Journal of Applied Pharmaceutical Science

Available online at www.japsonline.com

ISSN: 2231-3354
Received on: 05-04-2012
Revised on: 12-04-2012
Accepted on: 16-04-2012
DOI: 10.7324/JAPS.2012.2824

Quantitative determination of Asenapine in both bulk and formulations using neutralization titrations

Kiran Aarelly, Manish Kumar Thimmaraju, Raghunandan Nerella

Kiran Aarelly, Manish Kumar Thimmaraju, Raghunandan Nerella
Balaji Institute of Pharmaceutical Sciences Narsampet, Warangal, 506331, India.

For Correspondence
Manish Kumar Thimmaraju
Email:manishcancer@gmail.com
Phone: +91 9966463586

ABSTRACT

Asenapine is used in the treatment of schizophrenia disease.Asenapine mainly control the psychotic symptoms' mainly antagonist to various receptors like, serotonin (5-HT_{1A}, 5-$HT_{1B,}$5-HT_{2A},5-$HT_{2B,}$),histamine, and dopamine(D_1,D_2,D_3,D_4) receptors. It is also lower affinity towards muscaranic and acetylcholine receptors. In the present study, simple titrimetric method was developed. Respective quantities of Asenapine were taken in aqueous methanol titrated against 0.1N sodium hydroxide acid and 0.1N potassium hydroxide acid using phenolphthalein as an indicators for neutralization titration. This method were found to be sensitive and inexpensive, do not require any sample processing steps and can be utilized for estimation of asenapine in bulk and formulations.

Keywords: Asenapine, titrimetry,sodium hydroxide, potassium hydroxide, methanol.

INTRODUCTION

Asenapine (Org 5222, ASP) is a novel dibenzoxepinopyrrole [Trans - 5 - chloro- 2,3, 3a 12b – tetra hydro – 2 – methyl - 1H - dibenz (2, 3:6, 7) oxepino - (4, 5 - c) pyrrole (Z) - 2 - butenedioate (1:1)] (Figure 1) with unique receptor pharmacology and is available as a fast-dissolving tablet for sublingual administration. It has potent dopaminergic (D_1–D_4), serotonergic (5 - HT_{2A}, 5 -HT_{2C}, 5 - HT_6 and 5 - HT_7), adrenergic (α_1 and α_2) and histaminergic (H_1) activity, but it lacks significant anti muscarinic activity (Shahid et al., 2009). ASP is an atypical antipsychotic approved in the USA in adults for the treatment of schizophrenia and for the acute treatment, as monotherapy or adjunctive therapy to lithium or valproate; of manic or mixed episodes associated with bipolar I disorder. ASP is indicated in the European Union for the treatment of moderate to severe manic episodes associated with bipolar I disorder in adults (European Medicines Agency, 2010). In short - term trials, ASP has demonstrated superiority over placebo in the treatment of schizophrenia (Cohen, 2007, Alphs *et a.*, 2010). and acute manic episodes associated with bipolar I disorder (Cohem et al., 2009 & 2010). The proposed metabolism of ASP and the excretion profiles were recently published (Jacobs et al., 2011).

The present work aims to develop a simple, rapid and sensitive, accurate and economic titrimetric method for the determination of asenapine in pure form and pharmaceutical preparations using 0.1N sodium hydroxide and 0.1N a potassium hydroxide solvents. These methods do not require any sample processing and extraction steps and can be used for the quality control of these drugs in industry.The developed methods were validated as per ICH guidelines and USP requirements, suitable statistical tests were performed on validation data(S Bolton,1997,J.C,Miller,1984).

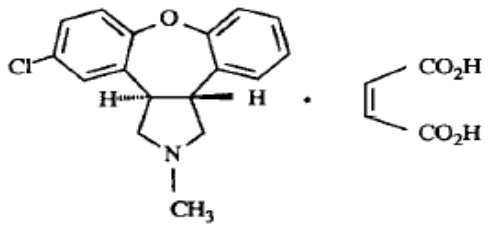


Fig. 1: Asenapine Maleate.

