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Original Article

Efficient Determination of Mometasone by Derivatization Method Using UV-VIS Spectrophotometer

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Abstract

Mometasone furoate is a synthetic glucocorticoid with anti-inflammatory and anti-allergic effects, used for the treatment of allergic rhinitis, asthma, and dermatoses. In this study, a spectrophotometric method, as a selective and sensitive method, was developed for the determination of mometasone furoate after derivatization. For this purpose, mometasone was first reacted with sodium cyanide to prepare the drug derivatives. After that, the effects of different variables such as reaction solvent, concentration of the reagents, pH, and reaction time were studied. The final results showed that the determination method was linear in the range of 2-18 µg/ml. It seems that after 24 hours, the reaction was complete. The reaction product was characterized by NMR and FT-IR spectroscopy, and the accuracy and precision of the developed method were also studied. At last, the method was checked on Mometasone Ointment (0.1%), and the results were compared with the results of the HPLC method as a standard method.

Keywords: Derivatization; Dosage form; Mometasone; Sodium cyanide; Solutions; Spectrophotometry.

1. Introduction

Mometasone furoate [MF], ($C_{27}H_{30}Cl_2O_6$), [9-chloro-17-(2-chloroacetyl)-11-hydroxy-10,13,16-trimethyl-3-oxo-,7,8,11,12,14,15,16-octahydrocyclopenta[a]phenanthren-17-yl] furan-2-carboxylate, (**Fig. 1**), is a synthetic glucocorticoid with anti-inflammatory and anti-allergic effects. The mometasone nasal spray is used for allergic rhinitis; oral inhalation of mometasone is used for asthma; and mometasone topical dosage forms (cream, lotion, ointment) can relieve the inflammatory and pruritic manifestations of corticosteroid-responsive dermatoses [1-4]. Due to the importance of determining the amount of active pharmaceutical ingredients in dosage forms, many methods have been reported for the

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determination of MF individually or in combination with other drugs like fusidic acid, terbinafine hydrochloride, nadifloxacin, and formoterol fumarate by spectrophotometry, high-performance liquid chromatography, and capillary electrophoresis [5-9]. UV-visible spectrophotometry is an efficient method for analytical applications because of a large number of its advantages, such as quick analysis ability and ease of use [10, 11]. On the other hand, derivatization reactions are applied for the analysis of organic compounds and, thus, are the most widely used methods in the field of analysis.

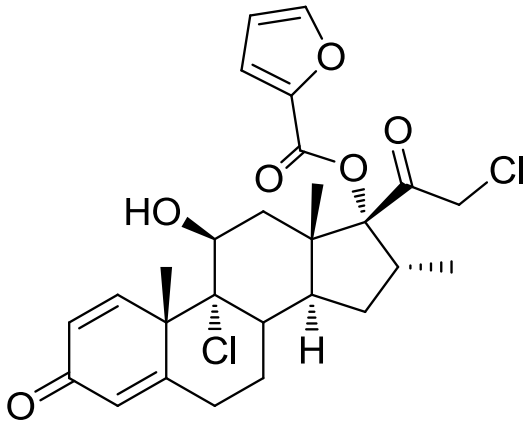

Figure 1. Chemical structure of mometasone.

Regarding the importance of the determination of mometasone, in this study, a novel and facile spectrophotometric method as a quick-response and easy-to-use analytical method was employed to determine the drug and its derivative. A mometasone derivative was prepared by nucleophilic reaction with the cyanide group (**Fig. 2**), and the absorption of mometasone furoate and its cyanide derivative were checked out to determine their amounts.

2. Materials and Methods

2.1. Chemicals

Mometasone was bought from Aburaihan Pharmaceutical Company in Tehran, Iran. Sodium cyanide and methanol were obtained from Sigma-Aldrich and distilled to be suitable for HPLC.

