

Thermogravimetric Method Validation And Study Of Lanthanum Carbonate Octahydrate And Its Degradants.

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Abstract: Lanthanum carbonate is used as a phosphate binder for the treatment of hyperphosphatemia. Lanthanum carbonate octahydrate has been characterized by Powder X-ray diffraction (PXRD), elemental analysis, thermogravimetric analysis (TGA) and infrared spectroscopy (FTIR) techniques. Analytical methods have been established by thermogravimetric analysis technique to estimate the water and carbonate content. The estimation of carbonate content has been validated according to the guidelines laid down by the regulatory agencies using thermogravimetric analysis. The thermal degradants formed by subjecting Lanthanum carbonate octahydrate in air and nitrogen atmosphere and at a high temperature. The thermal degradants formed were found to be gradual with the formation of the final degradants influenced by the type of atmosphere used during the degradation studies.

Keywords: Lanthanum carbonate, degradants, carbonate content, thermogravimetric analysis, method validation.

Introduction:

Lanthanum carbonate is used in the field of medicines for the treatment of acute renal failure. It acts as a phosphate binder. The usefulness of Lanthanum carbonate as an effective phosphate binder having various pharmaceutical compositions and formulations have been extensively studied and reported [1-4]. The effect of ultrasound irradiation on the morphology of Lanthanum carbonate and its decomposition has been studied for Lanthanum carbonate 1.7 hydrate and Lanthanum monooxycarbonate 1.4 hydrate [5]. The products were characterized mainly by powder X-ray diffraction, scanning electron microscope and transmission electron microscope. Lanthanum carbonate is reported to form Lanthanum hydroxycarbonate which exists in two different polymorphs viz. Form-I and Form-II. Since work on hydroxycarbonate is already reported, this study will not discuss on the hydroxycarbonate impurities [6-8].

The Pharmaceutical drug regulatory agencies lay down stringent levels of controlling and monitoring related substances, heavy metals content, etc in any pharmaceutical drug substance. Therefore there is a strong need to develop, monitor as well as validate either the potency of a drug substance or controlling of its impurities both organic as well as inorganic within the specified acceptable limits. Lanthanum carbonate consists of the cation

belonging to the Lanthanum group of elements. The carbonate content is usually estimated by complexometric titrations using EDTA. However, there are limitations to this estimation since Lanthanum carbonate is not soluble in water. Hence, estimating the carbonate content in Lanthanum carbonate hydrate is necessary which has not been explored previously. In this paper we report a novel method of simultaneously determining water and carbonate content in Lanthanum carbonate octahydrate using thermogravimetric analysis (TGA) technique. The method has also been validated according to the laid down guidelines [9].

Lanthanum carbonate octahydrate is found to give rise to various thermal degradants when exposed to temperature. The thermal impurities formed upon subjecting Lanthanum carbonate octahydrate to air and nitrogen atmosphere and high temperature of up to 900°C have been identified by PXRD and FTIR. The obtained data has also been compared vis-à-vis with TGA-FTIR data. A complete understanding of the behaviour of Lanthanum carbonate octahydrate and the degradants formed during the thermal decomposition has been presented in this paper.

Experimental:

Materials:

Lanthanum carbonate octahydrate was received from the Chemical Research Division of Matrix Laboratories Limited. Sample was analysed using different analytical techniques without any further purification.

Methodology / Instruments:

Powder X-ray Diffractometry. The X-ray powder diffraction (PXRD) patterns were obtained with a PANalytical X'Pert PRO diffractometer equipped with a θ/θ goniometer using Cu-anode, automatic divergence slit and X'celerator detector. Data was collected at a tube voltage of 40 kV and a tube current of 30mA, at a scan step of 0.03° in the angular range of 2 θ of 2-80°.

Thermogravimetric Analysis. TGA was performed with Q5000IR, TA Instruments. Samples of approximately 30 mg were placed on a pre-weighed ceramic pan. Temperature calibration of the instrument was performed using a ferromagnetic material such as nickel. The Curie-point temperature was measured and the instrument calibrated. Dry nitrogen was used as purge gas at a flow rate of 25 ml/minute. Data was collected at a heating rate of 10°C/minute over a temperature range of 30°C to 900°C. The weight calibration was performed using a 100 mg calibrated weight.

TGA-FTIR Method: TGA was performed on a Mettler Toledo TGA/SDTA 851e module. Samples were placed in open alumina pans for the TG experiments. The typical sample size was 10-15 mg for TGA. Temperature range was 30-400 °C with a heating rate of 10 °C/min. Samples were purged by a stream of nitrogen flowing at 80 mL/min. The TG instrument is coupled to a Bruker Tensor FT-IR spectrometer for evolved gas analysis. The evolved vapors from TGA instruments were passed through a coupled heated transfer line at 120 °C and characterized with a D1aTGS detector.