MATERIALS AND METHODS

Asenapine, sodium hydroxide, potassium hydroxide, methanol, phenolphthalein, potassium hydrogen phthalate, triple distilled water, starch, magnesium stearate, microcrystalline cellulose, talc

Preparation of 0.1N Sodium hydroxide

It was prepared by adding accurately weighed 4gm of sodium hydroxide was dissolved in 1000 ml of distilled water using standard volumetric flask.

Preparation of 0.1N Potassium hydroxide

It was prepared by dissolving accurately weighed quantity of 5.6gm of potassium hydroxide in distilled water and volume was made up to 1000 ml of distilled water using standard volumetric flask.

Standardization of 0.1N sodium hydroxide

Accurately measured quantity of 20.4gm of standard potassium hydrogen phthalate and dissolved in 1000 ml of distilled water, 5ml was pipette out into a clean conical flask and phenolphthalein indicator was added. Then the contents in the conical flask were titrated against standard solution of 0.1N sodium hydroxide, solution. Titration was carried out until color changes from colorless to pale pink. Results were obtained in triplicate for standardization using the following formula $N_1V_1=N_2V_2$, (Where N_1 and V_1 are the normality and volume of standard potassium hydrogen phthalate N_2 and V_2 are the unknown normality and consumed volume of sodium hydroxide).

Standardization of 0.1N potassium hydroxide

Accurately measured quantity of 20.4gm of standard potassium hydrogen phthalate and dissolved in 1000ml of distilled water, 5ml was pipetted into a clean conical flask and phenolphthalein indicator was added. Then the contents in the conical flask were titrated against standard solution of 0.1N potassium hydroxide, solution. Titration was carried out until color changes from colorless to pale pink. Results were obtained in triplicate for standardization using the following formula $N_1V_1=N_2V_2$, (Where N_1 and V_1 are the normality and volume of standard potassium hydrogen phthalate N_2 and V_2 are the unknown normality and consumed volume of potassium hydroxide.

Table . 1: Aqueous titration Standardization values of the 0.1N sodium hydroxide.

SNo	Volume of potassium hydrogen pthalate(ml)	Volume of sodium hydroxide consumed (ml)
1	05	5.3
2	05	5.1
3	05	5.5
1	Mean volume of sodium hydroxide consumed	5.2ml
2	Standard Deviation	0.070711
3	RSD	1.35
4	Normality of sodium hydroxide consumed	0.096 N

Table. 2: Standardization values of the 0.1N potassium hydroxide.

SNo	Volume of potassium Hydrogen Phthalate added (ml)	Volume of potassium hydroxide consumed (ml)
1	05	5.1
2	05	5.2
3	05	5.0
1	Mean volume of potassium hydroxide consumed	5.18ml
2	Standard Deviation	0.0.08366
3	RSD	1.61*
4	Molarity of potassium hydroxide consumed	0.09N

