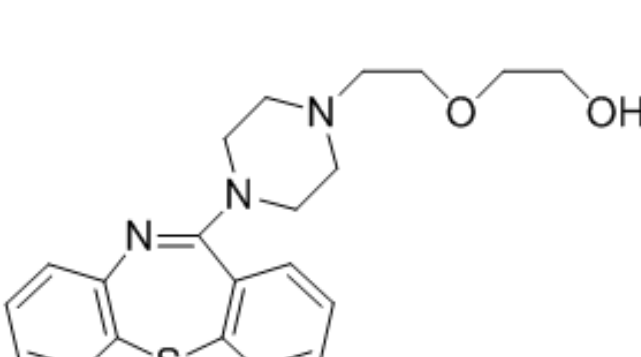
Aripiprazole



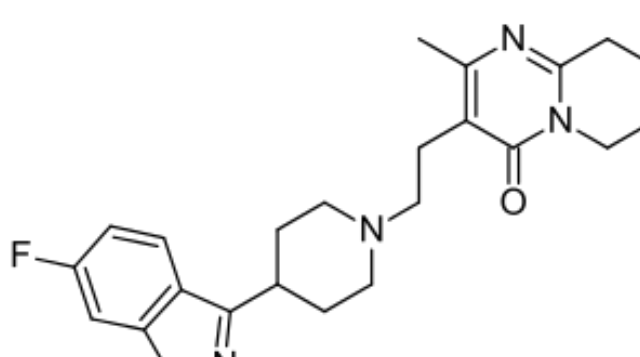
Clozapine



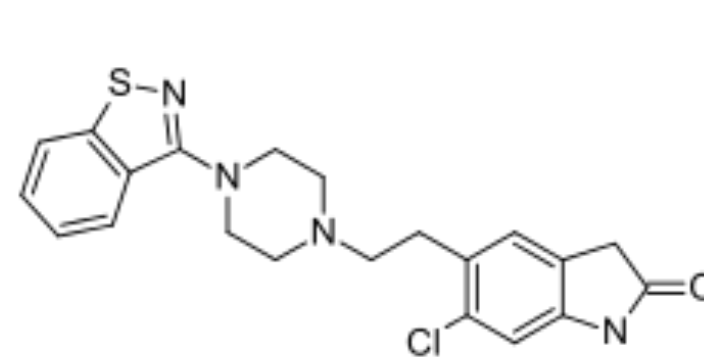
Olanzapine



Quetiapine



Risperidone



Ziprasidone

CONVENTIONAL SAMPLING



BLOOD

- ❖ Invasive collection
- ❖ Storage and transportation issues
- ❖ Need for refrigeration
- ❖ Enzymatic and bacterial degradation
- ❖ Time consuming pretreatment



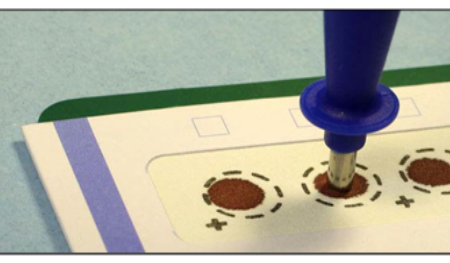
PLASMA
SERUM

- ❖ After-sampling processes
- ❖ Careful handling
- ❖ Biological hazard
- ❖ Risk for sample contamination
- ❖ High cost process

DRIED MATRIX SPOTS

Paper-like support issue related to:

- ❖ matrix effect
- ❖ quantitative extraction



BLOOD: Capillary blood from a finger prick blotted onto a card
PLASMA/SERUM: Collection of a sample fixed volume of 10 µL

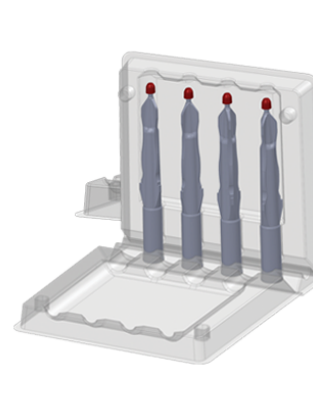
AIM OF THE RESEARCH

This study proposed an innovative and alternative approach for the TDM of psychiatric patients treated with some atypical antipsychotic drugs



10 µL of matrix by means of
VOLUMETRIC ABSORPTIVE MICROSAMPLING
and **DRIED MATRIX SPOTS**