Elemental analysis: The elemental analysis for Lanthanum carbonate octahydrate was determined using *Thermo Finnigan Flash-EA1112 Elemental analyser*.

Results and Discussion:

PXRD data: The single crystal data for Lanthanum carbonate octahydrate is reported [10]. It is reported to exist as an octahydrate with the water molecules in between the layers of lanthanum carbonate. The simulated powder pattern was processed from the single crystal data using *Highscore Plus* software. Lanthanum carbonate octahydrate was measured by Powder X-ray diffraction technique to confirm its polymorphic state with the reported and simulated pattern of Lanthanum carbonate octahydrate. The experimental powder pattern collected for the sample of Lanthanum carbonate showed characteristic peaks at 10.4°, 18.6°, 20.9°, 21.3°, 27.2°, 29.2° and 34.5° 2 θ ($\pm 0.2^\circ$) thereby confirming the polymorphic form as Lanthanum carbonate octahydrate (Figure 1). The stoichiometry of Lanthanum carbonate octahydrate was also confirmed by elemental analysis (Table 1).

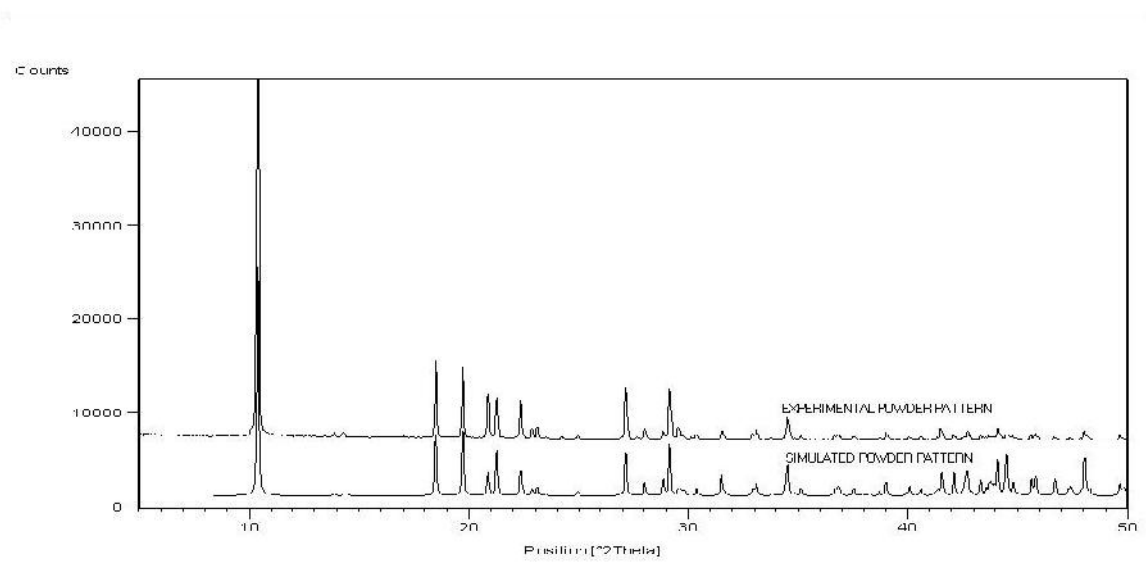


FIG.1. PXRD Overlay of experimental and simulated Powder X-ray diffraction pattern for Lanthanum carbonate octahydrate

Table 1. Elemental analysis of Lanthanum carbonate octahydrate.

Name of the Element	Theoretical value (%)	Experimental value (%)
Carbon	5.98	6.33
Hydrogen	2.69	2.61

The stoichiometry of Lanthanum carbonate octahydrate was confirmed from the carbon (5.98%) and hydrogen content (2.69%) as Lanthanum carbonate octahydrate.

The crystal structure of Lanthanum carbonate octahydrate shows a metal coordinated complex structure exists with intra- and inter-molecular hydrogen bonding. It forms a layered structure with four molecules of water within the lattice and one pair of water molecules each at above and below the lattice plane (Figure 2). Lanthanum carbonate exists in an orthorhombic structure in a Pccn type of space group with the following cell parameters (Table 2).

Thermogravimetric (TGA) and TGA-FTIR data: Determining the water content for Lanthanum carbonate octahydrate by Karl-Fischer technique is not a suitable technique since it is not soluble in the solvent media used for measuring water content in a Karl Fischer auto titrator. The coulometric technique was tried as an alternative to estimate the water content but only partial amount of water could be determined because of the lattice water molecules which require a higher temperature for complete removal of the lattice water. Similar failure was observed while trying to estimate the water content by loss on drying. The difficulty in measuring water content in Lanthanum carbonate is understandable based on the crystal structure of lanthanum carbonate octahydrate as described above. Lanthanum carbonate octahydrate was analysed by the thermogravimetric analyzer (TGA) in the above mentioned experimental conditions. The thermogravimetric data collected for Lanthanum carbonate octahydrate showed three weight losses observed from 30°C to 900°C (Figure 3).

