RESEARCH ARTICLE

Preformulation Studies of Pitavastatin Calcium– A Primary Step in Further Design of Chronotherapeutic Formulation Synchronized with Circadian Rhythm

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Received: 20th February, 2024; Revised: 27th March, 2024; Accepted: 15th August, 2024; Available Online: 25th September, 2024

ABSTRACT

The principal goal and objective of this present research work were to perform a preformulation analysis of Pitavastatin calcium to produce a further stable, efficient chroomodulated drug delivery system. Pitavastatin calcium was analyzed to study its micrometric properties, equilibrium solubility profile in different media, and determination of purity by subjecting to fourier-transform infrared spectroscopy (FTIR) studies, by determining the absorption maxima in the medium along with differential scanning Calorimetry- DSC. Spectral analysis of UV studies and calibration curve plotting was done for further analytical research. The melting point was analyzed, and PXRD studies were conducted to identify the crystallinity. The Pitavastatin calcium micromeritic properties were found to be good with bulk density- 0.408 g/mL, tapped density 0.476 g/mL, Carr's index 14.2%, Hausner's ratio 1.16 with 32.005^0 angle of repose. The equilibrium solubility study indicates drug has peak solubility in media 0.1 N Hcl and reduced solubility in distilled water. The infrared spectrum indicated peaks corresponding to functional groups conforming to the purity. The UV spectrum exhibited absorption maxima at 250 nm in media 0.1N HCl and 245 in pH phosphate buffer 6.8 and in all other mediums, which is the same as the standard literature indication. The calibration curve exhibited linearity in accordance with Beer Lambert's law. The PXRD studies produced 2θ values corresponding to pitavastatin calcium as per literature conforming to the crystallinity. The Preformulation analysis concludes that the drug was pure pitavastatin calcium with corresponding absorption maxima, an infrared spectral functional group with crystallinity. It specifies that the drug mandates the improvement of solubility for further formulation development.

Keywords: Pitavastatin calcium, Solubility, Infrared spectrum, Purity, Crystallinity.

International Journal of Drug Delivery Technology (2024); DOI: 10.25258/ijddt.14.3.46

How to cite this article: Anusha V, Umashankar MS, Kumar YG. Preformulation Studies of Pitavastatin Calcium– A Primary Step in Further Design of Chronotherapeutic Formulation Synchronized with Circadian Rhythm. International Journal of Drug Delivery Technology. 2024;14(3):1578-1585.

Source of support: Nil.

Conflict of interest: None

INTRODUCTION

Preformulation studies are generally considered the primary approach for the successful development of dosage forms encompassing suitable active pharmaceutical ingredients (API). The term Preformulation indicates an advanced study of physicochemical properties of pharmacologically active API alone and also in combination with formulating excipients.[1] They produce essential information about the physical, chemical, biological and mechanical properties of drugs and excipients, along with packaging and storage indications. This characterization of API holds an influence on effective dosage development.[2]

Preformulation studies will usually be carried out nearly after completing pre-clinical and clinical studies. The Research and development team does these studies before a formulation is developed to understand the physical and also chemical behavior of an (API) Active pharmaceutical ingredient (drug molecule). Preformulation studies are intended to estimate the effects of the physicochemical properties of a drug substance and also the excipient properties in the formulated dosage form, effects on the method involved in its manufacture and the pharmacokinetic behavior of the produced dosage form. This study helps us to identify and understand the properties of API, including its solubility, bulk density, tapped density, compressibility index, thermal properties, and FTIR spectra to identify the functional groups and spectra. It also provides compatibility with API and other formulating excipients. This study provides guidance to the formulator for choosing the

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correct physical form of a drug molecule and for improving the formulation properties, producing high bioavailability.[3] It assists in gathering complete knowledge of the new drug entity.