VOLUMETRIC ABSORPTIVE MICROSAMPLING



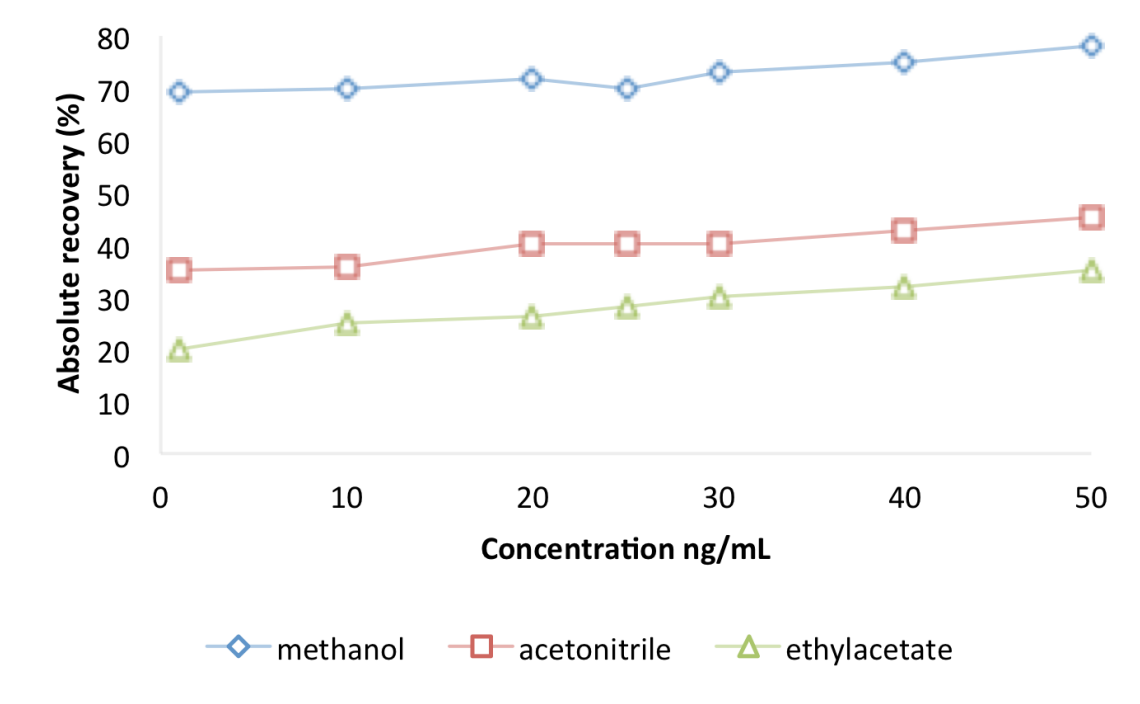
Polymeric tip which absorbs an accurate sample volume of 10 µL by wicking for 2 seconds and drying at RT

METHOD VALIDATION ON "BLANK" MATRICES: ABSOLUTE RECOVERY (%)

