REVIEW ARTICLE

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A Concise Review on Characteristics and Analytical Methods of Paroxetine

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Abstract: Paroxetine (PAX) is a powerful and selective serotonin reuptake inhibitor (SSRI) with some neuropharmacological properties used mainly for the treatment of anxiety and depression. Due to the first pass degradation, PAX suffers poor bioavailability issues and this limits its clinical application. In context to this, the present review focuses the various formulations related with transdermal liposomes, nano emulsion via olfactory region and brain targeted intranasal in-situ gelling spray for the management of depression. Additionally, we also discuss about the various analytical methods such as HPLC, HPTLC, UV, LC-MS/MS, GC-MS which are reliable and sensitive for the quantification of PAX in different pharmaceutical dosage forms. This concise review presents the survey of physiochemical properties, transdermal as well as intranasal drug delivery systems and analytical methods used for PAX determination, being carried out through scientific journals as well as official compendia.

INTRODUCTION

Drug Profile

Paroxetine (PAX) is a selective serotonin reuptake inhibitor (SSRI). [1] It is used to treat several diseases, including major depressive disorder, obsessive-compulsive disorder, social anxiety disorder, panic disorder, posttraumatic stress disorder, generalized anxiety disorder and premenstrual dysphonic disorder. It is used in the treatment of hot flashes and night sweats that are associated with menopause. As an SSRI class drug, PAX signature mechanism of action is to block the serotonin reuptake transporter (SERT) and thus increase the concentration of synaptic serotonin. [2] Current theory suggests that the diminished serotonin concentration in the depressed brain induces the up regulation of serotonergic receptors. By increasing the synaptic serotonin concentration, PAX thus induces the down regulation of the previously unregulated serotonin receptors, thus normalizing the receptor concentration. [3] Furthermore, in a radioligand study, PAX showed some affinity for muscarinic, adrenergic (alpha and beta), dopaminergic (D2), serotonergic (5-HT2) and histaminergic (H1) receptors. [4] These receptors have also appeared to contribute to its antidepressant effects, as well as its side effect profile. PAX is administered orally. The medication should be titrated based on the patient's symptoms and tolerance to dosage. The drug can be taken with or without food. In addition to regular tablets, it is available in a controlled-release tablet, as well as liquid form. PAX may be administered at any time of the day, depending on toleration. [5] The steady-state mean values of T1/2is 21 hours. PAX undergoes metabolism via hepatic CYPP450 2D6. The urine excretes 2%, 62% metabolized over a 10-day post-dosing period, 36% excreted in the feces. PAX inhibits CYP2D6 and thus, its own metabolism; plasma concentrations can potentially double following dosage increases of 50%.Concomitant use of MAOIs and PAX can precipitate serotonin syndrome. Concurrent use of thioridazine and PAX can induce cardiac arrhythmias; similar effects can occur with pimozide and PAX. PAX inhibits TCA metabolism, leading to possible TCA toxicity. TAM is active once metabolized by CYP4502D6; thus, PAX essentially inactivates tamoxifen.PAX is not recommended for use during pregnancy or if breastfeeding. Based on epidemiological studies, infants exposed to PAX during the first trimester had an increased risk for cardiovascular malformations. Though it is rarely lethal in overdose by itself, patients can develop somnolence, nausea, tremor, heart rhythm disturbances, confusion, vomiting, dizziness and mydriasis. During toxicity, a patient's airway, oxygenation and ventilation require evaluation first. The treatment for overdose includes symptomatic supportive treatment. There is no specific treatment for PAX toxicity.

Physicochemical Properties

PAX is an odorless, off-white powder, having a melting point range of 120° to 138°C and a solubility of 5.4 mg/moL in water. [2, 6] The Molecular formula of $C_{19}H_{20}FNO_3$•HCl•1/2H_2O. The molecular weight is 374.8 g/moL (329.4 as free base). Figure 1 represents the structural formula of PAX hydrochloride.

