

The number of drugs introduced into the market is increasing every year. These drugs may be either new entities or partial modifications of the existing ones. Very often, there is a time lag from the date of introduction of a drug into the market to the date of its inclusion in pharmacopoeias. This happens because of the possible uncertainties in the continuous and wider usage of these drugs, reports of new toxicities (resulting in their withdrawal from the market), development of patient resistance and introduction of better drugs by competitors. Under these conditions, standards and analytical procedures may not be available in pharmacopoeias. It becomes necessary therefore, to develop newer analytical methods for such drugs.

Market is flooded with combination of drugs in various dosage forms. The multi-components formulations have gained a lot of importance nowadays due to greater patient acceptability, increased potency, multiple action, fewer side effects and quicker relief. There is a plethora of analysis of such formulations without prior separation. Simultaneous analysis procedures are now being used more frequently for estimation of drugs in multi-component pharmaceutical formulations due to their inherent advantages viz. avoid time consuming extraction and separation, economical in the sense that use of expensive reagents is minimized are equally accurate and precise. For the estimation of multi-component formulation, the instrumental techniques, which are commonly employed, are spectrophotometry, HPLC, GLC, HPTLC etc. These methods are based upon the measurement of specific and nonspecific physical properties of the substances.

In brief, the reasons for the development of newer analytical methods of drug analysis are,

- the drug or drug combination may not be official in any pharmacopoeia,
- a proper analytical procedure for the drug may not be available in the literature due to patent regulations,
- analytical methods may not be available for the drug in the form of a formulation due to the interference caused by the formulation excipients,
- analytical methods for the quantitation of the drug in biological fluids may not be available,
- analytical methods for a drug in combination with other drugs may not be available,

- the existing analytical procedures may require expensive reagents and solvents. It may also involve cumbersome extraction and separation procedures and these may not be reliable.

Drugs are typically developed and manufactured into dosage forms prior to their use by patients. Dosage forms require a variety of tests and standards to assure therapeutic benefit. The intricacies of drug delivery systems complicate efforts to develop control assays and tests. Estimation of drugs in the biological fluids is used to access the performance of the formulations used in the clinical trials that provide evidence of safety and efficacy.

Analysis of single ingredient is easier when compared to the analysis of formulations and biological fluids. Interference from the excipients in the formulations or endogenous constituents in the biological matrix can no doubt occur. This interference can be avoided by adopting suitable sample preparations. Analysis of drugs in formulations and biological fluids by the extractions of the drug, however, is cumbersome and very often results in errors due to incomplete extraction. The complexity of dosage forms and biological samples thus presents challenges during the development of assay methods.

Most of the drugs in formulations forms and in biological samples can be analysed by UV spectrophotometric, HPLC and HPTLC methods because of the several advantages like rapidity, specificity, accuracy, precision, and ease of automation. These methods eliminate tedious extraction and isolation procedures. Some of the advantages of these methods are speed (analysis can be accomplished in shorter time), greater sensitivity (various detectors can be employed), improved resolution (wide variety of stationary phase), reusable columns (expensive columns but can be used for many analysis), ideal for the substances of low volatility, easy sample recovery, handling and maintenance, instrumentation lends itself to automation and quantitation (less time and less labour), precise and reproducible, calculations are done by integrator itself etc.

In the early part of this century, colorimetric and spectrophotometric methods were used for drug analysis due to reasons of economy and easy availability. These methods however are used to a lesser extent today because they lack specific, sensitivity and accuracy.

For the estimation of the drugs present in formulations or in biological fluids, UV spectrophotometric, HPLC and HPTLC methods are considered to be most suitable

since these are powerful and rugged methods. It is also extremely specific, linear, precise, accurate, sensitive and rapid. The UV, HPLC and HPTLC methods developed are proposed to validate for their transferability to other laboratories in terms of specificity, sensitivity, accuracy, precision, linearity, range, detection limit, ruggedness, robustness, stability and system suitability.

3.1 In summary, the primary objective of proposed work is to:

⇒ Develop new, simple, sensitive, accurate, and economical analytical methods for the simultaneous estimation of

3.1.1 ATOR and FENO by:

- a) Simultaneous equation method
- b) First derivative zero-crossing method
- c) Q- Absorbance method
- d) Ratio first derivative method
- e) Chemometric methods on zero order spectra
- f) RP-HPLC method
- g) HPTLC method

3.1.2 ATOR and AMLO by

- a) Ratio first derivative method
- b) Chemometric methods on zero order and first derivative spectra
- c) RP-HPLC method
- d) HPTLC method

3.1.3 ATOR and EZET by

- a) Q- Absorbance method
- b) Chemometric methods on zero order spectra
- c) RP-HPLC method
- d) HPTLC method

3.1.4 ATOR and RAMP by

- a) Simultaneous equation method
- b) First derivative zero-crossing method

- c) Ratio first derivative method
- d) Chemometric methods on zero order spectra
- e) RP-HPLC method
- f) HPTLC method

3.1.5 NEB and HCTZ by

- a) Simultaneous equation method
- b) First derivative zero-crossing method
- c) Ratio first derivative method
- d) Chemometric methods on zero order spectra
- e) RP-HPLC method

⇒ Validate the proposed methods in accordance with USP and ICH guidelines for the intended analytical application i.e., to apply the proposed method for analysis of these drugs in their combined dosage form.

⇒ Apply the proposed method for analysis of these drugs in their combined dosage form.

The proposed analytical methods was found be used in,

- Research institutions,
- Quality control department in industries,
- Approved testing laboratories,
- Biopharmaceutical and bioequivalence studies and
- Clinical pharmacokinetics studies.

On literature survey it was found that no method could be found for simultaneous estimation of above mentioned combination formulations, and also no method is available in the pharmacopoeias. In view of the need for a suitable method for routine analysis in combined formulations, attempts are being made to develop simple, precise and accurate analytical methods for simultaneous estimation of all title ingredients and extend it for their determination in formulation. As chromatographic method of analysis is a pre-requisite for the marketing of most of the formulation, one HPLC, HPTLC method along with the spectrophotometric methods namely Simultaneous equation method (Vierodt's method), Absorbance ratio (Q-Analysis) method, First derivative zero crossing method, Ratio derivative Spectrophotometry, and chemometric techniques CLS, ILS, PCR and PLS were developed and validated for the simultaneous determination of title drugs.

The utility of the developed methods to determine the content of title ingredients in commercial formulations were also demonstrated.

Reference

- (1) Naes, T.; Martens, H. *J. Chemometrics* 1988, 2, 155-167.