2.2. Instruments

UV-visible spectrometer (Shimadzu, 160A, Japan) with 1 cm quartz cells, analytical balance (Mettler Toledo), ultrasonic (Tecno-Gas), IKAMAG hot plate magnetic stirrer, Waters HPLC system (515 Pump, 717 Plus Autosampler, and 474 Scanning Fluorescence Detector) were used in this study. For recording NMR spectra, a Bruker FT-500 spectrometer (with tetramethylsilane as standard) was used. The IR spectra were obtained using a Perkin-Elmer Model 781 spectrograph.

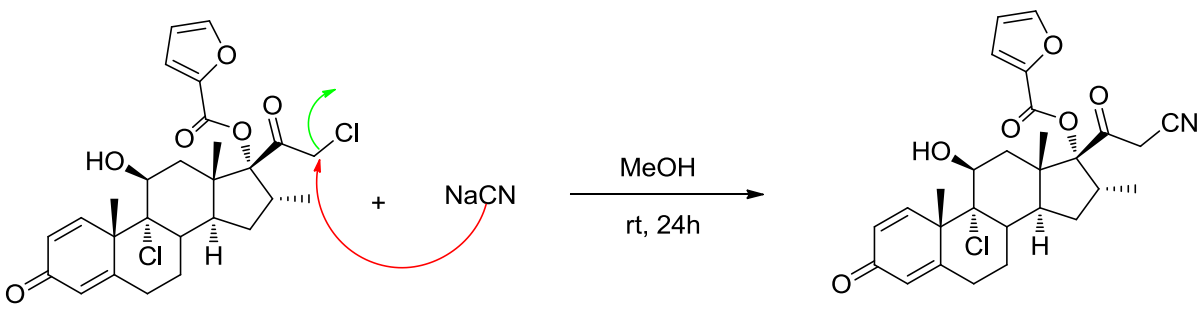

Figure 2. Reaction of mometasone with sodium cyanide.

2.3. Preparation of mometasone solution

For the preparation of a 260 µg/ml mometasone solution, 2.6 mg of mometasone furoate was weighed and transferred to a 10 ml volumetric flask and reached the volume by methanol.

2.4. Preparation of sodium cyanide solution

To prepare a 1000 µg/ml solution of sodium cyanide, 10 mg of sodium cyanide was transferred into a 10 ml volumetric flask, and after complete dissolution in 0.5 ml of distilled water, the solution reached 10 ml by methanol.

2.5. Preparation of calibration solutions

For the preparation of calibration solutions, 2 mg of mometasone furoate was weighed and dissolved in methanol. The solution volume reached 100 ml in a volumetric flask. Solutions containing 2, 4, 6, 8, 10, 12, 14, 16, and 18 µg/ml were prepared by subsequent diluting of the above solution.

2.6. General method for preparation of mometasone derivatives

Sodium cyanide was used for the preparation of mometasone derivatives. For this purpose, 1 ml of mometasone solution (8µg/ml) was mixed with 1 ml of sodium cyanide solution (400µg/ml) in a 10 ml volumetric flask and the volume was reached with methanol. The mixture was stirred at room temperature for 24 hours. Then, the absorption of the solution was measured at 330 nm by a UV-Vis spectrophotometer.

2.7. Preparation of pharmaceutical product solution

10 grams of two mometasone ointments (0.1%) manufactured by Aburihan Pharmaceutical Company were weighed and mixed together. 10 grams of the mixture were taken, poured into 40 ml of methanol, and placed in a Bain-Marie at 40°C for 20 minutes. Then put it in a sonicator for 10 minutes to dissolve the mometasone in methanol. The solution was centrifuged so that there was no turbidity in the solution. Then, the solution was brought to a volume of 50 ml to make a solution with a concentration of 200 µg/ml. Next, 1 ml of the solution was poured into a 25 ml flask and made up to volume with methanol. In this way, a solution with a concentration of 8 µg/ml of the medicinal product was obtained.