Equivalent factors

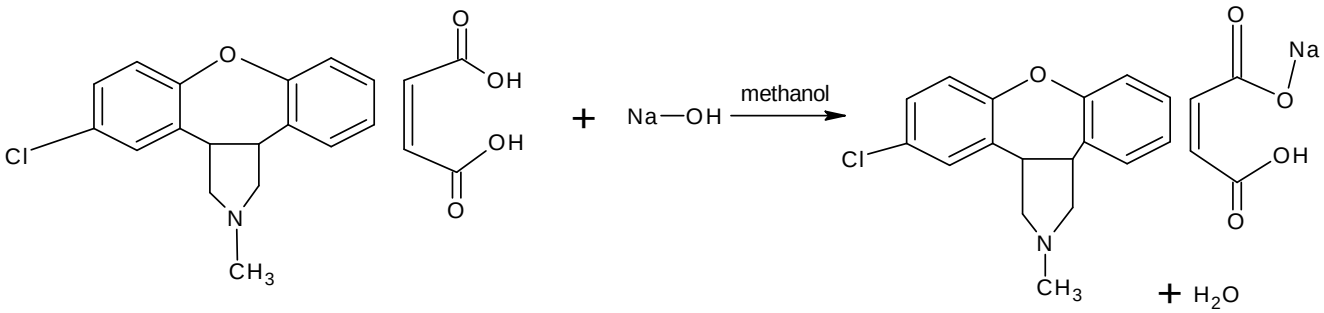
The exact amount of base consumed by the drug can be determined by stoichiometric equations were described in Figures 2 & 3. In both of these steps, one mole of drug was undergone reaction with sodium hydroxide and potassium hydroxide. Therefore, Each 1 ml of 0.1N sodium hydroxide or 0.1N potassium hydroxide is equivalent to 0.04018 gm of asenapine.

Assay procedure using 0.1N sodium hydroxide

Aliquots of asenapine were prepared by dissolving different amounts of drug (10-100mg) in 20 ml of methanol (methanol was previously neutralized with 0.1N sodium hydroxide) Aliquots were titrated using previously standardized 0.1N sodium hydroxide using phenolphthalein as an indicator to pale pink was observed for end point identification. Results were obtained in triplicates and asenapine was assayed. Assay reaction for titration is shown in figure 2.

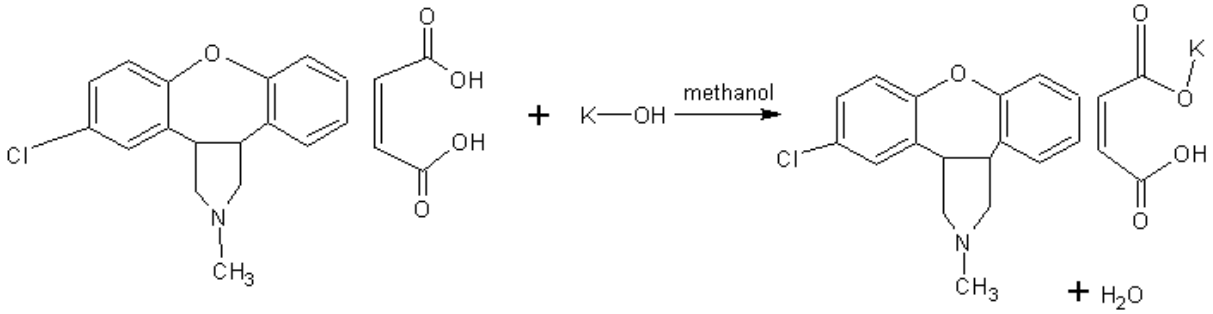
Assay procedure using 0.1N potassium hydroxide

Aliquots of asenapine prepared by dissolving different amounts of drug(10-100mg) in 20 ml of methanol was previously neutralized with 0.1N potassium hydroxide) aliquots were titrated using previously standardized 0.1N potassium hydroxide using phenolphthalein as an indicator pale pink was observed for end point identification. Results were obtained in triplicates and asenapine was assayed. Assay reaction for titration is shown in figure 3.



Asenapine maleate sodium hydroxide sodium salt asenapine maleate

Fig. 2: Neutralization titration with sodium hydroxide.



Asenapine maleate potassium hydroxide potassium salt of Asenapine maleate

Fig. 3: Neutralization titration with potassium hydroxide.

Table. 3: Assay of Asenapine with 0.1N sodium hydroxide.