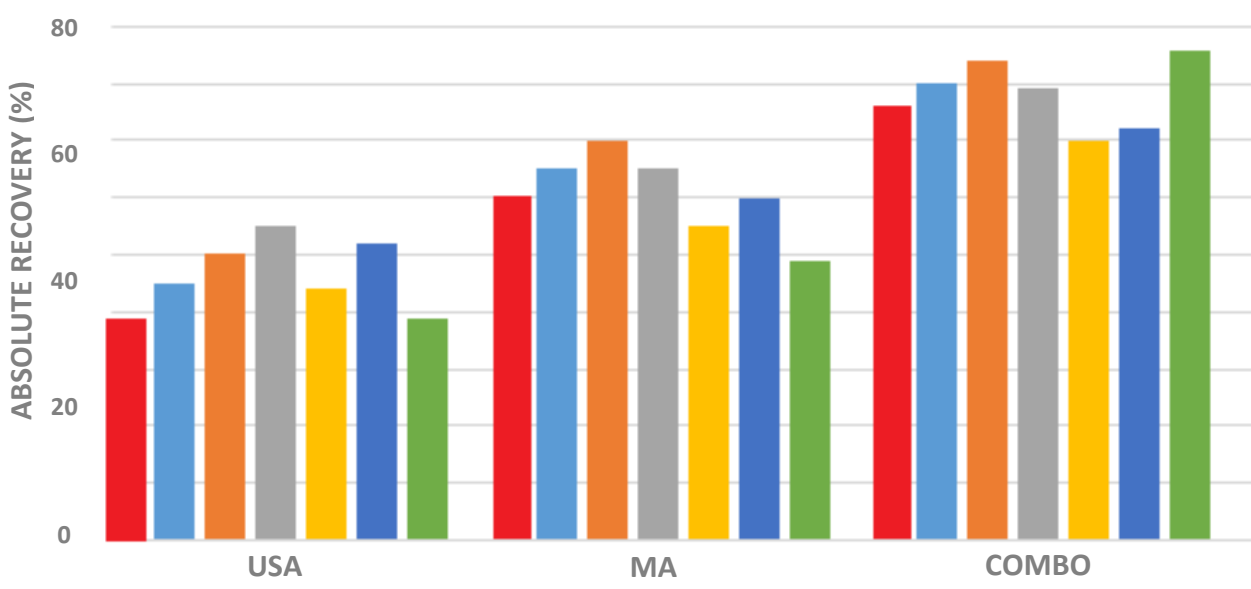
DRIED MATRIX SPOTS	BLOOD (DBS)	PLASMA (DPS)	SERUM (DSS)	VOLUMETRIC ABSORPTIVE MICROSAMPLING	FROM BLOOD	FROM PLASMA	FROM SERUM
AMISULPRIDE	65	65	64	AMISULPRIDE	67	70	70
ARIPRAZOLE	69	67	66	ARIPRAZOLE	70	71	70
CLOZAPINE	64	65	64	CLOZAPINE	73	72	72
OLANZAPINE	65	62	63	OLANZAPINE	69	70	69
QUETIAPINE	60	62	61	QUETIAPINE	60	60	61
RISPERIDONE	61	60	62	RISPERIDONE	63	64	55
ZIPRASIDONE	62	63	60	ZIPRASIDONE	77	76	74