Pitavastatin is (3R,5S, 6E)-7-[2-cyclopropyl-4-(4-fluorophenyl)quinolin-3-yl]-3,5-dihydroxyhept-6-enoic acid which is a lipid-lowering drug. It belongs to the statin category of therapeutic medications and treatment. They inhibit endogenous – internal cholesterol production in the liver specifically these statins will inhibit Hydroxy methyl glutaryl-coenzyme - A (HMG-CoA) Reeducates enzyme, which will convert HMG – CoA to mevalonate derivative mevalonic acid. This step is considered a crucial rate-limiting step in the synthesis of cholesterol.[4] This step also involves lipid derivative metabolism and their transport along with cholesterol and low-density lipoprotein (LDL. The statins use produced high health benefits with fewer side effects and low long-term effects; hence, they are considered one of the regularly prescribed medications for improved treatment of hypercholesterolemia, hyper-lipoproteinemia, hypertriglyceridemia and Pediatric Heterozygous Familial Hypercholesterolemia.[5] Pitavastatin is generally directed for reducing raised total Cholesterol -TC, low-density cholesterol, apo-lipoprotein-Apo B and also triglycerides. They help to uplift levels of high-density cholesterol. Pitavastatin acts principally in the liver, where the declined hepatic levels of cholesterol will stimulate and accelerate up-regulation of hepatic LDL receptors such that it upsurges the hepatic LDL uptake, which further diminishes the circulating LDL cholesterol levels. In comparison to various statins, pitavastatin exhibited comparatively great improved bioavailability due to entero-hepatic reabsorption in the intestine following intestinal absorption. The elimination half-life is nearly estimated as 12 hours.[6] The daily dosage of pitavastatin includes an initial starting dose of 2 mg once a day and is adjusted with dose accordingly. The maximum daily dosage is 4 mg. Marketed brands available include Livalo-Pitavastatin calcium, and Zypitamag - Pitavastatin magnesium and their dosages expressed in terms of Pitavastatin.[7,8]

The present research focuses on conducting preformulation studies of pitavastatin calcium for further successful development of a stable, strong, pharmacologically active and safe chronotherapeutic dosage form for the treatment of hypercholesterolemia. The characterization of pitavastatin was done by analyzing the powder Micromeritics characters, including bulk densities and tapped density, compressibility/ carr's index, angle of repose. The API solubility in different solvents was determined. The Fourier transform infrared spectrum provides information about functional groups and purity of the drug. Further, UV spectroscopic studies were conducted to identify λ max and for further analysis process. The drug excipient compatibility studies were performed to understand the compatibility. It can be concluded that Preformulation studies helps to identify the densities, compression properties, thermal stability, solubility, and spectral analysis of API such that it helps in formulating a successful dosage form with safety, efficacy and quality.

MATERIALS AND METHODS

The API Pitavastatin calcium was obtained from Solara Active Pharma, Industrial Complex, Tamil Nadu - India. The other reagents and chemicals, hydrochloric acid, potassium dihydrogen phosphate, sodium hydroxide - NaOH, and methanol, were obtained from Sigma-Aldrich and Research lab Fine Chem Industries, which are of pharmaceutical grade.

Preformulation Studies

Organoleptic characterization

The organoleptic characterization properties, including color, odor, physical state, and appearance, were inspected visually for Pitavastatin API.

Characterization of Micrometric Properties

Bulk density

Initially, the API was passed through sieve #20 to remove any lumps, followed by determining the bulk density of pitavastatin weighed 10 g of API sample was transferred accurately into 50 mL measuring cylinders.[9,10] The full volume occupied by mass without any compressing or disturbance was detected as apparent bulk volume. It was observed as, V_o, bulk density was computed with formula.

$$\text{Bulk density} = (M) / (V_o)$$

Such that,
M = Sample weight of API in g
V_o = apparent volume in mL of API

Tapped density

Previously 10 g of pitavastatin sample was filled and packed in 50 mL measuring cylinder. The cylinder was tapped using a tapped density tester at a minimal rate of 300 drops/ minute, which offers a fixed drop of 14 ± 2 mm, for an initial 500 times and V_o was noted as tapped volume based on the graduation markings on cylinder.[10] Tappings were processed for an additional 750 tapping times and V_b was noted as tapped volume. The variance between the two volumes was observed as lower than 2%, such that V_b was reflected as V_f the tapped volume..