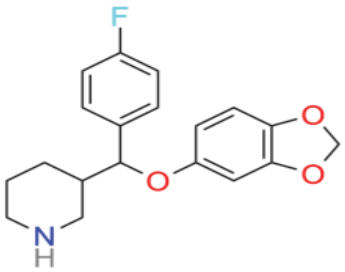

Figure 1: Molecular structure of paroxetine (PAX)

The pka value of PAX is 9.77 and hence it is a strongest base.PAX is official in USP. IUPAC name of TAX is (3S, 4R)-3- [(2H-1, 3-benzodioxol-5-yloxy) methyl]-4-(4-fluorophenyl) piperidine. Various dosage forms and multi-component solid forms were utilized to develop robust formulation of poorly water soluble drugs. [7-10]

PAROXETINE: TRANSDERMAL DRUG DELIVERY SYSTEM

PAX is the most potent serotonin reuptake blocker antidepressant clinically available. This study is aimed to

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reduce the side effects accompanied with the initial high plasma concentration after oral administration of PAX and fluctuations in plasma levels and also to decrease the broad metabolism of the drug in the liver by developing and optimizing liposomal transdermal formulation of PAX in order to improve its bioavailability. PAX liposomes were prepared by reverse phase evaporation technique using lecithin phosphatidylcholine (LPC), cholesterol (CHOL) and drug in different molar ratios. The prepared liposomes were characterized for size, shape, entrapment efficiency and in vitro drug release. The studies demonstrated successful preparation of PAX liposomes. The effect of using different molar ratios of (LPC: CHOL) on entrapment efficiency and on drug release was studied. Liposomes showed percentage entrapment efficiency of 81.22 ± 3.08% for optimized formula (F5) which composed of (LPC: CHOL, 7:7) and 20mg of PAX, with average vesicle size of 220.53 ± 0.757 nm. The selected formula F5 (7:7) was incorporated in gel bases of HPMC-E4M (2%, 4% and 6%). The selected formula of PAX liposomal gel of HPMC-E4M (2% and 4%) was fabricated in the reservoir type of transdermal patches and evaluated through *in-vitro* release. After that the selected formula of PAX liposomal gel transdermal patch was applied to rabbits for *in-vivo* bioavailability study in comparison with oral administration of the marketed PAX tablet. An HPLC method was developed for the determination of PAX in plasma of rabbits after transdermal patch application and oral administration of the marketed PAX tablets of 20 mg dose. The intra- and inter-day accuracy and precision were determined as relative error and relative standard deviation, respectively. The linearity was assessed in the range of 5-200 ng/ml. Pharmacokinetic parameters were determined as the C(max) of PAX liposomal transdermal patch was found to be 92.53 ng/ml at t(max) of 12h and AUC(0-48) was 2305.656 ng/ml and AUC(0-∞) was 3852.726 ng/ml, compared to the C(max) of 172.35 ng/mL after oral administration of the marketed PAX tablet with t(max) of 6h and AUC(0-24) was 1206.63 ng/ml and AUC(0-∞) was 1322.878 ng/ml. These results indicated the improvement in bioavailability of the PAX after liposomal transdermal patch application and sustaining of the therapeutic effects compared to oral administration. [11]

Effect of p-Menthane Derivatives on Skin Permeation of PAX

PAX, which is one of the most frequently prescribed antidepressants, is marketed as an oral preparation; however, a transdermal system is required to improve the patient's adherence. In this study, to enhance the penetration of PAX using p-menthane derivatives. The result from invitro skin penetration indicates that the permeability of PAX can be enhanced greatly by using a PAX hydrogel containing p-menthane derivatives. By increasing effects was affected by the thermodynamic activity of derivatives in hydrogel. In addition, Quantitative structure-activity relationship (QSAR) studies to relate the increasing effect of physiochemical properties of p-menthane derivatives. Result of QSAR studies indicated that the partition coefficient, absolute electron negativity, polarizability, solvent accessible surface area and dipole moment of p-menthane derivatives as important factors related by an enhancement effect. Result supports feasibility of delivering PAX transdermally using p-menthane derivatives. [12]

