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ANALYTICAL METHOD DEVELOPMENT AND VALIDATION OF NIMODIPINE: REVIEW

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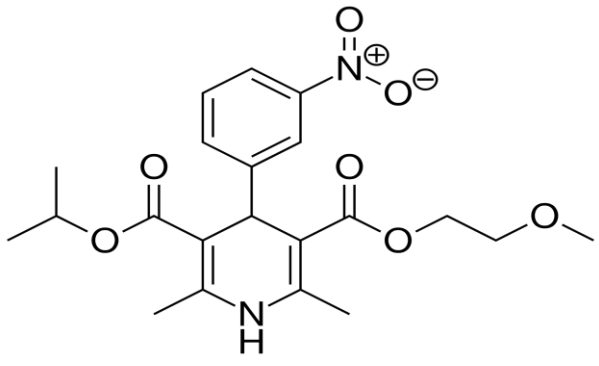
ABSTRACT
Analytical method development and validation are the continuous and inter-dependent task associated with the research and development, quality control and quality assurance departments. Analytical procedures play a crucial role in equivalence and risk assessment management. It helps in establishment of product-specific acceptance criteria and stability of results. Validations determine that the analytical procedure is suitable for its intended purpose. Literature survey reveals that the analytical methods based on UV spectrometry and RP-HPLC for the determination of Nimodipine personally and in combination with different drugs. The parameters were validated according to ICH guideline in terms of accuracy, precision, robustness and other components of analytical validation. The developed methods are simple, sensitive and reproducible and can be used for the analysis of Nimodipine in bulk and tablet dosage form.

KEYWORDS: Nimodipine, UV, HPLC, Validation, ICH Guidelines.

INTRODUCTION
Nimodipine, sold under the brand name Nimotop among others, is a calcium channel blocker used in preventing vasospasm secondary to subarachnoid hemorrhage (a form of cerebral hemorrhage). It was originally developed within the calcium channel blocker class as it was used for the treatment of high blood pressure, but is not used for this indication. Because it has some selectivity for cerebral vasculature, nimodipine's main use is in the prevention of cerebral vasospasm and resultant ischemia, a complication of subarachnoid hemorrhage (a form of cerebral bleed), specifically from ruptured intracranial berry aneurysms irrespective of the patient's post-ictus neurological condition.[1]



Nimodipine is chemically known as 3-(2-Methoxyethyl) 5-propan-2-yl 2,6-dimethyl-4-(3-nitrophenyl)-1,4-dihydropyridine-3,5-dicarboxylate with a molecular formula of $C_{21}H_{26}N_2O_7$ and a molecular weight of 418 g/mol. Nimodipine drug substance is a yellow and crystalline in nature and it is practically insoluble in water, freely soluble in ethyl acetate and sparingly soluble in absolute alcohol.

REVIEW OF LITERATURE
1. Rajesh S. Jadhav[2] *et al.*, The determination of Nimodipine formulation drug can be carried out by the development of simple, specific, rapid, precise and accurate UV Spectrophotometric method. The absorption maxima was observed at 239.0nm and was linear for a range of 5 µg/ml-25 µg/ml with correlation coefficient of 0.9996. The validation of the above proposed method was done by carrying out precision and accuracy studies. The analytical method showed good intra precision with relative standard deviation 0.522% and inter precision with relative standard deviation is 0.355% which is less than the percentage recovery at different levels i.e. 50%, 100% and 150% was found to be 49.9%,99.1% and 149.6% respectively. The proposed method was validated for the parameter specificity, precision, linearity and range, ruggedness, accuracy and recovery. Hence proposed analytical method for estimation of Nimodipine formulation drug by UV spectrophotometer

in pharmaceutical can be applied for the routine quality control analysis.

2. Sandeep Lahoti[3] *et al.,* A simple, sensitive and UV spectrophotometric method was developed for the estimation of Nimodipine in tablet dosage form. The optimum conditions for the analysis of the drug were established. The wavelength maxima for Nimodipine was found to be 238.5 nm. Beer's law was obeyed in the concentration range 5-30 mcg/ml having line equation y = 0.003x + 0.020 with correlation coefficient of 0.9981. The slope, intercept, correlation coefficient, detection and quantization limits were also calculated. Results of the analysis were validated statistically and by recovery study. The proposed method can be applied for the routine analysis of Nimodipine from tablet formulation.