$$\text{Tapped density} = \text{API sample weight taken} / \text{API sample final tapped volume } (V_f)$$

Compressibility Index (CI)

Inter-particle, particle–particle interactions will affect bulk properties, including the powder flow. Hence, comparing bulk densities and tapped densities will produce an extent of the comparative importance of such types of interactions in the given powdered sample.[11] In a powdered sample that is free-flowing, the interactions and connections would be lower such that the difference in bulk and tapped density would be low. In a powder with poor flow, the interactions would be high and the difference in bulk/tapped density would be high. The

difference can be understood by calculating compressibility or Carr's index.

$$CI\ (\%) = \frac{\text{Tapped density} - \text{Bulk density}}{\text{Tapped density}} \times 100$$

Hausner's Ratio

The difference in tapped densities and bulk densities can be understood by calculating the Hausner's ratio, which will reflect the behavior of inter-particle interactions along with density differences.[12]

$$\text{Hausner' s Ratio (H)} = \text{Tapped Density / Bulk Density}$$

Angle of Repose

The process involves a funnel method where the required amount of pitavastatin was discharged into a funnel while the funnel height was adjusted to 2.5 cm with a fixed height. The sample was poured in the funnel by closing the tip of the funnel, the sample is allowed to flow from the funnel once it is filled completely.[13] As the pile of samples was formed, the diameter and radius was computed by determining an average of three values. Then, the angle of repose was computed using:[14]

$$\theta = \tan^{-1}(h/r)$$

h = funnel height, r = circle radius.

Melting Point Determination

The capillary method was used to determine the melting point of pitavastatin. Mel-Temp apparatus was used. A slight quantity of drug samples was packed into capillary tubes, which were previously tapered at one end.[15] It was kept in the melting point apparatus and the heater was switched on. The temperature was noted at the point where the drug started melting into liquid.

UV Spectroscopic Method Development

Determination of λ_{max}

A 1-mg/mL stock solution of API was prepared in the medium, including 0.1 N Hcl, pH 6.8 phosphate buffer, along with the respective medium by dissolving a weighed quantity of 50 mg Pitavastatin calcium in 50 mL respective medium. Pitavastatin was easily soluble in 0.1 N HCl; hence no solvent was required for preparing stock solutions. For preparing the solution of stock in pH 6.8 phosphate buffer and other medium, initially, 2 mL of dimethyl-formamide was additionally added to dissolve API and the final volume was made and prepared to 50 mL with pH 6.8 phosphate buffer and respective media.[16,17] From this stock solution, 10 mL was taken and made up to 100 mL with respective medium to produce 100 µg/mL. From the prepared solution, 1-mL was obtained and made to 10 mL utilizing the respective medium to produce 10 µg/mL. It was analyzed by UV-visible spectrophotometer by scanning between 200 and 400 nm to determine the λmax of API in respective mediums.

Construction of calibration curve

A 1mg/mL stock solution was prepared in different medium of 0.1 N Hcl, pH 6.8 phosphate buffer, pH 7.4 phosphate buffer, water including methanol by dissolving weighed quantity of 50 mg drug in 50 mL respective medium as described above[18] If API was not soluble 2 mL of dimethyl formamide was added and the volume has been made to 50 mL utilizing respective media. From the prepared stock, 10 mL was taken and made up to 100 mL with respective medium to produce 100 µg/mL. From these stock solutions aliquots of 0.1 mL, 0.2, 0.3, 0.4... till 1.4 mL were taken and made up to 10 mL with respective mediums to produce 1,2, 3, 4, 5, 6, 7, 8, 9. 10, 11, 12, 13 and 14 *µg/*mL respectively. If required the filtration of samples was done using filter paper like whatman paper and absorbance was determined for these samples in their respective medium using the particular medium as blank at *λmax*.[19] The calibration/ standard curve was formed as a plot of API absorbances on the y-axis and concentration on the x-axis, using linear regression analysis plot and straight line for the best fit was formed.