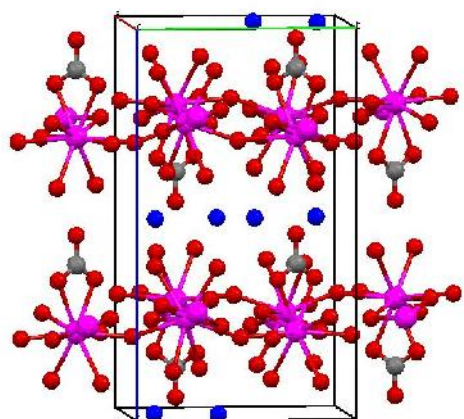


Figure 2. Crystal structure of Lanthanum carbonate octahydrate viewed along b-axis

Table.2 Crystallographic data of Lanthanum carbonate octahydrate

Crystallographic Parameters	Details
Name of the molecule	Lanthanum carbonate octahydrate
Empirical Formula	$\text{La}_2(\text{CO}_3)_3 \cdot 8\text{H}_2\text{O}$
Molecular Weight	601.82
Crystal system	Orthorhombic
Space group	Pccn
Lattice type	Primitive
Cell Parameters	
a (Å)	8.984 Å
b (Å)	9.58 Å
c (Å)	17.00 Å
$\alpha = \beta = \gamma$ (°)	90°
Volume Å ³	1463.13

The first derivative curve by TGA shows clear separation of the lattice water from the loss of carbon dioxide. The loss of lattice water equivalent to eight molecules of water was observed from 30°C to about 350°C. The theoretical water content for Lanthanum carbonate octahydrate is 23.9%. The first weight loss up to about 350°C is due to the eight molecules of water amounting to 24.27% was found to be comparable with the theoretical value. The second and third weight losses ranging from 350°C to 800°C are due to the decarboxylation of Lanthanum carbonate. Three molecules of carbon dioxide are lost in this temperature range which is equivalent to the three moles of carbonate present in Lanthanum carbonate octahydrate.

Theoretically, for Lanthanum carbonate octahydrate the total carbon dioxide weight loss is 22.0% which is equivalent to 29.9% of carbonate in Lanthanum carbonate octahydrate. The experimental carbonate content was found to be around 29.8%.

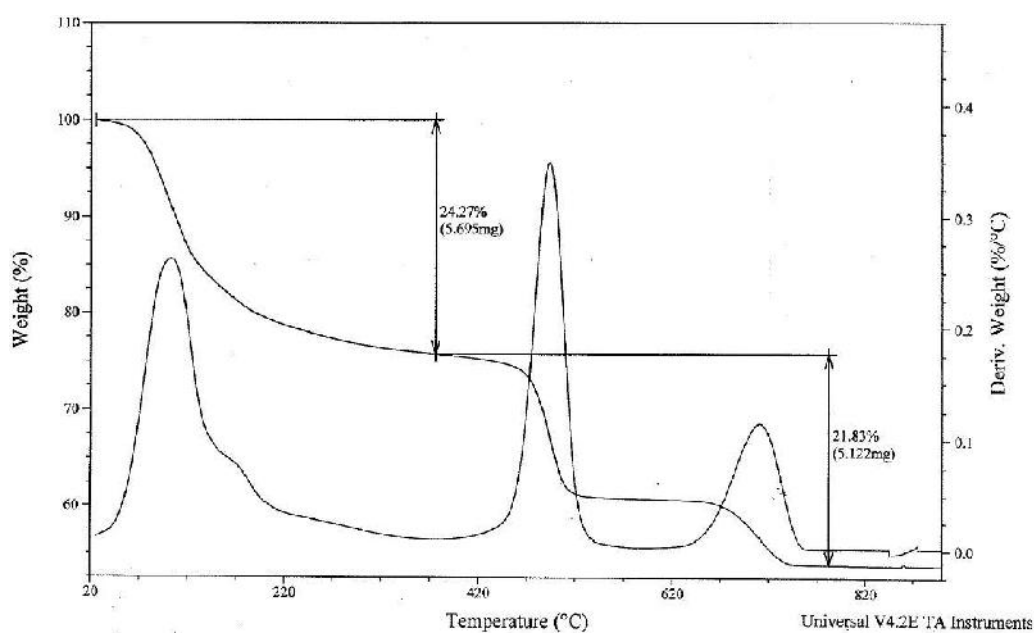


Fig.3. Thermogravimetric data for Lanthanum carbonate octahydrate

TGA-FTIR data shows the gradual loss of water with O-H bands observed around 3200-3400 cm^{-1} with increase in temperature up to about 400°C thereby confirming that removal of water occurs first and decarboxylation is a latter phenomenon which is observed beyond 400°C (Figure 4).