Brain Targeted Intranasal *In-Situ* Gelling Spray of PAX: Formulation, characterization and *In-Vivo* Evaluation

PAX is a medicine employed to treat major depression, social mental disturbances, panic and anxiety conditions etc. The high hepatic first pass effect of PAX leads to low oral bioavailability. Intranasal delivery of drug leads to bypassing of first pass metabolism by direct delivery of drug to site of action i.e., brain. [13]

Intranasal Delivery of PAXnano Emulsion via the Olfactory Region for the Management of Depression: Formulation, Behavioral and Biochemical Estimation

PAX is a selective serotonin reuptake inhibitor (SSRI) and is used for the treatment of depression and anxiety problems, but suffers from the drawback of poor oral bioavailability (less than 50%) due to its extensive first pass metabolism. The objective of the present study was to develop a PAX loaded nano emulsion (o/w type) for direct nose-to-brain delivery. Nano emulsions were prepared by the spontaneous emulsification technique using Capmul MCM, Solutol HS 15 and propylene glycol as oil phase, surfactant and co-surfactant, respectively, for delivery of drug directly to the brain through the nasal route for better management of depression. Formulations were studied for droplet size, polydispersity index (PDI), percentage transmittance, refractive index, viscosity, zeta potential, surface morphology and *in-vitro* permeation study. TEM images of optimized formulation showed spherical droplets with a mean diameter of 58.47±3.02 nm, PDI of 0.339±0.007 and zeta potential values of -33 mV. The formulation showed good results for transmittance (100.60±0.577%), refractive index (1.412±0.003) and viscosity (40.85±6.40 cP). Permeation studies revealed a 2.57-fold enhancement in permeation as compared to the PAX suspension. Behavioral studies such as the forced swimming test and locomotors activity test were done on Wistar rats to study the antidepressant effect of the optimized formulation. Treatment of depressed rats with PAX nano emulsion (administered intranasally) significantly improved the behavioral activities in comparison to PAX suspension (orally administered). Biochemical estimation results revealed that the prepared nano emulsion was effective in enhancing the depressed levels of glutathione and decreasing the elevated levels of TBARS. [14]

ANALYTICAL METHODS

UV Spectrometric Method

A simple, precise, accurate, economical and reliable UV spectrophotometric method has been developed for the estimation of PAX in tablet dosage form. The method was successfully applied to pharmaceutical formulation because no interferences from the tablet excipient were found. It was

Table 1: Chromatographic Technique Used for Determination of PAX in Given in Various Dosage Form

Method	Analytical Conditions	Detection	Matrix	Reference
HPTLC	S.P: Precoated Silica gel 60F254 Aluminium sheets M.P: ethyl acetate: acetic acid: water (7.5:1.5:1%v/v)	296nm	Tablet	[18]
HPTLC	S.P: Aluminium Precoated silica Gel 60F254 M.P: butanol: acetic acid: water (8:2:0.5 v/v/v)	295nm	Bulk drug	[17, 18]
HPLC	Column: XDB C-18 5µm Mobile phase: Acetonitrile: Phosphate buffer (30:70 v/v) Flow rate: 1ml/min	Fluorescence Detector excitation Λ=295nm And emission Λ=350nm	Plasma	[19-21]
Green Chromatography (TLC+RP-HPLC)	TLC: S.P: Silica gel 60F254 M.P: ethyl Acetate: ethanol: Ammonia (8:2:0.05) RP-HPLC: Xterra HPLC RP C18 Column M.P: methanol:KH_2PO_4 (70:30 v/v) Flow rate: 1ml/min	TLC: 240nm RP-HPLC: 240nm	Rat plasma	[22] [23]
RP-HPLC	Column C18(ODS) M.P: Phosphate Buffer: Acetonitrile (50:50 v/v) Flow rate: 2ml/min	265nm	Bulk and tablet Dosage form	[24, 25]
HPLC	Column: Isocratic Mobile phase: Phosphate buffer: Acetonitrile (50:50 v/v)	-	Human plasma	[26-28]
LC-MS/MS	Ammonium buffer M.P: Water: Ammonium formate (1000:20 v/v)	-	Human Plasma	[29]
LC-MS/MS	Column- C18 M.P: Ethyl acetate/Hexane (50/50 v/v)	-	Human Plasma	[17]
GC-MS	Column: Methyl siloxane Capillary Carrier gas: Helium Flow rate: 1ml/min Retention time: 4.18	-	Used in Postmortem fluids and tissue	[30-32]

