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Original Article

NON-DESTRUCTIVE RAMAN SPECTROSCOPIC METHOD FOR ESTIMATION OF MONTELUKAST FROM TABLET DOSAGES FORM

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ABSTRACT

Objective: A rapid, non-destructive and non-solvent raman spectroscopic method for estimation of Montelukast from tablet dosages form

Methods: Quantification was carried out by measuring the intensity of analyte peak at 1440 cm^{-1}. Each Raman spectrum corresponded to an accumulation of 4 scans with an exposure time of 5 sec for each scan with a total integration time of 20 sec.

Results: The method exhibited linearity between 2 mg-24 mg show well resolve quantification From MON. The linearity equation was calculated as y = 13.036x+70.819 and the correlation coefficient was found to be 0.997 for MON. LOD (limit of detection) and LOQ(limit of quantification) values were calculated using the calibration curve slope and standard deviation of the response. The LOD (limit of detection) and LOQ (limit of quantification) values were found to be 1.71 mg and 5.13 mg respectively.

Conclusion: The developed method was successfully applied for assay of montelukast in the intact formulation. The method was validated according to an international conference on harmonisation guidelines. A recent study, montelukast sodium had been analysed by the raman method, but, looking into the tremendous potential of raman spectroscopic method; it can be extended as a process analysis and technology tool in various quality checks during manufacturing of pharmaceutical products.

Keywords: Nondestructive Raman spectroscopy, ICH guidelines, Montelukast Sodium

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INTRODUCTION

Raman spectroscopy has been increasingly used for real-time measurements of critical process and product attributes, as it allows rapid and non-destructive measurements without sample preparations. The raman spectra can be recorded directly inside the container (glass vial and plastic blisters) without removing the formulation from the container. Raman spectra can be recorded with very small amount of sample and analysis time is from few seconds to few minutes. The non-destructive nature, speed of analyses and applicability of method directly on solid materials make raman spectroscopy an excellent process analytical technology (PAT) tool for in-line measurement of active pharmaceutical ingredient (API) content during continuous manufacturing of apis and other production processes [1].

Compared to conventional chromatographic and spectroscopic techniques, raman spectroscopy is a promising technology offering various rewards like a high signal to noise ratio and lower secondary fluorescence. Raman imaging combines spectral and spatial information and generates a chemical image of a two-dimensional area of a sample. The main drawback of this instrument is its high cost, and selection of wavelength to avoid fluorescence and thermal emission backgrounds.

The introduction of fibre optics and chemomatric techniques helped spectroscopies for fast characterization of the raw plant material and the isolation of the target structures during phytoextraction [2-4]. Raman spectroscopy is an efficient and promising tool in replacing traditional time-consuming, monotonous and destructive technologies for detecting spoilage microorganisms in various raw and processed food products [5].

Raman spectroscopy was found to be superior as compared to the other techniques for numerous key criteria including a complete safety for operators and their occupational environment, a non-invasive procedure, no need for consumables, and a low operating cost [6]. In the recent era, raman spectroscopy has a number of applications and is gradually emerging and explored in various pharmaceutical fields [7-12].

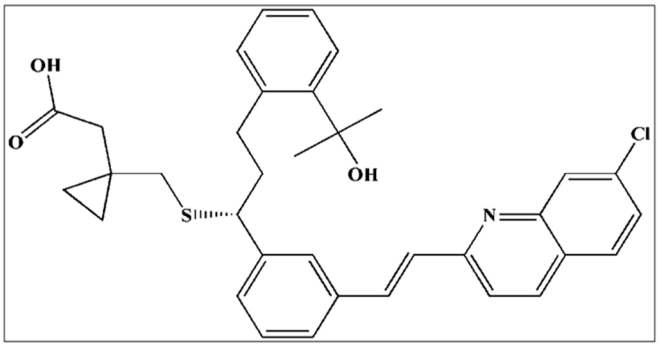

Fig. 1: Chemical structure of MON [7]

Montelukast sodium (MON) is chemically 1-[[[(1R)-1-[3-[(1E) 2-(7-chloro-2-quinolinyl) ethenyl] phenyl]-3-[2-(1-hydroxy-1-methylethyl) phenyl] propyl] thio] methyl] cyclopropane acetic acid (fig. 1). It is a selective and orally active leukotriene receptor antagonist that inhibits the cysteinyl leukotriene $CysLT_1$ receptor. It is approved for treatment and prevention of various allergic disorders. Various UV-visible spectrophotometry, high-performance liquid chromatography (HPLC) and high-performance thin-layer chromatography (HPTLC) techniques have been reported for estimation of MON in various matrices [13-15]. The Process Analytical Technology (PAT) framework, is of all most importance to obtain critical process and formulation information during pharmaceutical processing. Raman has the potential to insight into process understanding, optimisation and monitoring in the development and scales up operations [16, 17].