Further HPLC analysis was performed for the Pitavastatin calcium

Equilibrium solubility determination

To determine the solubility, the Shake flask method has been employed. Into a five separate 100 mL conical flask 20 mL each of pH 6.8 phosphate buffer, pH 7.4 phosphate buffer, 0. 1 N Hcl, distilled water and methanol were transferred into respective flask to determine and compute saturated equilibrium drug solubility in that particular medium. An Excess quantity of Pitavastatin sample was added into each of the above flask and checked for presence of un-dissolved excess solid at the bottom of flask, the sample should be added until an excess solid remains in the beaker.[20] The flask after covering suitably were stirred continuously for 24- 48 hours using magnetic stirrer at set 50 rpm to attain equilibrium at 37 +1 ºC. Saturation was confirmed by presence of un-dissolved excess solid at bottom, the samples were filtered to remove un-dissolved API and to separate supernatant from samples, using whatman filter paper of pore size 0.45 µ. Then samples were analyzed to obtain absorbance with a UV Visible Spectrophotometer at corresponding *λmax* in respective medium after required dilutions with same medium which is used for its solubility determination.[21] Then it was converted into concentration term using standard graph of drug in respective medium and solubility was determined.

Fourier transform infrared spectroscopy

The infrared spectrum acts as crucial proof that provides sufficient information on a compound's structure. The FTIR method provides a range that includes a band of absorption from which information about the structure of compound can be deduced.[22] The FTIR spectra was obtained by using Agilent technologies FTIR spectral Analyzer, the sample of Pitavastatin calcium was placed on the holder of analyzer and the spectra was run between the range as per the IR functional group requirements.[23]

Drug-excipient compatibility studies

The compatibility among the drug molecule and formulation excipients must be analyzed which helps to identify any specific interaction between them. IR spectroscopy will be used to identify the interaction by observing the peaks produced representing their functional groups.[24,25] The weighed quantity of Pitavastatin calcium was mixed with recommended quantity of *excipients* and the blend was subjected to IR studies and also observed for physical changes.

Differential scanning calorimetry (DSC)

DSC helps to identify and determine the purity of an API. The melting point obtained will be sharp and will remain constant in pure API substances. In a crimped aluminum pan, 2- 4 mg of the sample was heated from temperature range 0 to 270 ^{0}C. Then plot is obtained between heat flow versus temperature,[26,27] The curve is used to calculate the enthalpies of transitions, area measure under the peak is always directly proportional to the heat liberated or which is absorbed during reactions. Then melting point of the pitavastatin was determined using the thermogram of DSC. The process of melting is considered as physical procedure and a process resulting in transition of phases where substances get converted from a solid state to liquid state.[28]

PXRD

It is the technique frequently used to evaluate the crystallinity of a substance. Powder X-Ray Diffraction (PXRD) was utilized for analyzing crystallinity of Pitavastatin calcium.[29,30] The measurements were made using Cu as anode material, with generator Settings at 30 mA, 45 kV, Intended Wavelength Type - K-α1. The sample of API was scanned for *a 2 θ range up to 40*°C.

RESULTS AND DISCUSSION

Organoleptic Characteristics

The organoleptic properties like color, odor, physical state, appearance were inspected visually for Pitavastatin API and results are specified in the Table 1.

Micromeritics

The micromeritic characterizations of pitavastatin were inspected for bulk density, tapped densities, compressibility/ carr's index, angle of repose, Hausner's ratio. The results found are published in Table 2. The studies indicated that Compressibility index of the pitavastatin was found to be 14.2% which indicate the flow property is good. The angle of repose was 32.005° indicating good flow property and the data is presented in Table 2.