2.8. Relative recovery

To calculate the relative recovery, three series of solutions were prepared. The first series of solutions contains the standard sample (with a concentration of 8 µg/ml), the second series contains the drug product (with a concentration of 8 µg/ml of mometasone), and the third series contains a mixture of the standard sample of mometasone (8 µg/ml) and the drug product (8 µg/ml). Each solution was transferred to a 10 ml volumetric flask, and 1 ml of standard sodium cyanide solution was added and made up to volume with methanol. To check the relative recovery, the absorbance values of the ointment sample, the standard solution, and their mixture were read using the mentioned method at a wavelength of 330 nm.

3. Results and Discussion

3.1. Characterization of the product

As mentioned in the experimental section, a reaction was performed between mometasone

furoate and sodium cyanide. Monitoring the reaction by TLC showed that the reaction was completed after 24 hours of stirring at room temperature. After the reaction's completion, both FT-IR and NMR spectroscopy were used for the exact characterization of the product. A peak at 2200 cm^{-1} observed in the IR spectrum is correlated to cyanide functionality (**Fig. S1**, supplementary information). Mometasone's ^{1}HNMR spectrum shows that following derivatization, peaks in regions 4–5 ppm vanish and a singlet in 3.55 ppm takes their place (**Fig. S2**). Furthermore, for this derivative, a peak at 113.3 is observed in the ^{13}C NMR spectra (**Fig. S3**). This proves the nucleophilic attack of cyanide on the C--Cl bond in mometasone.

3.2. Optimization of the reaction conditions

Different experimental parameters affecting derivative formation should be optimized to establish the derivatization reaction. The first step in reaction optimization is the selection of the solvent for the derivatization reaction. It should be noted that mometasone furoate is insoluble in water and ethanol. Therefore, other organic solvents such as methanol, acetone, acetonitrile, and dichloromethane were tested.

On the other hand, the reagent, sodium cyanide, should be dissolved in the same solvent or a solvent that is fully miscible with the reaction solution. Based on the results, methanol was used as the reaction solvent. The UV-visible spectrum of mometasone was different from the mometasone derivative. Mometasone shows an absorption peak at 248 nm, but the λ_{max} of its derivative with sodium cyanide was observed at 330 nm. Sodium cyanide showed no absorption peak in the range of 200-800 nm (**Fig. 3**).

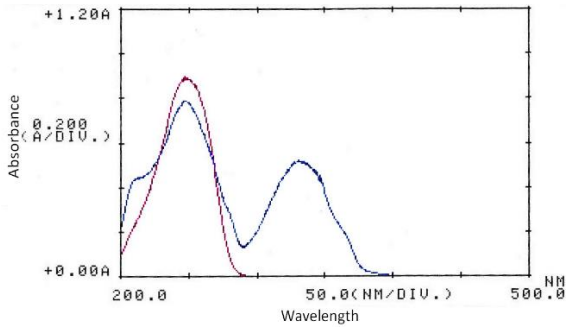

Figure 3. UV-Vis spectrum of mometasone furoate (red line) and cyanide derivative of mometasone (blue line).

The effect of time on the completion of the reaction was studied. As shown in **figure 4**, the absorbance value of the derivative increases as the reaction times lengthen, and the absorption value remains unchanged after 24 hours. Therefore, 24 hours are necessary for the reaction of mometasone with sodium cyanide to be completed.

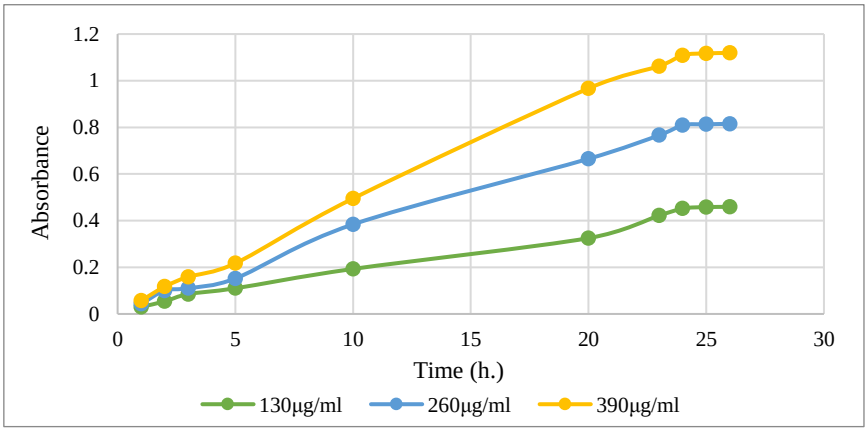

Figure 4. The effect of time on the mometasone derivative absorption at 330 nm in three different concentrations (130, 260 and 390µg/ml).