None of the researchers has reported, raman spectroscopic method for estimation of MON from the formulation, hence by looking into advantages of this techniques, it was endeavoured to develop and validate Raman spectroscopic method for estimation of MON from tablet formulation.

MATERIALS AND METHODS

Raman instrumentation

Dispersive R-3000 Raman spectrophotometer, (Raman Systems Inc., USA), consisting of diode laser optic sampling probe fitted with a charge-couple device detector was used. The laser excitation wavelength used during the experiments was 785 nm and the probe was equipped with special focusing caps for solids and liquids. All spectra were recorded at approximately 250 mW laser power at spectral resolution 4 cm^{-1} and the scattered light was collected at an angle of 180 °. It was calibrated using verification probe consisting of Teflon coating. Data collection and transfer were automated using RSI scan software.

Methods

MON API was generously gifted from Torrent Research Centre, Bhat, Ahmedabad. Excipients such as lactose, hydroxyl-propyl-methyl-cellulose (HPMC), microcrystalline cellulose (MCC), sucrose, magnesium stearate and talc were of analytical grade and purchased from Central Drug House Pvt. Ltd., New Delhi, India. Commercial MON tablet (Montair-10, Cipla Ltd.) was purchased from local market.

Raman measurement

Samples were prepared by the triturating fixed amount of MON in a mortar with different quantities of excipients for 5 min to make it homogenised. The spectra of all samples were recorded by taking 10 mg powder mixture in a low-density polyethene bag and spreading it to form a layer of uniform thickness. MON was estimated at 1441 cm^{-1}. each raman spectrum corresponded to an accumulation of 4 scans with an exposure time of 5 s for each scan, accounting to a total integration time of 20 s. to take into account its heterogeneity, five measurements were made on each sample; the spectrum presented is the average of all recorded spectra. Tablets were analysed directly under the probe, horizontally without any sample preparation within its primary packaging system if blister pack is non-coloured. If the blister pack is coloured then tablets are required to be removed from primary packaging material and then analysed.

Method validation

Method validation was performed based on ICH guideline [18, 19].

Linearity: API samples of MON were prepared in different content ratio keeping the total weight of powder mixture 200 mg using talc. For linearity, 2 mg, 4 mg, 6 mg, 8 mg, 10 mg, 12 mg, 14 mg, 16 mg, 18 mg, 20 mg, 22 mg and 24 mg MON was taken and mixed with talc to get total mixture weight of 200 mg.

Precision: Interday and intraday precision study were carried out at three different concentration levels (8 mg, 12 mg and 16 mg). Raman spectra were recorded for the said concentrations within a single day and on three different days. Peak count was calculated and % RSD was reported.

Accuracy: Recovery study was carried by the addition of standard MON API to tablet powder containing 10 mg of MON. Recovery was studied at three different concentrations level 80 %, 100 %, 120% of assay value in triplicate.

Robustness: Robustness of the method was studied by deliberate changes in optimised experimental conditions. Raman spectra were recorded by varying±10% of integration time, frame size and power strength.

Assay: Twenty tablets were accurately weighed and crushed in mortar and pestle. Powder equivalent to one tablet was taken and spread uniformly for the estimation. The Raman spectrum was recorded by placing the laser probe on the powder in the bag.

LOD and LOQ: Limit of detection and limit of quantification was calculated using the following equation.

$$LOD = 3.3 \times \frac{\sigma}{S}, \quad LOQ = 10 \times \frac{\sigma}{S}$$

Where, σ = Standard deviation of the response

S = Slope of the calibration curve

RESULTS AND DISCUSSION

The intensity of a Raman line depends on a number of factors including the incident laser power, the frequency of the scattered radiation, the absorptivity of the materials involved in the scattering and the response of the detection system. Raman spectra of most commonly used excipients such as lactose; HPMC, MCC, sucrose, magnesium stearate and talc were recorded. All excipients except talc did not have any Raman scattering and fluorescence at an excitation wavelength of the laser (785 nm), but talc had shown two Raman peaks at 295 cm^{-1} and 1092 cm^{-1}. Talc was selected as a diluent so as to check interference of talc at the estimating Raman shifts of MON.