Table 1: Organoleptic characteristics of API Pitavastatin calcium

S. No	*Organoleptic Characteristics*	*Inference*
1.	Colour	White
2.	Odour	Odourless
3.	Physical state	Solid

Table 2: Micromeritic characterization of Pitavastatin calcium

S. No	*Micrometritic character*	*Observed result*	*Inference for flow*
1.	Bulk density	0.408 g / mL	Good
2.	Tapped density	0.476 g / mL	Good
3.	Angle of repose	32.005^0	Good
4.	Compressibility index	14.2 %	Good
5.	Hausner's ratio	1.16	Good

Melting Point

The melting point of Pitavastatin calcium was determined and computed using method of capillary which confirms the melting-point and purity of the drug.[31,32] The procedure was carried out for three times and three melting point determinations were done and the average of three replicates was considered as final melting point which was 135.2°C, which was nearly synchronized with literature value. This will confirm the purity of pitavastatin and are indicated in Table 3.

UV Spectroscopic Method Development

Determination of λmax

The λ max of pitavastatin was determined by UV-Vis spectrophotometer. The solvent medium utilized includes 0.1 N Hcl, pH 6.8 buffer and respective medium. The λ max in 0.1 N Hcl was found to be 250 nm which is nearly same and comparable to literature standard *λmax* of pitavastatin in 0.1 N Hcl[33] and respective spectra is presented in the Figure 1.The λ max in pH 6.8 phosphate buffer was determined as 245 nm which is exactly same and comparable to literature standard *λ*max of Pitavastatin,[34] relative spectra is presented in the Figure 2. The *λmax* was found to be same 245nm in all the other medium including water, methanol and 7.4 buffer.