For checking the influence of pH, the effects of acidic and basic media must be checked. The influence of basic media on the reaction was studied by using different concentrations of sodium hydroxide. The addition of NaOH to the reaction mixture leads to the hydrolysis and degradation of mometasone. Also, because of the presence of CN^- in the reaction mixture that can make poison HCN, the effect of the acidic situation was not checked. According to these situations, the reaction was performed at a neutral pH.

Finally, the effect of the cyanide amount was studied using the mole ratio method. The maximum absorbance was obtained at a ratio of 50:1 sodium cyanide/mometasone for the derivatization reaction (**Fig. 5**).

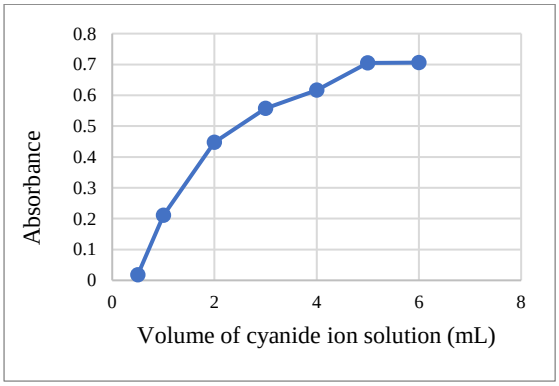

Figure 5. Molar ratio of mometasone with CN^- reagent in methanol.

3.3. Linearity

As mentioned in the experimental section, the calibration curves were drawn for mometasone furoate in the concentration range of 2-18 µg/ml. The equation for the best trend line drawn for this concentration range was:

$$Y = 0.027208\ X - 0.0355$$

The standard deviation of the slope was 1.97×10^{-4}, and the correlation coefficient was 0.9993, which proved the reliability of the method (**Table 1**).

Table 1: Analytical parameters of the calibration curve of mometasone furoate.

Parameters	Mometasone furoate
Linearity	2.00 – 18.00 µg/ml
Limit of detection	0.408 µg/ml
Limit of quantification	1.236 µg/ml
Regression equation	Y = 0.027208 X - 0.0355
SD of slope	1.97×10^{-4}
RSD of slope	0.723
SD of intercept	3.36×10^{-3}
Coefficient correlation	0.9993

The between-day and within-day precision and accuracy were calculated using mometasone furoate solution at 4, 8, 12, and 18 µg/ml in triplicate for 3 days. The results proved that the method is accurate and reliable for the determination of mometasone furoate. The results are shown in **Table 2**.

3.4. Determination of mometasone furoate in commercially available drugs

Finally, mometasone furoate was determined in mometasone ointment (0.1%). Each determination was repeated three times, and the mean value was compared with the results of the HPLC method as a standard method (**Table 3**) [12]. The results did not show a significant difference between the two methods. Therefore, the introduced method could be applied for the accurate determination of mometasone furoate in pharmaceutical dosage forms.

Table 2: Within-day and between-day accuracy and precision of mometasone furoate.

Added (µg/ml)	Within-day (n=3)			Between-day (n=9)		
	Found (µg/ml)	CV (%)	Error (%)	Found (µg/ml)	CV (%)	Error (%)
Mometasone λ=330nm						
4.00	4.03 ± 0.12	2.99	0.85	4.06 ± 0.09	2.15	1.47
8.00	8.02 ± 0.15	1.91	0.23	7.99± 0.12	1.52	-0.11
12.00	11.99± 0.08	0.67	-0.09	11.96± 0.18	1.54	-0.35
18.00	18.09± 0.07	0.39	0.48	18.11± 0.09	0.48	0.61

Table 3: Comparison of the developed method with the reference method for the determination of mometasone furoate.