To better understand the thermal decomposition behaviour of lanthanum carbonate octahydrate, FTIR data was also collected for samples of Lanthanum carbonate isothermally heated at 370°C, 575°C 790°C and 900°C. The FTIR data collected for lanthanum carbonate octahydrate shows carbonate peaks at ~ 850 and 1337 cm^{-1} (**Figure 5**). The carbonate peak gradually decreases and finally disappears at 790°C. This confirms that the loss of water and carbonate in the form of carbondioxide is not a simultaneous phenomenon.

Since no overlapping loss of water and carbondioxide was observed, the TGA method for determining water and carbonate content was found to be an accurate and rapid technique.

Method validation of carbonate content by TGA: The determination of carbonate content in Lanthanum carbonate octahydrate by TGA was validated. The method was validated by demonstrating that the method is linear, accurate, precise and rugged. The working amount for determining the carbonate content was fixed at approximately 30 mg. The linearity of the method was determined by analyzing five samples of Lanthanum carbonate octahydrate at different concentration levels (i.e. 80%, 90%, 100%, 110% and 120%) of the working amount as per the analytical method.

The linearity results were obtained by integrating the second and third weight losses in milligrams equivalent to amount of carbonate present in the sample and a good correlation ($R= 1.00$) was obtained (Figure 6).

The accuracy of the method was established at three different concentration levels of the working amount. The accuracy was determined based on nine measurements which was actually each concentration level in triplicates. The calculated and obtained carbonate content in milligram was found to be in good agreement with the percentage recovery of 99.7% to 101.1%.

The method precision was established by measuring Lanthanum carbonate octahydrate six times and calculating the percentage carbonate content from the total weight loss due to carbondioxide using the following equation (1).

$$\% \text{ Carbonate content} = \frac{M \times F \times 100}{Z} \quad \text{Equation (1)}$$

Where, M = Total weight loss obtained due to loss of CO₂ (mg), Z = Weight of the sample taken (mg) and F = 1.3636 or 180mg /132mg (where 180mg is equivalent to 3 molecules of CO₃ and 132 mg is equivalent to 3 molecules of CO₂).

The method was found to be precise as indicated from the low percentage relative standard deviation of 0.16%. The intermediate precision or ruggedness of the method was established by variation of analyst on two different days. The carbonate content obtained by both the analysts and calculated based on equation (1) was in good agreement with a low variation of less than 0.1.

Therefore estimation of the carbonate content in Lanthanum carbonate octahydrate by thermogravimetric analysis is an accurate and precise method.