Raman spectra of standard MON was recorded and shown in fig. 2. From, the spectra it is apparent that the most intense vibration for MON is at 1599, 1634 and 1440 cm^{-1}. But, at 1599 and 1634 cm^{-1}, the linearity was not obtained hence, 1440 cm^{-1} was selected as detection and quantification wavelength. At 1440 cm^{-1} the spectra of MON shows no interference from the excipient talc. Hence, 1440 cm^{-1} wavenumber can be used for the qualitative and quantitative analysis of MON. Raman counts were calculated at 1440 cm^{-1} by using the following equation.

$$Raman\ count = Peak\ hight\ (1440) - \frac{(Start\ \ peak + End\ \ peak)}{2}$$

Quantitative Raman spectra analysis of solid mixture is complex because the intensity depends on the reproducibility of same factors such as particles size and packing density of the sample. To get homogeneous sample mixture and to avoid variation of detector responses on the sample mixture, all the samples were triturated for 5 min.

Spectra were taken by taking different samples from the homogeneous mixture and putting the lase probe at random position. During the course of study, it was observed that by putting the laser probe at a different portion of the sample does not yield any significant change in Raman counts. The intermigration time and frame size were optimised to 20 s and 5 s respectively. Laser intensity was optimised at 2500 mW. At lower intensity laser power Raman counts get hampered while at high laser intensity, the incidence of fluorescence is very high.

The linearity of MON was evaluated by analysing different concentrations of the drug. In this study, twelve different concentrations were chosen between 2 mg-24 mg of MON. The intensity of Raman peaks corresponding to the drug concentration shows a concentration dependent change in spectra. Spectra were recorded for each mixed sample (standard MON API and talc) and plot of intensity versus concentration was plotted. The linearity equation was calculated as y = 13.036x+70.819 and the correlation coefficient was found to be 0.997 for MON (fig. 3). Linearity spectra for MON is shown in fig. 4.