Table 3: Melting point of Pitavastatin calcium

S. No	*Melting point*	*Average melting point*
1.	135.4°C	135.2°C
2.	135.8°C	
3.	134.6°C	

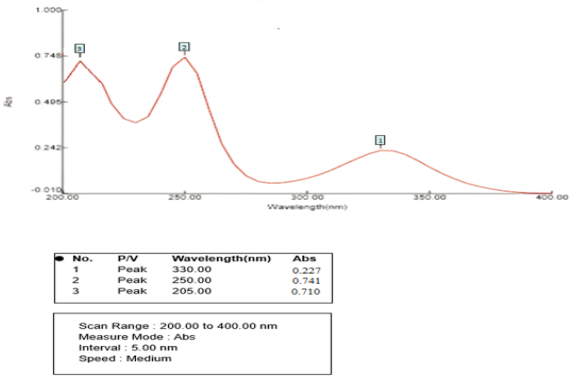

Figure 1: Spectrum of Pitavastatin calcium in 0.1 N Hcl

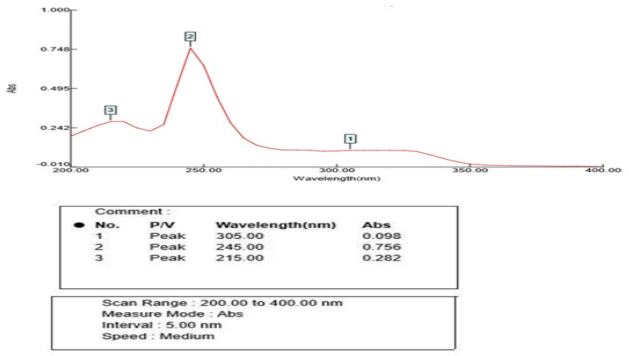

Figure 2: Pitavastatin calcium spectrum in pH 6.8 phosphate buffer

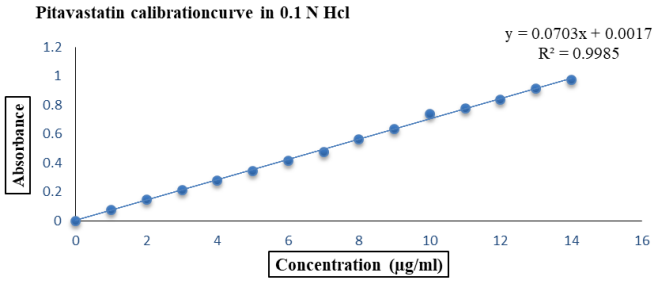

Figure 3: Pitavastatin Calibration curve in 0.1 N Hcl

Construction of calibration curve

The solvent media utilized for determination of calibration curve includes 0.1 N Hcl, distilled water, phosphate buffer 6.8, phosphate buffer pH 7.4, and methanol. Pitavastatin calibration curve was determined using UV-Visible-spectrophotometer by scanning at the respective wavelength 250 nm in 0.1 N Hcl and at wavelength 245 nm in pH 6.8phophate buffer and all other media. The resultant absorbance data and constructed curve followed Beer Lambert's law. The calibration curves in 0.1 N hcl, water and phosphate buffer 6.8, 7.4 exhibited linearity and followed Beer Lambert's law, the curves are represented in Figures 3-6 respectively. The corresponding data in 0is presented in Tables 4 and 5. The regression value produced in methanol also exhibited linearity.

Table 4: Pitavastatin Calibration curve in 0.1 N Hcl

S. No	*Parameter*	*Value*
1.	Absorption maxima	250
2.	Beer's law range	1–14 µg/mL
3.	Regression equation	0.0703x + 0.0017
4.	Correlation coefficient (R^2)	0.9985

Table 5: Pitavastatin calibration curve in pH 6.8 phosphate buffer

S. No	*Parameter*	*Value*
1.	Absorption maxima	245
2.	Beer's law range	1–14 µg/mL
3.	Regression equation	0.071x + 0.0088
4.	Correlation coefficient (R^2)	0.9986