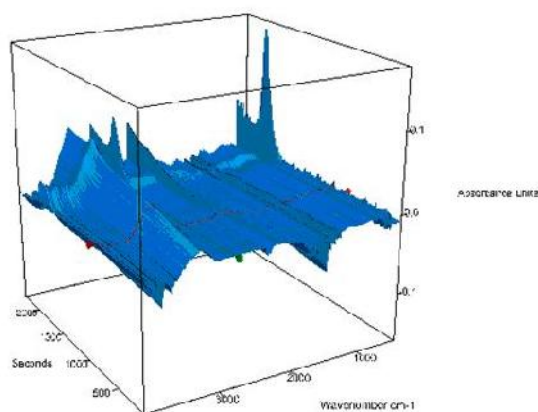


Fig.4 TGA-FTIR 3D plot

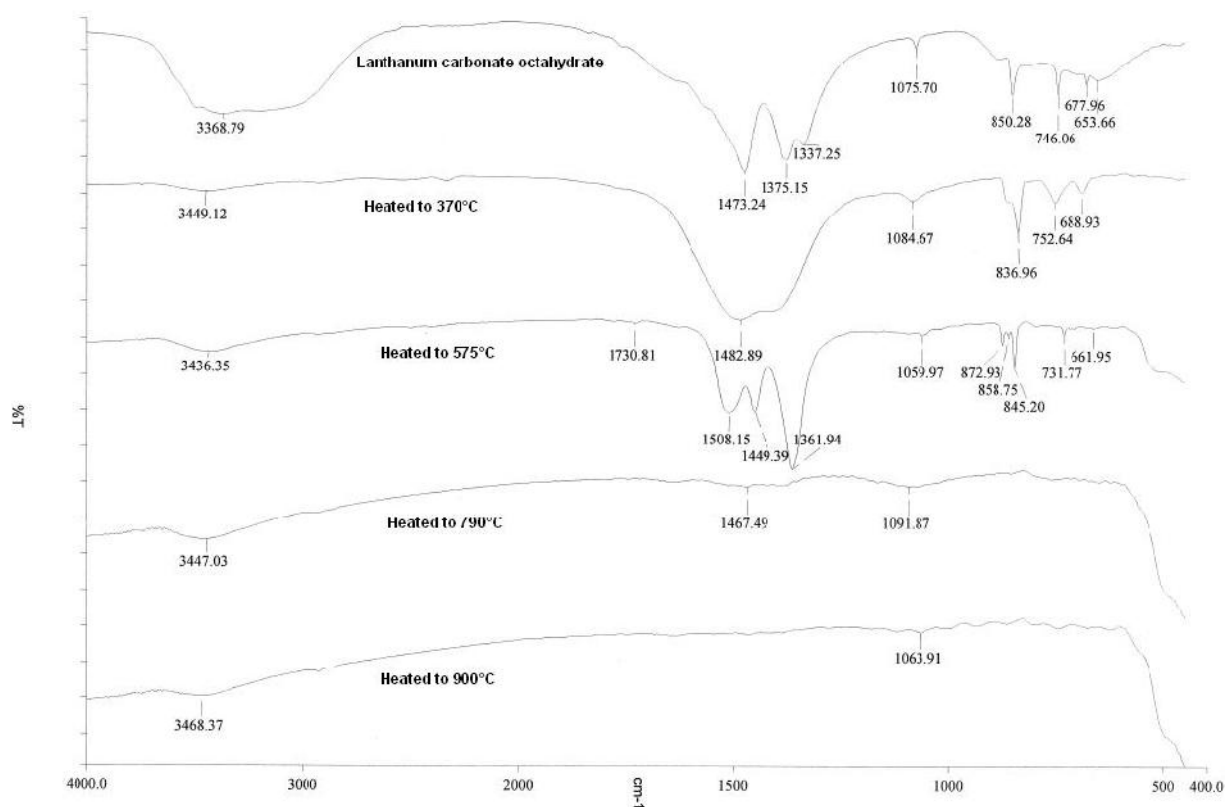


Fig 5. FTIR Overlay of Lanthanum carbonate octahydrate heated at different temperatures

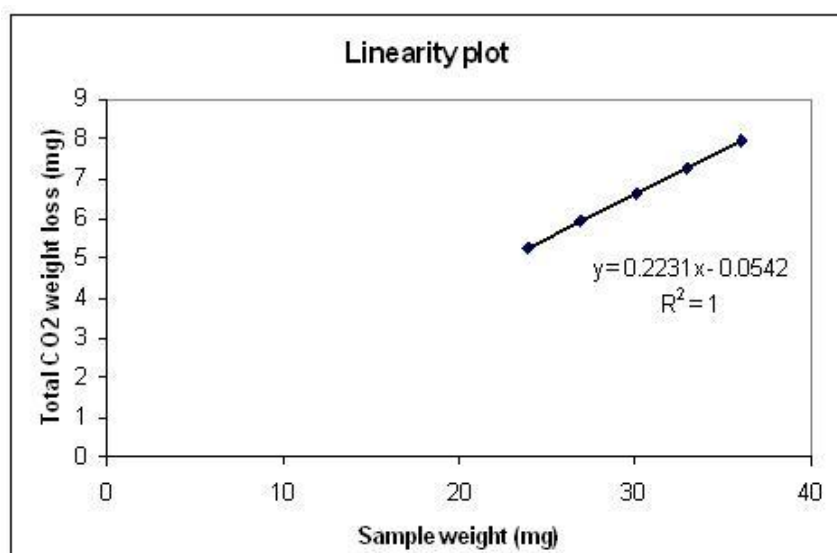


Fig.6. Linearity plot for carbonate estimation in Lanthanum carbonate octahydrate

Thermal impurities of Lanthanum carbonate octahydrate:

Lanthanum carbonate octahydrate was subjected to variable temperature under air and nitrogen atmosphere and samples drawn at different intervals were measured by Powder X-ray diffractometer and FTIR to identify the degradants formed. The polymorphic form is more or less retained below 100°C. Between 100°C

to 345°C complete dehydrate takes place with the formation of anhydrous Lanthanum carbonate [4]. At 575°C the PXRD pattern was identified as Lanthanum dioxycarbonate [11-13]. The same degradants were found to form when heated up to 575°C under both air and nitrogen atmosphere respectively (Figure 7a and 7b). Initially a gradual loss of the eight molecules of water occurs after which decarboxylation is observed at 575°C with the formation of Lanthanum dioxycarbonate from Lanthanum carbonate anhydrous. The formation of decarboxylated impurities like dioxycarbonate is only possible at a very high temperature of above 500°C.