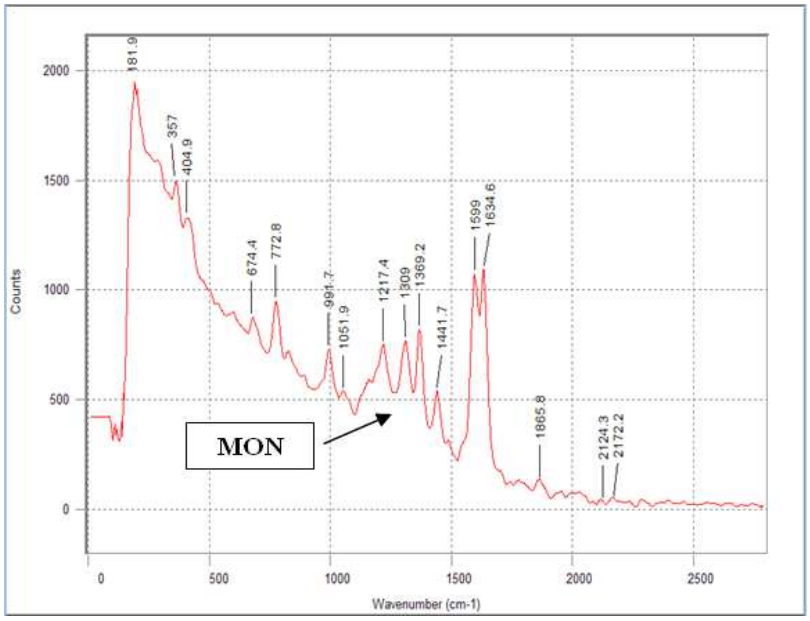

Fig. 2: Raman spectra of MON recorded at 1440 cm^{-1}

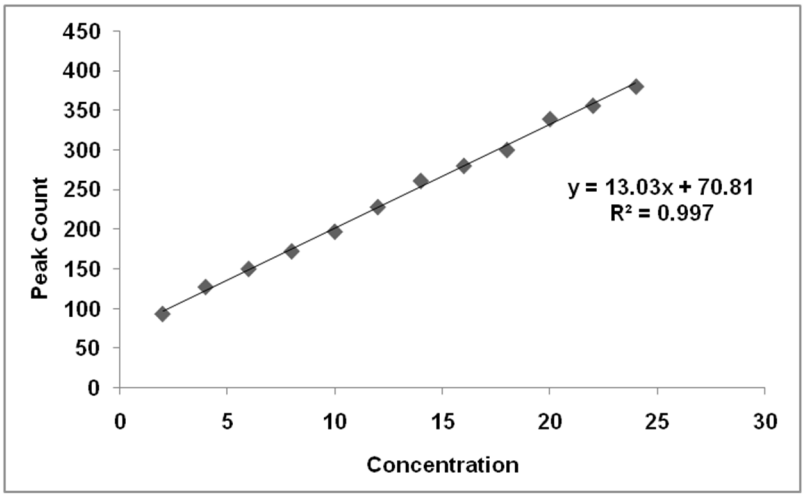

Fig. 3: Linearity curve of MON

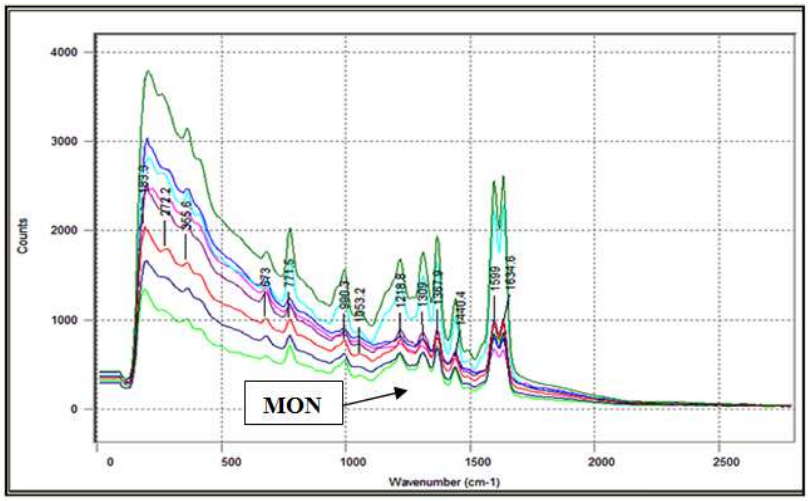

Fig. 4: Linearity overlay of montelukast

The % relative standard deviation values for intraday, interday precision and repeatability were found to be less than 2, which indicate that developed method is precise for estimation of MON. The accuracy of the method was studied by % recovery of MON from marketed tablet formulation (table 1). Robustness of the method was studied by changing frame size±1 s and integration time±5s. All results were within±2% of the obtained assay values of tablets. LOD and LOQ values were calculated using the calibration curve slope and standard deviation of the response. The LOD and LOQ values were found to be 1.71 and 5.13 respectively.

Table 1: Accuracy study of MON

Level	Standard concentration (mg)	Amount added (mg)	Total amount (mg)	Amount recovered (mg)	Mean % recovery±SD
80	10	8	18	18.1	100.5±0.0
	10	8	18	18.1	
	10	8	18	18.1	
100	10	10	20	20.0	94.3±4.93
	10	10	20	18.2	
	10	10	20	18.4	
120	10	12	22	23.1	103.3±2.88
	10	12	22	22.2	
	10	12	22	23.1	

Table 2: Summary of validation parameters for developed Raman spectroscopic technique

Parameters	Mon
Linearity (% w/w)	2–24
R^2	0.997
Linear regression equation	Y = 13.036x+70.819
LOD (% w/w)	1.71
LOQ (% w/w)	5.13
Repeatability (%RSD)	1.02-1.66
Interday (%RSD*)	1.28-1.62
Intraday (%RSD*)	1.28-1.63
% Recovery#	94.3–103.3
% Assay	100.2

*Six determinations, #Triplicate determination

The purpose of this method development and validation was to carry out analysis of MON in API and in the intact tablet. Raman spectra of both; intact tablet and crushed tablet powder was recorded as shown in fig. 5 and 6 respectively. It was found that no effect and interference of packaging material and density or thickness of the material is there on Raman wavenumber and intensity of Raman count.