3. Meshwa M. Patel[4] *et al.,* Three simple, sensitive and economical UV spectrophotometric methods have been developed for the estimation of nimodipine in soft gelatin capsule. Methods were based on the zero order (Method A), first order derivative spectroscopy (Method B) and area under curve method (Method C).All proposed methods obeyed Beer's law in the concentration range of 4-20 µg/ml with correlation coefficient r = 0.9984 in Method A, r = 0.9960 in Method B and r = 0.9989 in Method C. Accuracy of the method was confirmed by recovery studies and mean recovery was found to be 99.93-99.86% for Method A,98.74-99.24% and 99.27-99.92% for Method B and 98.43-99.19% for Method C. The intraday and inter day precision were found to be within limits. The proposed methods have adequate specificity, sensitivity, and reproducibility for quality control assay of nimodipine in soft gelatin capsule.

4. CH. Raghunath[5] *et al.,* The aim of present work is to develop and validate simple, sensitive and accurate spectrophotometric method has been developed for determination of Nimodipine in pure form and in pharmaceutical formulations. Nimodipine in dimethyl sulphoxide shows maximum absorbance at 238.50 nm. The drug obeyed Beer's law in the concentration range of 15µg/ml in methanol. The proposed methods were successfully applied for the determination of drug in commercial tablet preparations. The results of the analysis have been validated statistically and by recovery studies.

5. V. Ravinchandran[6] *et al.,* A simple and sensitive spectrophotometric method has been developed for the determination of Nimodipine in bulk and pharmaceutical dosage forms. The method is based on diazotisation pf reduced Nimodipine with nitrous acid followed by its coupling with β-naphthol in alkaline medium to form an orange red coloured chromogen with an absorption maximum of 555nm. Good agreement with Beer's law was found in the range of reduced Nimodipine concentration of 0-10µg/ml. The optimum reaction conditions and other analytical parameters are evaluated. The proposed method has been successfully applied to the bulk drugs and their dosage forms. No interference was observed from talc, starch, dextrose and magnesium stearate in the proposed method. Statistical comparison of the results with those of reported method showed good agreement and indicated no significant difference in precision. This method does not require any extraction or heating.

6. Lubna B. Shaikh[7] *et al.,* A simple, linear, precise, accurate, robust and selective RP-HPLC method has been developed for the estimation of Nimodipine impurity in bulk and formulation. The methanol: acetonitrile: water in proportion of 35v:40v:25v as mobile phase was used at the flow rate of 0.8ml/min. The HPLC system consisting of LC20AD Prominence Liquid Chromatography SPD 20-A Shimadzu Japan. The UV-VIS detector and C18 column with dimension of 250×4.6 mm was used at wavelength 234nm.Finally Nimodipine impurity was quantified from bulk Nimodipine and its tablet formulation. It was revealed that amount of impurity present in tablet was found to be 0.0876% and in the bulk 0.0219% respectively. Thus, Nimodipine impurity was found to be within the limit which was given in ICH guidelines.(Not more than 0.1%)

7. Xiaojun Shang[8] *et al.,* A rapid, sensitive and reproducible reverse phase high performance liquid chromatography (RP-HPLC) method with UV detector for the determination of Nimodipine in sustained release tablets was developed. The method involved using a SinoChoom ODS-BP C_{18} reverse phase column (5µm,4.6mm ✕ 200mm) and mobile phase consisting of methanol: acetonitrile: water (35:38:27, v/v). The flow rate is 1.0ml/min, the UV detector was operated at 237nm, and the column was maintained at 25°C.The method was validated according to official compendia guidelines. The calibration curve of Nimodipine for RP-HPLC method was linear over the range of 10-100µg/ml. The retention time was found at 7.50min for Nimodipine. The variation for interday and intraday assay was found to be less than 0.72%. The proposed RP-HPLC was proved to be suitable for the determination of Nimodipine in sustained release tablets.