Interestingly, the degradation pattern is followed differently when Lanthanum carbonate is heated above 575°C. Lanthanum carbonate is assumed to convert to Lanthanum oxide when heated to high temperatures of 900°C and beyond. Two types of Lanthanum oxide is reported – cubic and hexagonal [13]. Under nitrogen, Lanthanum carbonate when heated to 900°C converted the freshly formed Lanthanum dioxycarbonate (at 575°C) to hexagonal Lanthanum oxide (JCPDS No. 05-602) (Figure 8) whereas under air atmosphere it was found to form Lanthanum trihydroxide (Figure 9).

The formation of Lanthanum trihydroxide is intriguing since literatures reveal that annealing of Lanthanum carbonate or Lanthanum dioxycarbonate will result to cubic or hexagonal Lanthanum oxide [14-15]. However, a repetition of the analysis and this time under nitrogen was performed with annealing the sample at ambient atmosphere. A mixture of hexagonal Lanthanum oxide and Lanthanum trihydroxide formed indicating the annealed hexagonal Lanthanum oxide is unstable in ambient air and transforms to Lanthanum trihydroxide (Figure 10) [17-19].

Formation of the hexagonal Lanthanum oxide dominated with its conversion to Lanthanum hydroxide when exposed to ambient atmosphere. Hence, it can be concluded that the nature of the atmosphere dictates the formation of the degradants above 600°C. The type of degradants formed above 600°C was found to depend of the type of atmosphere the sample was exposed to i.e. nitrogen or air.