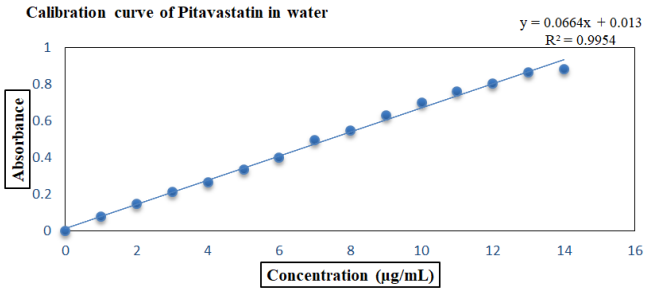

Figure 4: Pitavastatin calibration curve in water

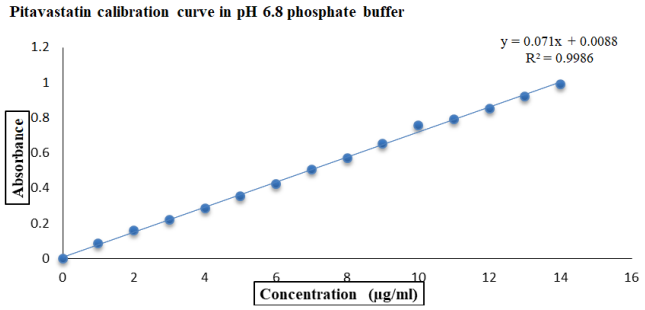

Figure 5: Pitavastatin calibration curve in pH 6.8 phosphate buffer

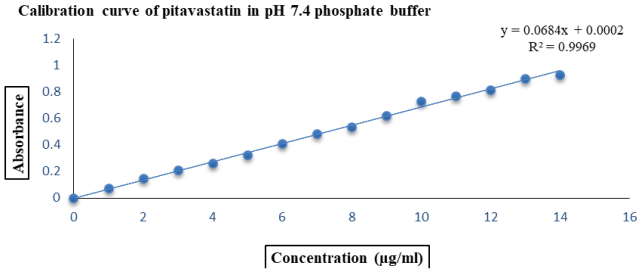

Figure 6: Pitavastatin calibration curve in pH 7.4 phosphate buffer

Equilibrium Solubility

The equilibrium saturated solubility of the drug pitavastatin was studied in water, 0.1 N HCl, methanol and phosphate buffer solutions of pH 6.8 and 7.4. The study was conducted for 24 to 48 hours and sample analysis was done by UV spectroscopic method at 250 nm in the 0. 1 N HCl. It was performed at 245 nm in all the other solvent media since the λ max was the same for identifying the concentration of the drug medium. All the results produced specified that the drug had limited solubility in distilled water and the highest solubility in 0.1 N HCl. All results of the study are displayed in Figure 7 and Table 6.

Fourier-Transform Infrared Spectroscopy

FTIR studies of pitavastatin were done by using FTIR-Agilent technologies. The spectrum was a plot of wavenumber (cm^{-1}) *versus* transmittance (%). The functional groups were determined by observing peaks obtained through the FTIR study. The graph of FTIR is presented in Figure 8 and the interpretations are displayed in Table 7. The spectrum represents C-H stretching, along with O-H stretching, C-0

Table 6: Solubility studies of Pitavastatin calcium in a different medium

S. No	*Drug*	*Solvent/Medium*	*Solubility* (mg/mL)
1.	Pitavastatin calcium	Water	0.88
2.	Pitavastatin calcium	0.1 N HCl	35
3.	Pitavastatin calcium	pH 6.8 Phosphate buffer	2.15
4.	Pitavastatin calcium	pH 7.4 Phosphate buffer	1.68
5.	Pitavastatin calcium	Methanol	5.2

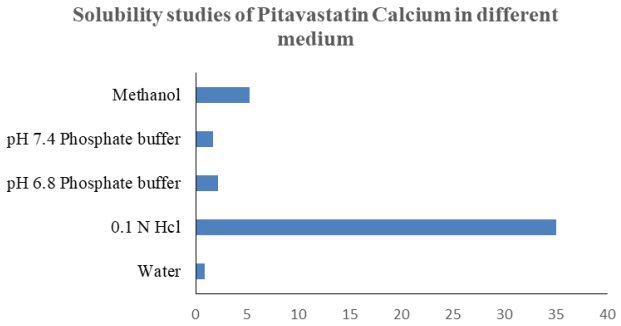

Figure 7: Solubility studies of Pitavastatin calcium in different medium

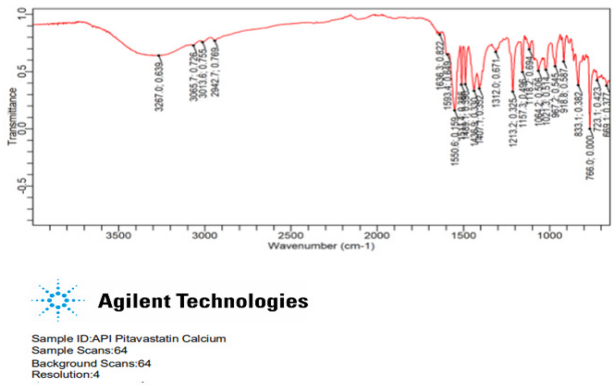

Figure 8: FTIR spectrum of pitavastatin calcium

stretchings, C=O stretch, C-F stretchings, C=C stretch and bending of 0-H. The interpretation confirms functional groups present in API.

Drug-excipient Compatibility Studies

The weighed quantity of Pitavastatin calcium was mixed with the recommended quantity of excipients and the blend was subjected to IR studies along with further observation for physical changes like Colour change, liquefaction, etc. after storing for the required duration. The study indicated that the drug and excipients were compatible.

DSC- Differential Scanning Calorimetry

DSC studies help in the identification of the purity and melting point of the API pitavastatin calcium. In the DSC thermogram, the peak was observed at 134.5°C, which indicates the melting point of the drug. The thermogram contains a single endothermic peak, which indicates the absence of impurities and purity of pitavastatin as the melting point is close to the corresponding literature melting point range. The DSC thermogram indicating the melting point endothermic peak is exemplified in Figure 9.