Table 2: Parameters of Micellar Liquid Chromatography

Parameters	Variation	Sensitivity
Applied voltage(V)	0.78-0.82	56.6±1.3(2.24)
Flow rate	0.9-1.1	56.4±0.6(0.99)
Injection volume	18-22	56.5±1.1(1.87)
1-Pentanol (%)	5.5-6.5	56.5±0.4(0.72)
SDS(M)	0.145-0.155	56.3±0.5(0.81)
Ph	2.8-3.2	56.4±0.6(1.06)

Table 3: PAX Combined with Other Drugs in the Different Matrices

Other Combined Drugs	Method	Analytical Condition	Detection	Matrix	Reference
PAX+ clonazepam	HPTLC	S.P: Aluminium plates precoated silica gel 60 F254 M.P: methanol: glacial acetic acid: water (9:2:0.5%v/v)	288nm	Bulk and tablet	[35]
PAX+ clonazepam	RP-HPLC	Column: Interstile ODS 3V column C18 M.P: Phosphate buffer: methanol: water (3:2:5) Flow rate: 1ml/min	224nm	Pharmaceutical dosage form	[24]
PAX+ 7-chloro- 4-nitrobenzo-2-oxa-1,3-diazole	HPLC	Column: Nucleosil M.P: Acetonitrile: sodium acetate buffer: methanol (47:47:6 v/v)	530nm	Human plasma	[36]

found to be accurate and reliable for routine quantification of PAX. In this UV method, analytical conditions as follows:

Maximum wavelength (λ_{max}) = 293nm;

LOD=0.38814µg/ml;

LOQ=1.17618µg/ml. [15, 16]

Chromatographic Techniques

Chromatographic analytical methods for qualitative and quantitative determination of PAX are important in the discovery and development of pharmaceutical and biopharmaceutical product. Some different analytical methods such as HPLC, HPTLC, Green chromatography, LC-MS/MS and GC-MS. [17]

Micellar Liquid Chromatography

It is a mode of HPLC in which solution of surfactants at a concentration above their critical micellar concentration are employed as mobile phases. It can distribute between the aqueous mobile phase and the micellar mobile pseudo phase, between the stationary phase and micellar pseudo phase and between stationary and aqueous mobile phases. For highly hydrophobic compounds, a direct- transfer mechanism from the micellar to the stationary phase has been proposed. [33] Table 2 represents all the characteristic parameters of micellar liquid chromatograph. [34]

PAX WITH OTHER COMBINED DRUGS

Table 3 demonstrates the various quantification methods of PAX with other drug combinations used for assaying drugs in different matrices.

CONCLUSION

Among the studies analyzed in this review, most described the use of HPLC technique for PAX determination, but also report the use of UV/Vis spectrophotometric method, GC-MS and LC-MS/MS. This article also reviews brain targeted intranasal gelling spray and nano emulsion which enhanced bioavailability of PAX. MLC technique is specific, rapid, precise and inexpensive for routine analysis of PAX in serum and urine. Review of transdermal drug delivery system with the help of liposome for enhancing bioavailability of PAX. Simple, accurate and validated chromatographic methods HPLC and MLC were proposed for the simultaneous determination of CLZ and PAX. From the present review, the analytical methods have greater importance for therapeutic monitoring of PAX, which is used for management of depression.

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