METHOD VALIDATION ON "BLANK" MATRICES: EXTRACTION SOLVENT

TESTED EXTRACTION SOLVENTS:
♦ methanol
♦ acetonitrile
♦ ethylacetate



METHOD VALIDATION ON "BLANK" MATRICES: EXTRACTION PROCEDURE TYPE

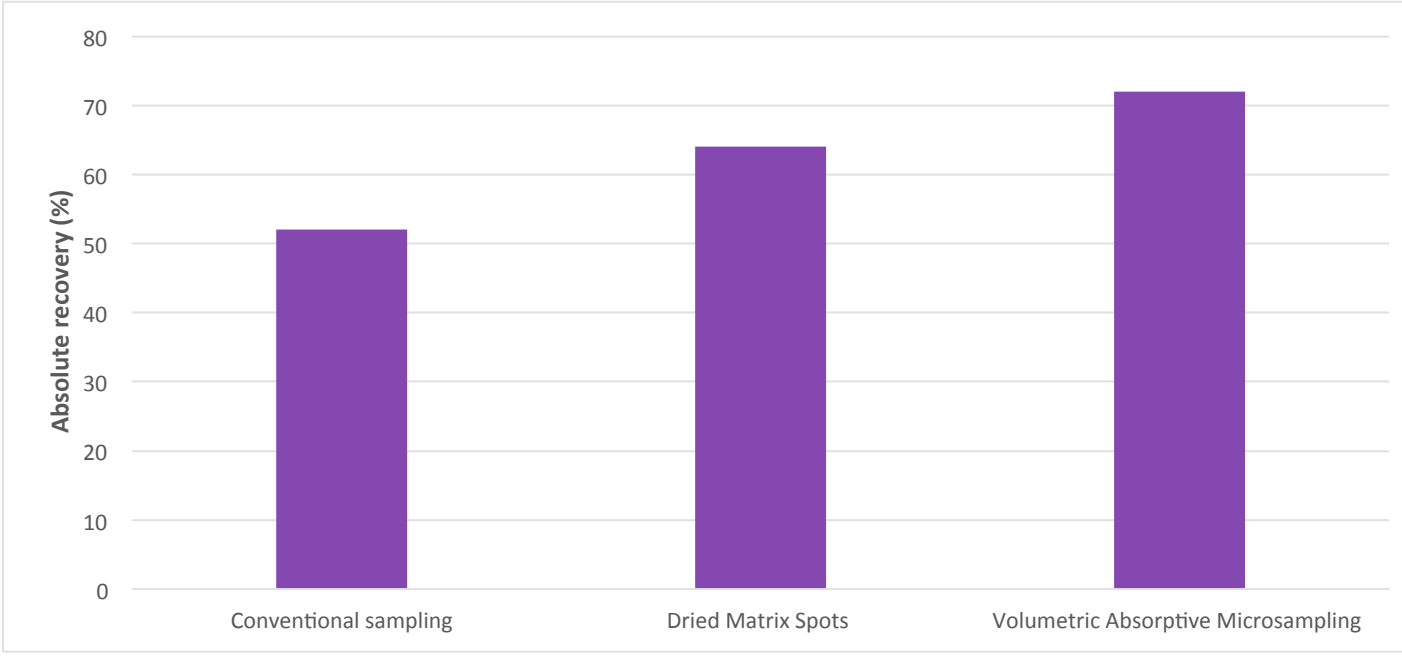


USA = ultrasound agitation (5 min)
MA = microwaves (15 sec)
COMBO = USA (5 min) + MA (15 sec)

♦ AMISULPRIDE
♦ ARIPIRAZOLE
♦ CLOZAPINE
♦ OLANZAPINE
♦ QUETIAPINE
♦ RISPERIDONE
♦ ZIPRASIDONE

COMPARATIVE STUDY ON "BLANK" MATRICES: ABSOLUTE RECOVERY (%)

CONVENTIONAL SAMPLING
= liquid-liquid extraction
DRIED MATRIX SPOTS
= DBS, DPS, DSS
VOLUMETRIC ABSORPTIVE MICROSAMPLING
= from blood, plasma, serum



COMPARATIVE STUDY ON "REAL" SAMPLES: TDM OF PSYCHIATRIC PATIENTS

CONVENTIONAL SAMPLING	BLOOD	PLASMA	SERUM
PATIENT 1 amisulpride	320 ng/mL	318 ng/mL	320 ng/mL
PATIENT 2 aripiprazole	120 ng/mL	124 ng/mL	119 ng/mL
PATIENT 3 clozapine	400 ng/mL	410 ng/mL	397 ng/mL
PATIENT 4 olanzapine	22 ng/mL	23 ng/mL	21 ng/mL
PATIENT 5 quetiapine	110 ng/mL	112 ng/mL	111 ng/mL
PATIENT 6 risperidone	23 ng/mL	22 ng/mL	22 ng/mL
PATIENT 7 ziprasidone	140 ng/mL	138 ng/mL	139 ng/mL

DMS	BLOOD (DBS)	PLASMA (DPS)	SERUM (DSS)
PATIENT 1 amisulpride	321 ng/mL	320 ng/mL	319 ng/mL
PATIENT 2 aripiprazole	123 ng/mL	124 ng/mL	120 ng/mL
PATIENT 3 clozapine	410 ng/mL	415 ng/mL	403 ng/mL
PATIENT 4 olanzapine	22 ng/mL	24 ng/mL	23 ng/mL
PATIENT 5 quetiapine	115 ng/mL	112 ng/mL	113 ng/mL
PATIENT 6 risperidone	24 ng/mL	22 ng/mL	24 ng/mL
PATIENT 7 ziprasidone	148 ng/mL	141 ng/mL	141 ng/mL

VAMS	FROM BLOOD	FROM PLASMA	FROM SERUM
PATIENT 1 amisulpride	323 ng/mL	321 ng/mL	320 ng/mL
PATIENT 2 aripiprazole	125 ng/mL	124 ng/mL	119 ng/mL
PATIENT 3 clozapine	408 ng/mL	412 ng/mL	400 ng/mL
PATIENT 4 olanzapine	21 ng/mL	21 ng/mL	20 ng/mL
PATIENT 5 quetiapine	116 ng/mL	112 ng/mL	114 ng/mL
PATIENT 6 risperidone	22 ng/mL	22 ng/mL	24 ng/mL
PATIENT 7 ziprasidone	144 ng/mL	139 ng/mL	143 ng/mL

CONCLUSION

The present method was validated on "blank" matrices and then applied to "real" samples from psychiatric patients treated with atypical antipsychotics. The TDM has been performed on dried fluids obtained as dried matrix samples and volumetric absorptive microsamples (blood, plasma and serum).

The use of dried microvolumes has proved to be able to grant the golden standard features for drug determination, therapeutic and side effect correlations, but allowing to overcome issues and weaknesses due to traditional analyses.

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