Compound	Label claimed (mg/100g)	Found (mean ± sd)				Statistical Tests*
		Proposed method		HPLC method		
		mean±sd	Recovery (%)	mean±sd	Recovery (%)	
Mometasone	100.00	98.25±0.62	98.25	98.88±0.33	98.88	t = 0.889 F = 0.034

4. Conclusion

In conclusion, we have introduced a novel method for the determination of mometasone furoate based on derivatization with cyanide by spectrophotometry. Most of the present methods are based on HPLC, densitometry, and immunoassay, which are more complicated. UV-Vis spectrophotometry is more facile and less costly than the mentioned methods. Consequently, this method can be an appropriate alternative to previously reported methods, and in quality control samples, it can be used for rapid analysis of active ingredients.

Acknowledgments

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Conflict of interest

The authors declare to have no conflict of interest.

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Supplementary files:

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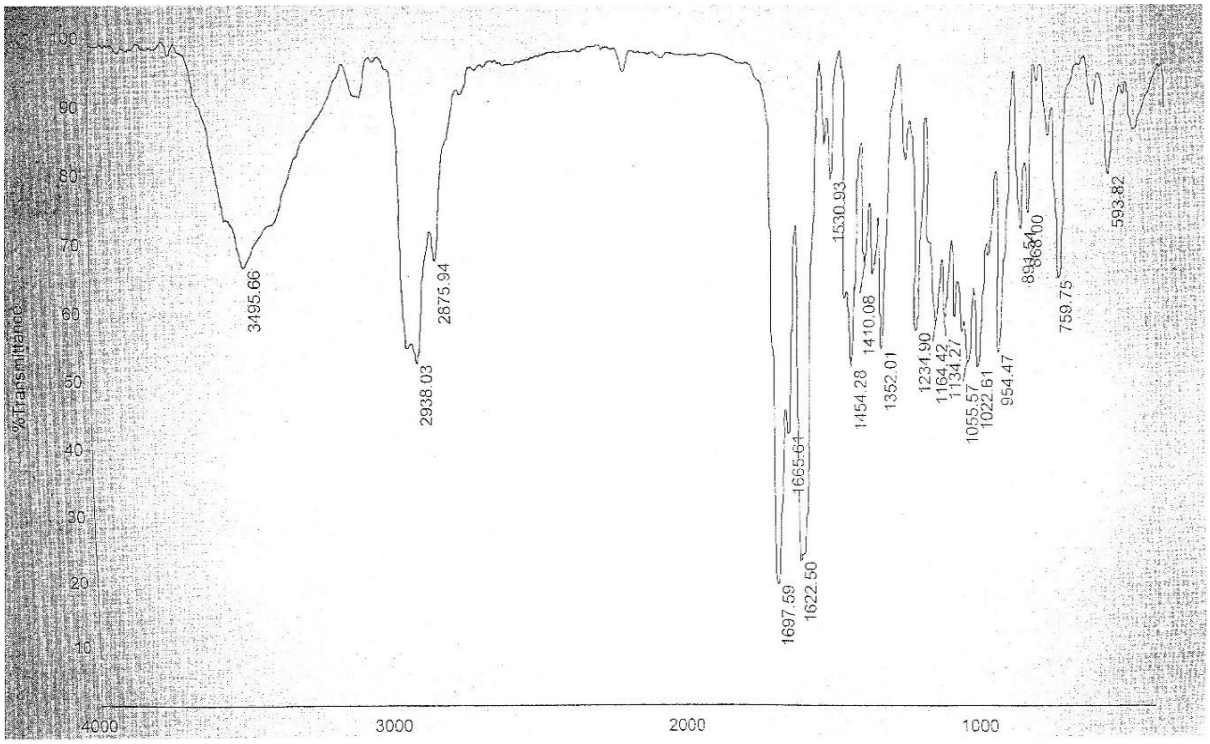

Figure S1. The IR spectrum of cyanide derivative of mometasone furoate.