SNo	Amount of asenapine added (mg)	Mean volume of sodium hydroxide consumed(ml)	RSD*(mg)	Mean amount found (mg) †	% Recovery
1	10	0.27±0.004	2.03	102.86	102.86
2	20	0.56±0.02	1.51	205.71	102..35
3	40	1.1±0.04	1.84	407.62	101.90
4	80	2.2±0.2	2.3	800.00	100.00
5	100	2.8±0.1	1.88	1028.90	102.89

SNo	Blend equivalent (mg)	Mean volume of sodium hydroxide consumed(ml)	RSD*(mg)	Mean amount found (mg) †	% Recovery
1	200 mg	0.56±0.03	1.45	205.71	102.85
2	400 mg	1.14±0.04	1.34	400.00	100.00

*Relative standard deviation (n=5)

† Each 1 ml of 0.1N S0dium hydroxide is equivalent to 0.04018 gm of asenapine

Table. 4: Assay of Asenapineby with 0.1N potassium hydroxide

SNo	Amount of asenapine added (mg)	Mean volume of potassium hydroxide consumed(ml)	RSD*(mg)	Mean amount found (mg) †	% Recovery
1	10	0.27±0.02	1.88	101.05	101.05
2	20	0.57±0.04	1.69	205.71	102.86
3	40	1.1±0.15	1.68	396.99	99.25
4	80	2.2±0.25	2.21	793.98	99.25
5	100	2.66 ±0.26	2.05	1013.52	101.35

SNo	Blend equivalent (mg)	Mean volume of potassium hydroxide consumed (ml)	RSD*(mg)	Mean amount found (mg)	% Recovery
1	200 mg	0.57±0.02	1.48	205.71	102.86
2	400 mg	1.12±0.24	1.88	404.21	101.05

*Relative standard deviation (n=5)

† Each 1 ml of 0.1M potassium hydroxide is equivalent to 0.04018 gm of asenapine

Linearity

To establish the linearity of proposed methods, five separate series of solutions of drug ranging from 10mg-100mg were dissolved in 20 ml of previously neutralized methanol and add 10ml of distilled water. Then the resulting solution was titrated against 0.1N sodium hydroxide and 0.1N potassium hydroxide by using phenolphthalein as an indicator, end point pale pink color.

Specificity

Specificity is the ability of an analytical method to differentiate and quantify the analyte in the presence of other components in the sample (Chandran *et al.*, 2007).

The specificity of these methods were determined by adding inert excipients such as starch, microcrystalline cellulose, magnesium stearate and talc individually with known concentration of the drug and titrated by using standard solutions.

Estimation from excipient blends

The in-house prepared tablet formulation blends were prepared, since no marketed formulations were available. These tablet blends were prepared by adding immediate release excipients such as starch, microcrystalline cellulose, magnesium stearate and talc. The crushed blend equivalent 200 mg and 400 mg were transferred to conical flask and respective solvents were added; solutions were filtered through Whatman filter paper number (#40) and the filtrate was titrated with standard solutions using indicator. Simultaneous blank determinations were conducted to confirm specificity and to nullify the effect of each ingredient. Assay results were shown in Table 3 and 4. Calibration curves were shown in figure-4 and 5