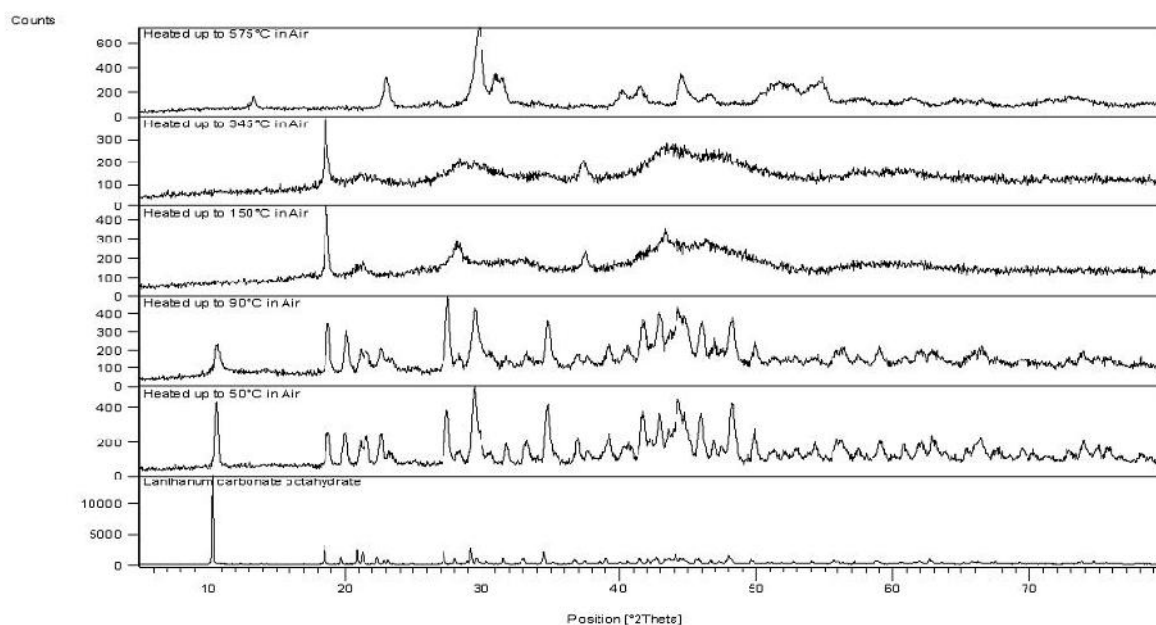


Fig7a. PXRD overlay of Lanthanum carbonate octahydrate heated in Air

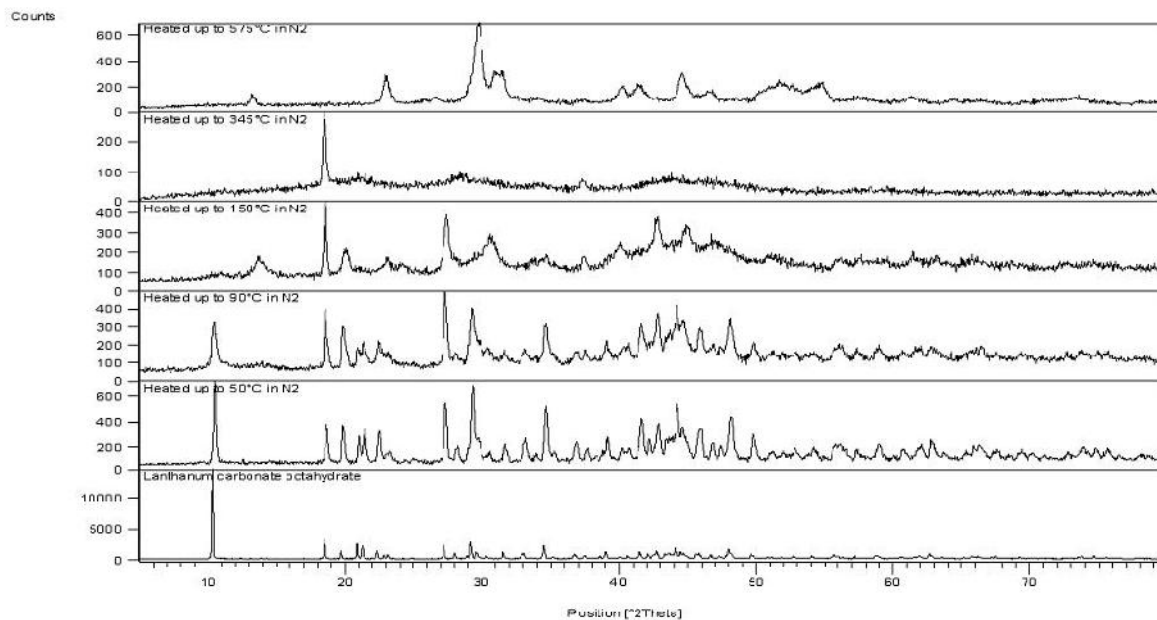


Fig7b. PXRD overlay of Lanthanum carbonate octahydrate heated in Nitrogen

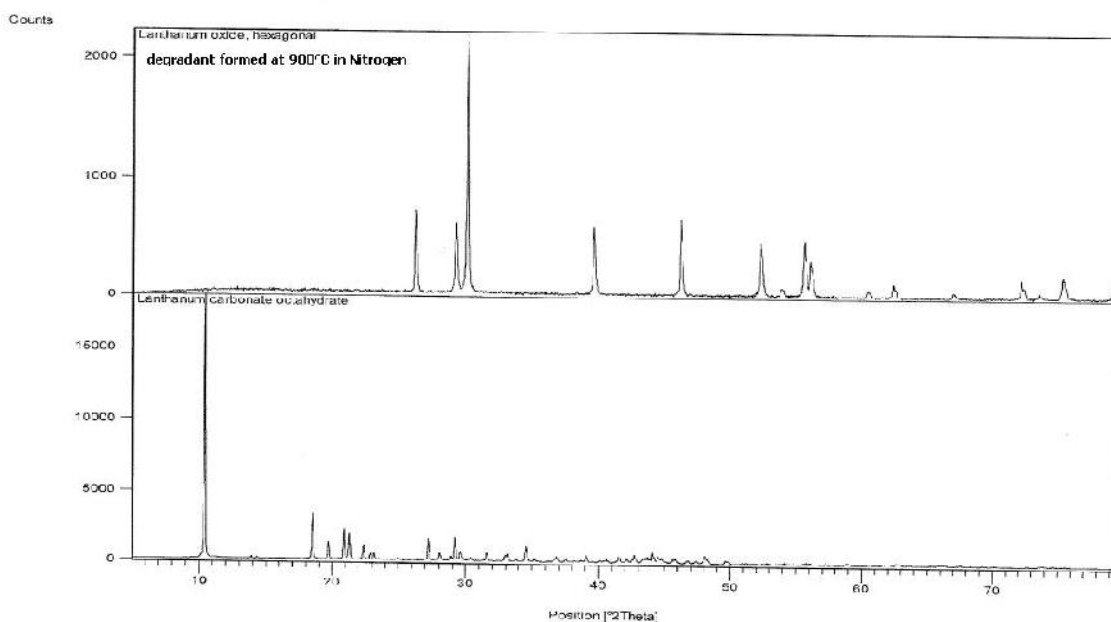


Fig 8. Lanthanum carbonate octahydrate at 900°C in nitrogen

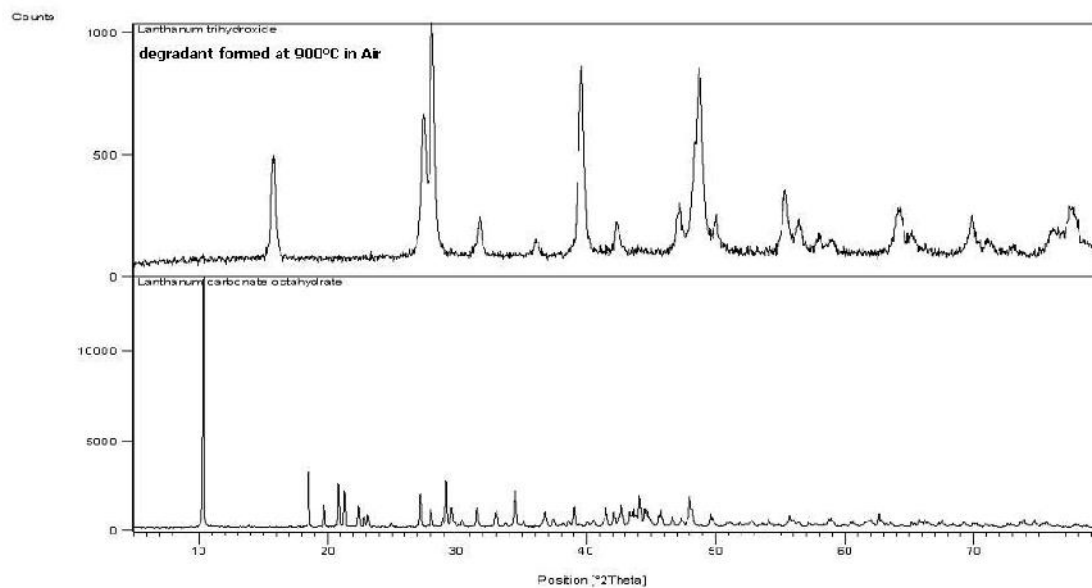


Fig 9. Lanthanum carbonate octahydrate at 900°C in air

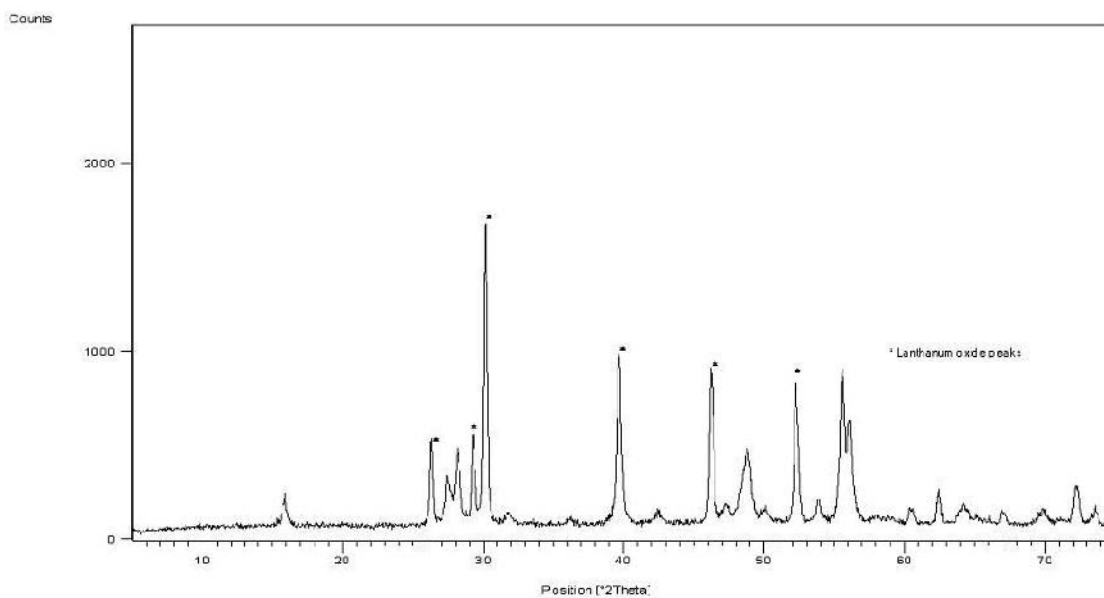


Fig 10. PXRD data of Lanthanum carbonate octahydrate annealed at 900°C in air

Conclusion

The thermogravimetric method has been validated for the determination of carbonate content and water in Lanthanum carbonate octahydrate. The results obtained prove the potentiality of thermogravimetric analysis as an alternative technique over chemical analysis. The uniqueness of Lanthanum carbonate octahydrate has been explored and the effect of temperature on it has been extensively studied. The formation of thermal impurities were studied which revealed some interesting insight into what type of degradants are most probable to form. The route map of thermal degradation of Lanthanum carbonate octahydrate begins with the dehydration of water to form anhydrous lanthanum carbonate. Anhydrous lanthanum carbonate converts to Lanthanum dioxycarbonate and subsequently depending on the atmosphere forms either Lanthanum oxide or Lanthanum trioxide.

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