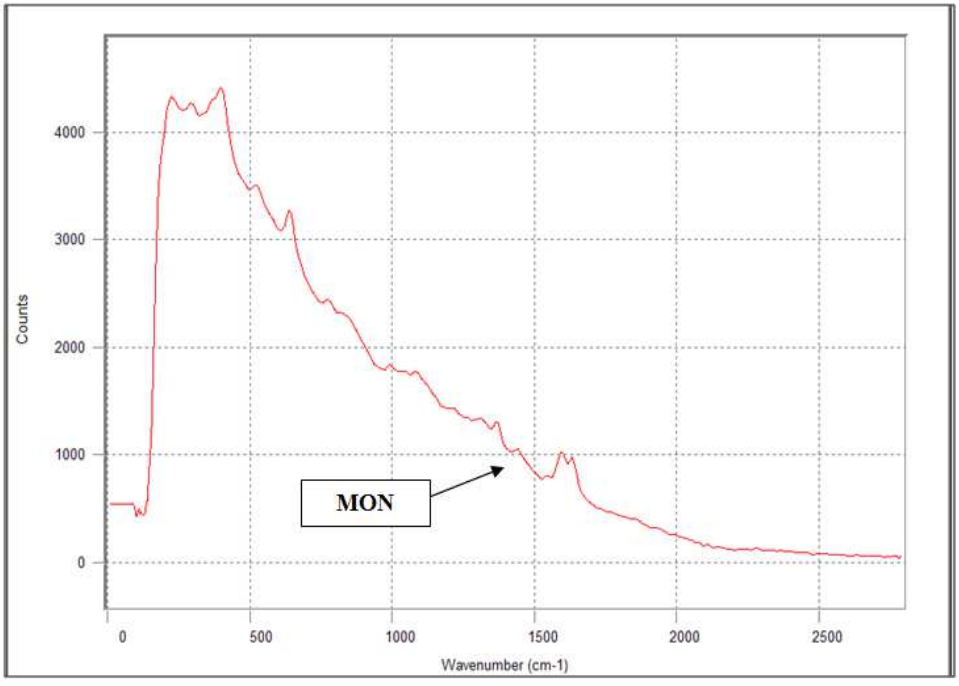

Fig. 5: Raman spectra of intact tablet (10 mg MON) recorded at 1440 cm^{-1}

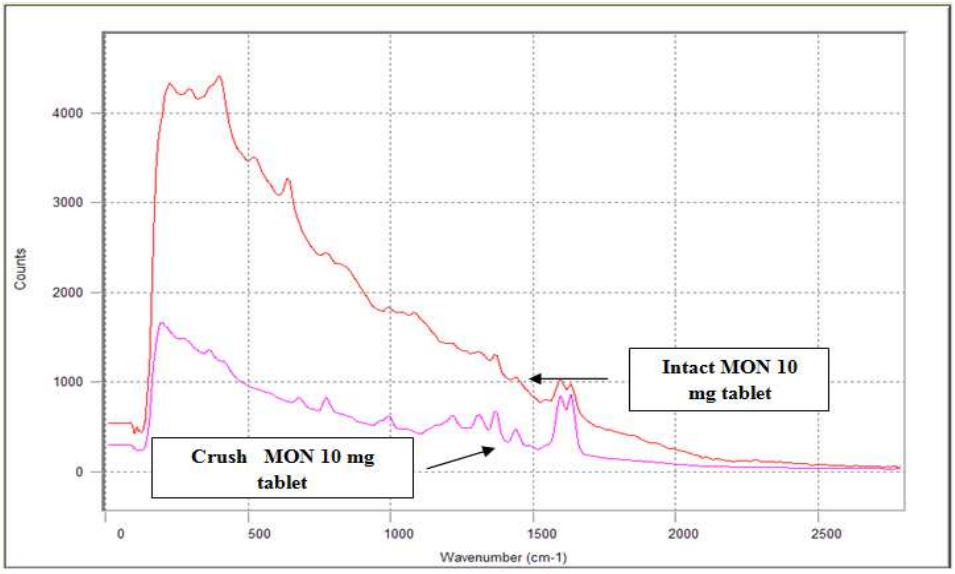

Fig. 6: Comparison Raman spectra of intact tablet and crushed tablet of MON recorded at 1440 cm^{-1}

CONCLUSION

A simple, rapid, non-destructive and solvent free Raman spectroscopic technique was developed and validated for the estimation of MON in API and in the dosage form. Tablets can be directly analysed through its colourless primary packing material using the developed Raman method; thus, it is a promising technique for its applicability as a PAT tool for in-line and at online analysis in routine quality control check in pharmaceutical industries. In addition, Raman is also gaining popularity in the arsenal of green analytical chemistry.

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CONFLICT OF INTERESTS

Declared none

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