A Review : Effect of Combination of Olanzapine And Samidorphan Drug

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Abstract- *Olanzapine is a second-generation antipsychotic with established efficacy in several psychiatric disease states, but its use is limited because of weight gain and metabolic side effects. Samidorphan is a novel opioid antagonist that binds to mu-opioid, kappa-opioid, and delta-opioid receptors and is hypothesized to reduce cravings for high-calorie foods thus attenuating antipsychotic-induced weight gain. The combination product olanzapine/samidorphan was approved by the US Food and Drug Administration in June 2021 for the treatment of schizophrenia and bipolar I disorder.Olanzapine-samidorphan combination tablets (OLZ/SAM), branded as Lybalvi, is a newly FDA approved formulation aimed at attenuating antipsychotic induced weight gain via modulation of the endogenous opioid system with samidorphan, while retaining the robust antipsychotic efficacy of olanzapine.OLZ/SAM had no clinically relevant effect on electrocardiogram parameters in a dedicated thorough QT study. Overall, safety and tolerability findings from clinical studies with OLZ/SAM indicate a similar safety profile to that of olanzapine, with the exception of less weight gain. As OLZ/SAM contains the opioid antagonist samidorphan, it is contraindicated in patients using opioids and in those undergoing acute opioid withdrawal. Clinical trial results from more than 1600 subjects support the use of OLZ/SAM as a new treatment option for patients with schizophrenia or BD-I.*

Keywords- Olanzapine Samidorphan, RP-HPLC, HPTLC, UV,Synchronous Fluorescence.

I. INTRODUCTION

Olanzapine is a synthetic derivative of thienobenzodiazepine with antipsychotic, antinausea, and antiemetic activities. As a selective monoaminergic antagonist, olanzapine binds with high affinity binding to the following receptors: serotoninergic, dopaminergic, muscarinic M1-5, histamine H1, and alpha-1-adrenergic receptors; it binds weakly to gamma-aminobutyric acid type A, benzodiazepine, and beta-adrenergic receptors. The antinausea and antiemetic effects of this agent appear to be due to the blockade of 5-HT2 and 5-HT3 receptors for serotonin. Although its exact mechanism of action in schizophrenia is unknown, it has been proposed that olanzapine's antipsychotic activity is mediated through antagonism to dopamine D2 receptors with rapid ligand-receptor dissociation kinetics that help to minimize extrapyramidal symptoms (EPS). Olanzapine may also stimulate appetite.

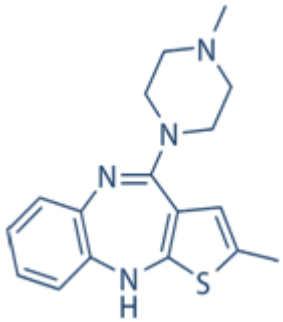

Figure1.Olanzapine

Figure2.PharmacologyofOLZ

Mechanism:

Olanzapine is an atypical (second-generation) antipsychotic that exerts its action primarily on dopamine and serotonin receptors. It works on dopamine D2 receptors in the mesolimbic pathway as an antagonist, blocking dopamine from potential action at the post- synaptic receptor. Olanzapine binds loosely to the receptor and dissociates easily, allowing for normal dopamine neurotransmission.The effect on the D2 receptors leads to a decrease in positive symptoms in patients, including hallucinations, delusions, and disorganized speech, thought, and behavior. Olanzapine works similarly on serotonin 5HT2A receptors in the frontal cortex

as an antagonist.The effect of olanzapine on serotonin leads to a decrease in negative symptoms, including anhedonia, flat affect, alogia, avolition, and poor attention.

Pharmacokinetics:

Olanzapine has a half-life of 21 to 54 hours, with an average of 30 hours. Daily administration of olanzapine leads to reaching the steady-state plasma concentration in about one week. Thus, Olanzapine has linear pharmacokinetics when dosed within the FDA approval range. The volume of distribution is approximately 1000 liters, and the medication is distributed widely throughout the body. It is 93% bound to plasma proteins, primarily albumin and alpha-1 acid glycoprotein.Olanzapine is highly metabolized by the liver extensively via direct glucuronidation and the cytochrome P450 system.

Samidorphan is a novel opioid antagonist structurally related to naltrexone, with a higher affinity for opioid receptors, more potent μ-opioid receptor antagonism, higher oral bioavailability, and a longer half-life, making it an attractive candidate for oral dosing.