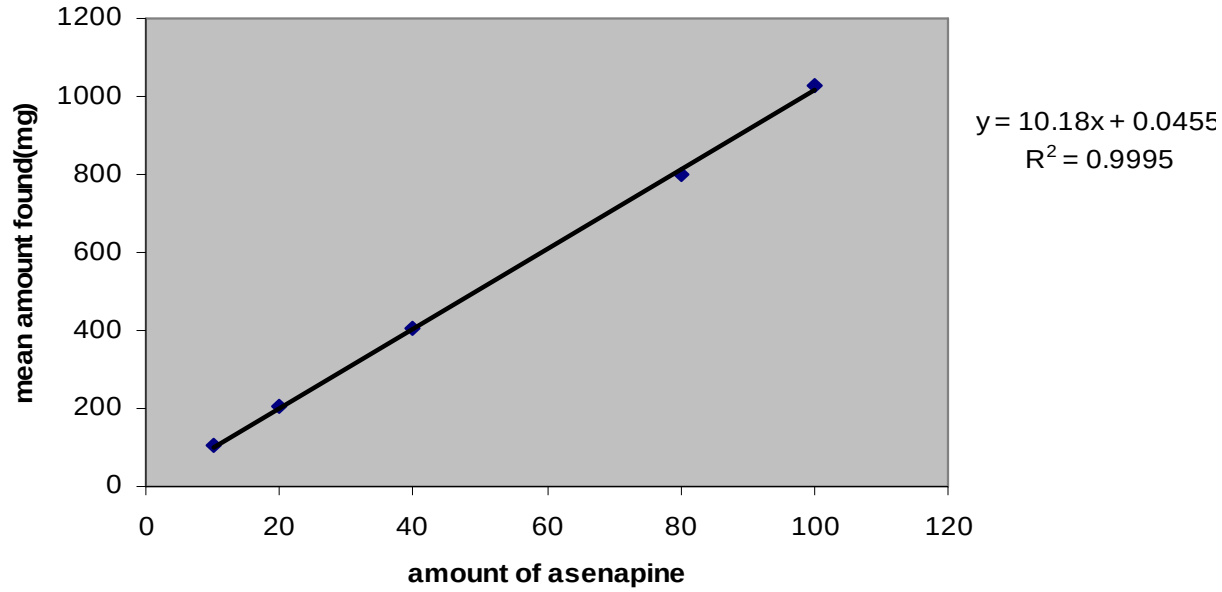


Fig. 4: Calibration curve- Assay of Asenapine with 0.1N sodium hydroxide.

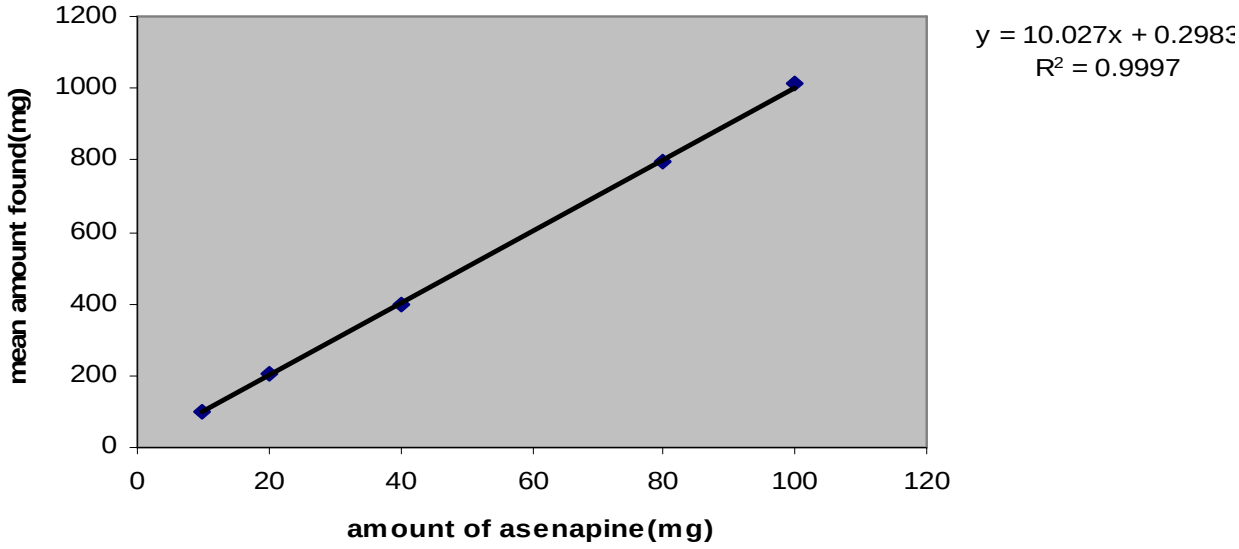


Fig. 5: Calibration curve- Assay of Asenapine with 0.1N potassium hydroxide.