8. M. M. Patel[9] *et al.,* A simple, precise, rapid and accurate isocratic reverse phase high performance liquid chromatography method was successfully developed and validated for estimation of Nimodipine in soft gelatin capsule. Chromatographic separation was achieved on an Inertsil ODS-3V column (150mm ×4.6mm,5µm) using mobile phase containing methanol: tetrahydrofuran: water (30:20:50 v/v/v) at the flow rate 2.0 ml/min with UV detection at 235nm.The column was kept at 40°C. A linear response was observed in the range of 60-180µg/ml with correlation coefficient of 0.9998. Themean percent recoveries of nimodipine in soft gelatin capsule were found to be in the range of 98.92-100.31%. The intraday and inter day precision was

found to be within limits. The proposed method was adequate specificity, sensitivity and reproducibility for quality control assay of nimodipine in soft gelatin capsule dosage form without any interference from excipients.

9. Kasture V.S.[10] *et al.,* The process related impurity of nimodipine diethyl 1,4-dihydro-2, 6-dimethyl pyridine 3,5 dicarboxylate in bulk and formulations was synthesized, characterized and RP-HPLC method was developed according to ICH Q2B guidelines for quantitation of impurity in bulk and formulations. The synthesis of intermediate was carried out by Hantzch process using m-nitrobenzaldehyde, ethylacetoacetate, in presence of ammonia and methanol as catalyst. The percentage yield was found to be 75%. The impurity was recrystallized and purified. The preliminary evaluation was done on lab scale viz. melting point, TLC and elemental analysis. The melting point of impurity was found to be 156℃. The TLC of impurity was carried out by using benzene and methanol (6:1) and the R_f was found to be 0.80. The confirmation of structure of synthesized impurity was carried out by using sophisticated instrument viz, FT-IR, NMR, GS-MS etc. Finally, the RP-HPLC method was developed to identify and quantify the impurity in Nimodipine bulk and formulation as per ICH Q2B guidelines. The method was validated as per ICH guidelines. The method was found to be linear, precise, accurate, robust and rugged. Finally, diethyl 1,4-dihydro-2,6-dimethyl pyridine 3,5 dicarboxylate impurity was quantified from bulk Nimodipine and its marketed tablet formulation. It was revealed that the amount pf impurity present in tablet batch I and II was found to be 0.28% and 0.33% respectively and the bulk was found to be negligible. As per the ICH limit the amount of impurity more than 0.1% indicates that the impurity found in tablet formulations is potential impurity.

10. Panagiotis Barmpalexis[11] *et al.,* In the present study an isocratic reversed-phase high-performance liquid chromatography was investigated for the separation of Nimodipine and impurities(A,B and C) using statistical experimental design. Initially, a full factorial design was used in order to screen five independent factors: type of the organic modifier – methanol or acetonitrile – and concentration, column temperature, mobile phase flow rate and pH .Except pH, the rest examined factors were identified as significant, using ANOVA analysis. The optimum conditions of separation (optimum values of significant factors) determined with the aid of central composite design were: (1) mobile phase: acetonitrile/H_2O (67.5/32.5, v/v), (2) column temperature 40^0 C and (3) mobile phase flow rate 0.9ml/min. The proposed method showed good prediction ability (observed-predicted correlation). The analysis was found to be linear, specific, precise, sensitive and accurate. The method was also studied for robustness and intermediate precision using experimental design methodology. Three commercially available nimodipine tablets were analysed showing good % recovery and %RSD. No traceable amounts of impurities were found in all products.

CONCLUSION

Literature survey suggested that various UV[1-5], RP-HPLC[6-10] and few simultaneous methods were developed and reported. The published methods were validated for various parameters as per ICH guidelines. Statistical analysis proved that the published methods were reproducible and selective. Thus, it can be concluded that the reported and published methods can be successfully applied for the estimation of Nimodipine in pure and pharmaceutical dosage form.

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