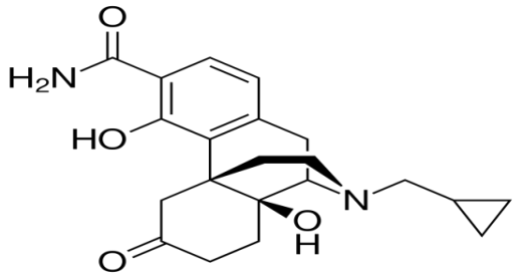

Figure3.Samidorphan

Mechanism:

Samidorphan is a novel naltrexone analogue containing a 3-carboxamido group that functions as an opioid receptor modulator, both in vitro and in vivo.1,11 Numerous in vitro studies have demonstrated that samidorphan binds with high affinity to the μ-, κ-, and δ- opioid receptors with Ki values of 0.052 ± 0.0044, 0.23 ± 0.018, and 2.7 ± 0.36 nM, respectively.2,3,4,11 Samidorphan acts as an antagonist at the μ-opioid receptor when it signals through Gαi proteins, a partial agonist when the receptor signals through GαoA, GαoB, and Gαz proteins, and essentially lacks β-arrestin-mediated signalling; samidorphan also acts as a partial agonist at both the κ- and δ-opioid receptors in vitro.2 In addition, both the major N- dealkylated and the major N-oxide human metabolites bind to the μ-, κ-, and δ-opioid receptors (Ki values of 0.26, 23, and 56, and 8, 110, and 280 nM, respectively); the former functions as a μ-opioid receptor agonist and the latter as an antagonist.11 Overall, samidorphan functions primarily as a μ-opioid antagonist in vivo.

Pharmacokinetics:

Samidorphan pharmacokinetics are linear over the range of clinically relevant concentrations, and steady-state kinetics are reached by seven days with once-daily oral administration. Upon reaching steady-state, with a once-daily dose of 10 mg samidorphan combined with 20 mg olanzapine, samidorphan has a mean Cmax of 45.1 ± 11.4 ng/mL and an AUC24h of 364 ± 112 ng*h/mL. Samidorphan has an absolute oral bioavailability of 69% and a Tmax of 1-2 hours.Samidorphan pharmacokinetics are not significantly impacted by food; following a high-fat meal, the Cmax was 0.85 (90% CI 0.76, 0.94) and the AUC 1.03 (90% CI 1.0, 1.05) that for the fasted state. An apparent volume of distribution between 336.59 ± 75.42 and 557.6 ± 120.51 L, depending on age, gender, and concomitant food consumption. Samidorphan is between 23 and 33 percent bound to plasma proteins. Samidorphan is primarily metabolized by CYP3A4, with minor contributions from CYP3A5, CYP2C19, and CYP2C8. Samidorphan is primarily renally excreted, with 67% of unchanged parent and metabolites eliminated in urine and another 16% in feces. Samidorphan has a mean half-life of 7-11 hours. Samidorphan has a mean clearance of 35-45 L/h.

II. ANALYTICALMETHOD

This all methods which are used for the determination of Elbasvir and Grazoprevir drug combination in Bulk, pharmaceutical dosage form and also in biological fluid like human plasma. This all analytical method which are seen during the literature survey are reported. This article describes the review on the reported analytical method with specific conditions.

1. Chromatographic Method:

Different type of chromatographic methods are utilized for the determination and quantification of the Olanzepine and Samidorphan drug combination as well as single dosage form in marketed formulation and in biological fluid . chromatographic methods such as High performance liquid chromatography (HPLC), Liquid chromatography etc are used for determination of olanzepine and samidorphan .Below table shows the summary of the various chromatographic methods .