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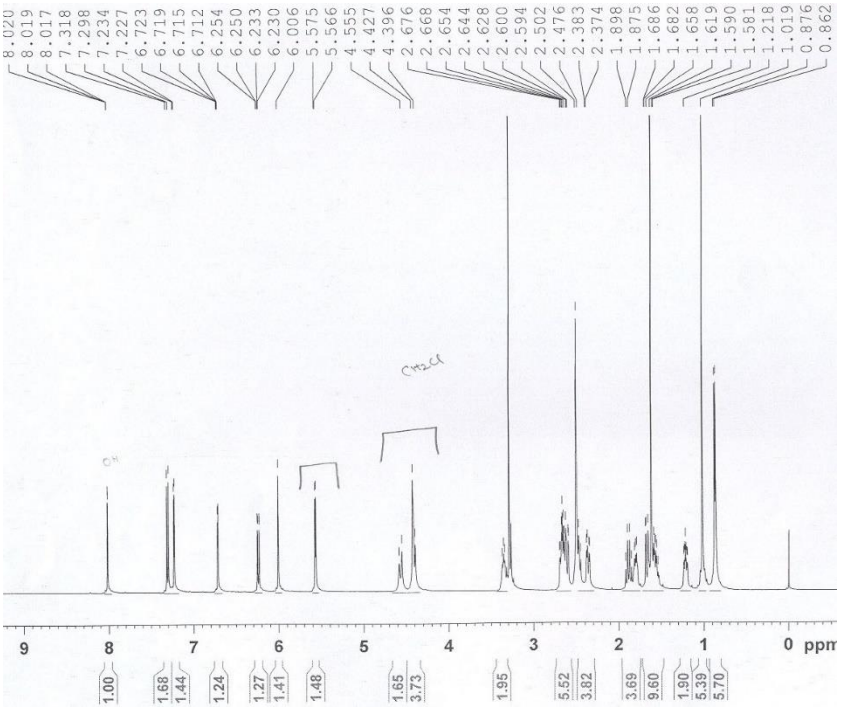