RESULTS & DISCUSSIONS

The mean five normality values are calculated and approximate values obtained, which were equivalent to normality of 0.1. Methanol was used to dissolve asenapine .Add 10ml of distilled water, did not produce any precipitate. The proposed reactions were found to be simple neutralization of asenapine using basic solvents like sodium hydroxide and potassium hydroxide. During the process of titration, the amount of base consumed was calculated.

Specificity & Linearity

An accurately consumed 1.33±0.04 ml (RSD 1.3) of 0.1N sodium hydroxide is equivalent to 506.66 mg of asenapine and 1.34±0.05 ml (RSD 1.61) of 0.1N potassium hydroxide is equivalent to 510.47±1.2 mg of asenapine respectively. The correlation coefficient was found to be 0.9995 for 0.1N sodium hydroxide and 0.9997 for 0.1Npotassium hydroxide..

Assay & Recovery studies

The assay procedure was performed and percent recovery values were determined for actual drug and blend equivalents (Table 3 and 4). The estimated drug content with extremely low value of RSD established the precision of the proposed methods. Recovery experiments using the developed assay procedures further indicated absence of interference from pharmaceutical excipients used in the selected formulation blends.

CONCLUSION

A new titrimetric method has been developed to be routinely applied to estimate in asenapine bulk and formulation.

These methods have proved to be specific, linear, well recovered.Hence the method is recommended for routine quality control analysis.

REFERENCES

Chandran, S., Singh, S.P. Comparison of various international or analytical method validation. Pharmazie 2007; 62, 4–14.

European Medicines Agency.Sycrest asenapine. 2010. Available from.http://www.ema.europa.eu/ema/index.jsp?curl=pages/medicines/human/medicines/001177/human_med_001379.jsp&murl=menus/medicines/medicines.jsp & mid=WC0b01ac058001d124&jsenabled=true ,accessed 28 September 2010.

J.C. Miller,J.N.Miller, in Statistics for analytical chemistry,2nd ed,Wiley,New york,(1984) 83-11

Kane JM, Cohen M, Zhao J, Alphs L, Panagides J.Efficacy and safety of asenapine in a placebo- and haloperidol-controlled trial in patients with acute exacerbation of schizophrenia.Journal of Clinical Psychopharmacology. 2010; 30: 106–115.

McIntyre RS, Cohen M, Zhao J et al A 3-week, randomized, placebo-controlled trial of asenapine in the treatment of acute mania in bipolar mania and mixed states.Bipolar Disorder. 2009a; 11: 673–686.

McIntyre RS, Cohen M, Zhao J et al.Asenapine in the treatment of acute mania in bipolar I disorder: a randomized, double-blind, placebo-controlled trial. Journal of Affective Disorders. 2010; 122: 27–38.

Potkin SG, Cohen M, Panagides J.Efficacy and tolerability of asenapine in acute schizophrenia: a placebo- and risperidone-controlled trial.Journal of Clinical Psychiatry. 2007; 68:1492–1500.

Saphris®.Asenapine sublingual tablets. Full prescribing information. Schering Corporation, a subsidiary of Merck & Co. Inc. 2010. Whitehouse Station, NJ0. Available from: http://www.spfiles.com/pisaphrisv1. pdf. Accessed January 2011.

Shahid M, Walker GB et al. Asenapine: a novel psychopharmacologic agent with a unique human Receptor signature.Journal of Psychopharmacology. 2009; 23: 65–73

S.Bolton, in: pharmaceutical statistics:practical and clinical applications,3rd edition,Marcel Dekker, New york,1997,pp.216-264.

Van de Wetering-Krebbers SFM, Jacobs PL, Kemperman GJ et al. Metabolism and excretion of asenapine in healthy male subjects.Drug Metabolism and Disposition. 2011; 39: 580 – 590.