Table No. 1 : Summary of chromatographic method of olanzepine and samidorphan

Title	Method	Mobile phase	Stationary phase	Wavelength	Ref.
New validated method for the estimation of olanzepine and samidorphan using Hplc and study of its degradation	HPLC	Buffer : Acetonitrile (60:40)	C18 Column	261 nm	11
Stability Indicating reverse phase (RP)-high performance liquid chromatography method development and validation for the simultaneous estimation of Olanzepine and Samidorphan in bulk and tablets,	RPHPL C	0.1% formic acid in water :methanol:acetonitrile (10:40:50)		285nm	12
Development of validated HPLC method for simultaneous determination of olanzapine and aripiprazole in human plasma	HPLC	Phosphate buffer and acetonitrile	Monolithic coloumn	255nm	14
Isocratic high performance liquid chromatographic assay of olanzapin: method development and validation	Isocratic HPLC	Disodium hydrogen phosphate buffer(35:65)	Intersil ODS column	254nm	15
Bioanalytical method development and validation of samidorphan and olanzapine using HPLC in human plasma	HPLC	Ammonium acetate buffer: acetonitrile (60:40)	Intersil 250 column	228nm	16

2. Spectroscopic Method:

Spectrophotometric method is economical and versatile particularly for developing countries. Spectrophotometric method has some advantages such as being easy, less time and less expensive consuming compared with most of the other methods. A simple, precise and economical spectrophotometric method for the Simultaneous estimation of the Olanzapine and Samidorphan in pharmaceutical bulk and tablet dosage form was developed and validated. Various method like Simultaneous estimation, dual wavelength, UV spectrophotometry, synchronous fluorescence spectroscopic method and derivative method are used for determination of olanzapine and samidorphan drug combination in marketed formulation. Following table describe the different spectroscopic method with the method description and condition which are reported on review literature.

Table No. 2 : Summary of spectroscopic method of olanzapine and samidorphan

Title	Method	Wavelength for olanzepine	Wavelength for samidorphan	Ref.
Spectrofluorimetric first derivatives synchronous approach for determination of olanzapine and samidorphan used for the treatment of schizophrenia in pharmaceutical formulation and human plasma.	Spectrofluorimetr ic method	300nm	350nm	17
Kinetic spectrophotometric and spectrofluorimetric methods for the analysis of olanzapine using 4-chloro-7-nitrobenzofurazan.	Spectrophotometr ic and spectrofluorimetri c method	463nm and 540nm	-	18
Determination of olanzapine by UV spectrophotometry and non-aqueous titration.	UV Spectrosopy	226nm	-	19

This method was proved to be fast, precise, selective, robust, and easy, and it may be used to a recently FDA approved OLA and SAM drug combination. This type of analysis may be used to determine the drug's safety, effectiveness, and quality in a cost-effective way. The developed technique was validated in accordance with ICH guidelines, and stability studies showed that the approach was effective in monitoring drug stability. It may also be used for regular analysis in bioanalytical laboratories, hospital research institutes, quality control divisions of pharmaceutical companies, formulation dissolution studies, and accredited testing laboratories.

3. Stability Indicating Method:

Stability indicating method is used to check out the stability of drug in different conditions like in acidic, basic, oxidative, photolytic and thermal degradation. Following table describes the various stability indicating method with the method description and condition which are reported on review literature.

Table No. 3 : Summary of Stability indicating method of olanzapine and samidorphan

Title	Method	Moilephase	Stationary phase	Wavelength	Ref.
RP-HPLC method development ,validation and stability indicating study of olanzapine in tablet dosage form .	RP-HPLC mehod	KH2PO4: Acetonitrile (60:40)	DThermoC 18column	257nm	20
Development of a stability indicating HPTLC method for the estimation of olanzapine in pharmaceutical dosage forms	HPTLC method	Toluene:Methanol(5:5)	Silicagel60 F_{254}	297nm	21

III. DISCUSSION

The presented review highlight on various analytical methods reported for determination of olanzapine and samidorphan in bulk,pharmaceutical dosage form and biological fluid like human plasma.UV,RP-HPLC and

Stability indicating RP-HPLC method were found to be most commonly used methods.These methods are found to be rapid ,accurate, sensitive, economical and reproducible for determination of olanzapine and samidorphan.

IV. CONCLUSION

This method was proved to be fast, precise, selective, robust, and easy, and it may be used to a recently FDA approved OLA and SAM drug combination. This type of analysis may be used to determine the drug's safety, effectiveness, and quality in a cost-effective way. The developed technique was validated in accordance with ICH guidelines, and stability studies showed that the approach was effective in monitoring drug stability. It may also be used for regular analysis in bioanalytical laboratories, hospital research institutes, quality control divisions of pharmaceutical companies, formulation dissolution studies, and accredited testing laboratories.

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