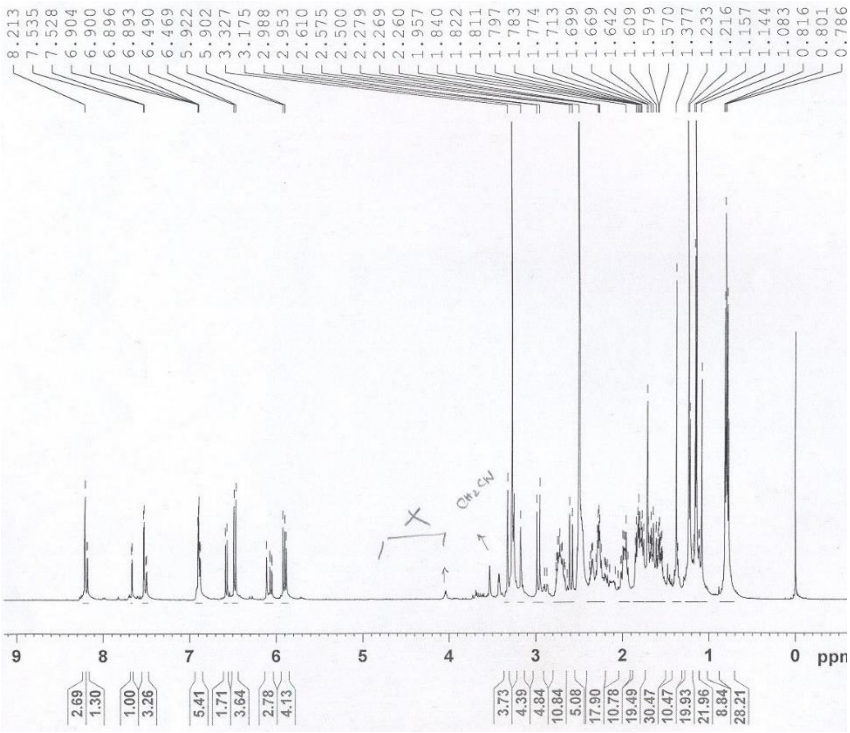

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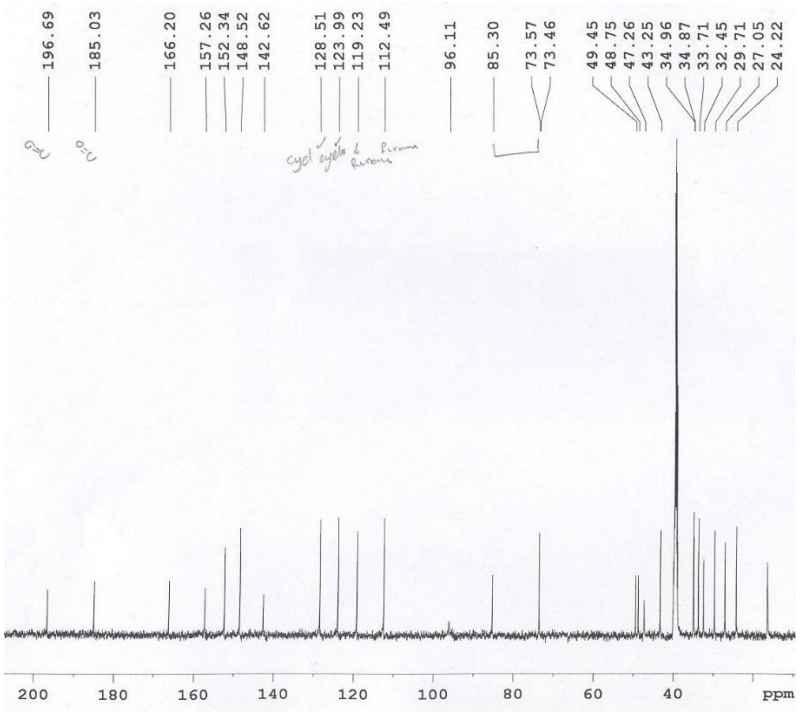
Supplementary files:

Figure S2. a) The HNMR spectrum of mometasone furoate. b) The HNMR spectrum of cyanide derivative of mometasone furoate.



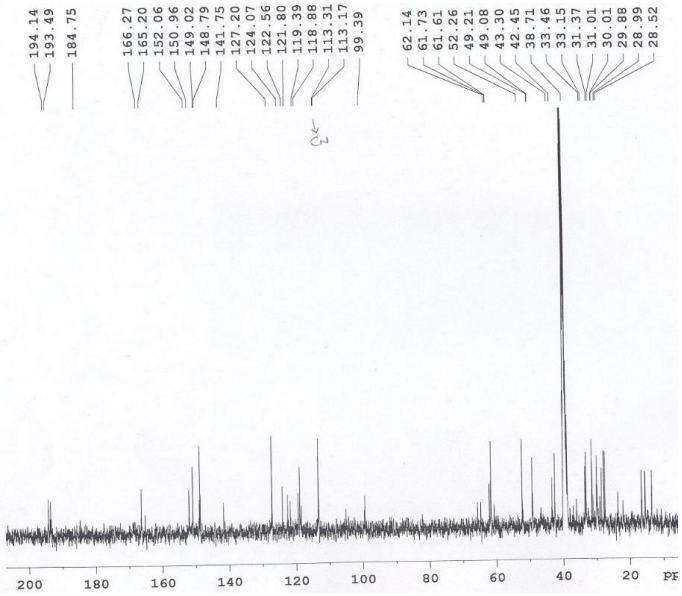


Figure S3. a) The CNMR spectrum of mometasone furoate. b) The CNMR spectrum of cyanide derivative of mometasone furoate.