Table 7: FTIR interpretation of pitavastatin

S. No	*Observed peak*	*Functional group interpretation*	*Mode*
1.	3065.73	O-H	Stretching
2.	3013.55	C-H	Stretching
3.	1636.30	C=O	Stretching
4.	1550.57	C=C	Stretching
5.	1213.24	C-O	Stretching
6.	1118.20	C-F	Stretching
7.	1436.88	O-H	Bending

*The functional groups were interpreted by comparing with standard literature indicated values

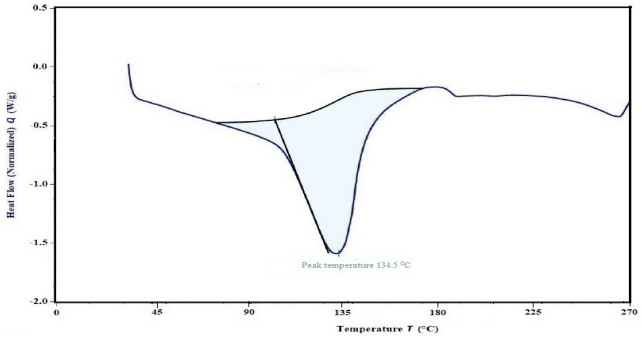

Figure 9: DSC thermogram of pitavastatin calcium

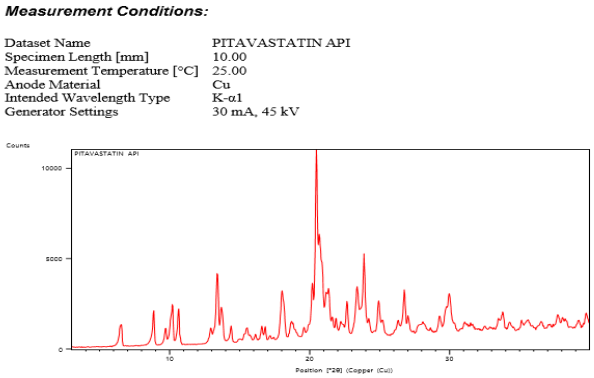

Figure 10: PXRD analysis of pitavastatin calcium

PXRD

In PXRD analysis, the measurements were made using Cu as anode material, with generator Settings at 30 mA, 45 kV, Intended Wavelength Type - K-α1. The samples of API were scanned for a 2 θ range up to 40. The analysis is presented in Figure 10. The 2θ values were observed at 6.53, 29.69, 13.68, 29.97, 21.3, 23.3, 20.9, 13.4, etc., which matches with the literature 2θ values of Pitavastatin calcium with ±0.2 deviation indicating the authenticity of sample. The sharp peak indicates the crystallinity of the API.

CONCLUSION

Preformulation analysis is considered as the preliminary, essential phase in formulation development as it supports to identification of physical-chemical characterizations of an API-active pharmaceutical ingredient. The information produced from the study assists in the further development of efficient, safe and stable dosage forms. In the present research work, the preformulation analysis of Pitavastatin calcium was done. Physical characteristics studies indicated good flow and compressibility properties. The solubility of the drug was found to be high in 0.1 N HCl. The purity was established by infrared spectra, which presented characteristic functional peaks and groups, the DSC with a corresponding single peak at its melting point and with UV spectroscopy, which showed absorption maxima at 245 nm corresponding to literature. The drug also exhibited compatibility with the formulation excipients. PXRD studies indicated the crystallinity of the drug. The study of solubility and crystalline nature of the drug further indicates that suitable solubility enhancement has to be performed for successful formulation development to improve the solubility along with crystallinity modification. This research illustrates a suitable satisfactory result for all the characterization studies and directs that the Pitavastatin calcium was a suitable molecule for further formulation development.

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