Journal of Advances in Science and Technology

Vol. VII, Issue No. XIV, August-2014, ISSN 2230-9659

A STUDY ON PHARMACEUTICAL DRUG SUBSTANCES

AN INTERNATIONALLY INDEXED PEER REVIEWED & REFEREED JOURNAL

www.ignited.in

Journal of Advances in Science and Technology
Vol. VII, Issue No. XIV, August-2014, ISSN 2230-9659

A Study on Pharmaceutical Drug Substances

Salinder Singh[1]* Dr. Vivek Verma[2]

[1] Research Scholar of Himalayan University, Itanagar, Arunachal Pradesh, India

Abstract – It has been known since the middle of 18th century that many substances could be obtained in more than one crystalline form but the subject of drug polymorphism has received extensive academic and industrial attention since the early pioneering reports of Aguiar and colleagues at Parke-Davis in which effect of polymorphism on dissolution and bioavailability were highlighted for Chloramphenicol palmitate. The existence of different crystal structures of the various polymorphs of a substance often causes these solids to exhibit a variety of different physical and chemical properties. Because of differences in the dimensions, shape, symmetry, capacity i.e. number of molecules and void volumes of their unit cells, the different polymorphs of a given substance have different physical and chemical properties arising from differences in molecular packing. Such properties include molecular volume, molar volume i.e., molecular volume multiplied by Avogadro's number, density, refractive index along a given crystal axis, thermal conductivity, electrical conductivity, hygroscopicity, hardness, solubility, rate of dissolution in different solvents, chemical stability and interactions with biological systems. Differences in melting points of the various polymorphs arise from differences of the cooperative interactions of the molecules in the solid state compared with the liquid state.

----------♦----------

INTRODUCTION

X-ray powder diffractometry (XRPD) is a widely used technique for the identification and quantification of polymorphic forms of drug substances since it is non-destructive in nature and requires relatively small amounts of sample. However, when the different polymorphic forms of the drug substance do not exhibit a distinct X-ray powder pattern and not having more intense characteristic peaks of unwanted polymorphic form of drug substance, then it is difficult to quantify the unwanted form with low limit of detection by XRPD. Raman spectrometry is not very sensitive to the physical apparition of the sample, which means that many solid samples can be studied directly without sample preparation, but it is sensitive to conditions at the molecular level. Thus, differences are often seen between the Raman spectra from different crystal forms of a compound or between crystalline and amorphous forms. The technique requires no sample preparation and shows minimum interference from water. Chemo metrics is equally applicable for the analysis of Raman spectral data when univariate analysis is inappropriate.

At the present time regulatory authorities require pharmaceutical companies to investigate and control polymorphism of drug substances to ensure product quality, safety and performance. Manufacturers have to declare that their API and product does not suffer solid phase transformation within the shelf life, which could affect bioavailability as well as to prove the non-infringement with respect to the of claimed polymorph form. Stability relationships between different solid forms of the substance and the storage conditions avoiding phase transitions have to be established.

Gaining such information needs suitable solid state analytical methods to be able to differentiate polymorphic forms of the substance and often, methods of quantifying these solid forms.

Also observed are differences in spectroscopic properties, kinetic properties, and some surface properties. Differences in packing properties and in the energetic of the intermolecular interactions i.e., thermodynamic properties among polymorphs give rise to differences in mechanical properties. These differences in physical properties among the crystal forms of a polymorphic system have become extremely interesting to pharmaceutical scientists because their manifestation can sometimes lead to observable differences that have implications for processing, formulation, and drug availability.

REVIEW LITERATURE:

The area under a DSC peak is directly proportional to the heat absorbed or evolved by the thermal event. Two types of DSC measurement are possible, which are usually identified as power-compensation DSC and heat-flux DSC. In power compensated DSC, the sample and reference materials are kept at same temperature by the use of individualized heating elements, and the observable parameter recorded is the difference in power inputs to the two heaters. In heat-flux DSC, one simply monitors the heat

differential between the sample and reference materials.

DSC can be used to obtain useful and characteristic thermal and melting point data for crystal polymorphs or solvent species. This information is of great importance to the pharmaceutical industry since many compounds can crystallize in more than one structural modification. The polarizing microscope is essentially a light microscope equipped with a linear polarizer located below the condenser, and an additional polarizer mounted on top of the eyepiece. A rotating stage is also found to be very useful, as is the ability to add other optical accessories. Polarization optical analysis is based on the action of the analyte crystal on the properties of the transmitted light. This method can yield several directly measured parameters, such as the sign and magnitude of any observed birefringence, knowledge of the refractive indices associated with each crystal direction, what the axis angles are, and what the relations among the optical axes are.

To conduct a polarizing microscope analysis, the light from the source is rendered linearly polarized by the initial polarizer. The analyzer is oriented such that its axis of transmission is orthogonal to that of the initial polarizer. In this condition of "crossed polars," no transmitted light can be perceived by the observer. The passage, or lack thereof, of light though the crystal as a function of the angle between the crystal axes and the direction of polarization is of key importance to the method.

RESEARCH METHODOLOGY:

The absorption of Infra-red radiations causes an excitation of molecule from a lower to the higher vibrational level. We know that each vibrational level is associated with a number of closely spaced rotational levels. Clearly, the Infra-red spectra are considered as vibrational rotational spectra. All the bands in a molecule are not capable of absorbing infra-red energy but only those bonds which are accompanied by a change in dipole-moment of the molecule are called infra-red active transitions. Thus, these are responsible for absorption of energy in the infra-red region. On the other hand, the vibrational transitions which are not accompanied by a change in dipole-moment of the molecule are not directly observed and these are infra-red inactive. For example, vibrational transitions of C=O, N-H, O-H etc. bands are accompanied by a change in dipole-moment and thus, absorb strongly in the infra-red region. But transitions in Carbon-Carbon bonds in symmetrical alkenes and alkynes are not accompanied by the change in dipole-moment and hence do not absorb in the infra-red region. It is important to note that since the absorption in the infra-red region is quantized, a molecule of the organic compound will show a number of peaks in the infra-red region.

Infra-red (IR) spectroscopy, especially when measured by means of the Fourier transform method (FTIR), is another powerful technique for the physical characterization of pharmaceutical solids. In the IR method, the vibrational modes of a molecule are used to deduce structural information. When studied in the solid, these same vibrations normally are affected by the nature of the structural details of the analyte, thus yielding information useful to the formulation scientist. The FTIR spectra are often used to evaluate the type of polymorphism existing in a drug substance. The FTIR method makes simultaneous use of all the frequencies produced by the source, thus providing a large enhancement of the signal-to-noise ratio when compared with that of a dispersive instrument.

OBJECTIVES OF THE STUDY:

In our current study the combination of chemo metrics with spectroscopy method has been developed for the quantification of Lamivudine Form II content in Lamivudine Form I drug substance. Lamivudine, which is a 1,3-oxathiolane nucleoside analogue, has proven anti-viral activity and exists in at least two polymorphic modifications. This reverse transcriptase inhibitor is in clinical use for HIV-positive and hepatitis B-positive patients. The existence of two polymorphic forms of Lamivudine viz., needle-shaped crystals (Form I) and bipyramidal crystals (Form II) are known. It has also been established that Form I is a hydrate having one molecule of water to every five molecules of Lamivudine. It is stated that when Lamivudine is crystallized from aqueous solution or methanol, needle-shaped crystals (Form I) are obtained and when it is crystallized from non-aqueous solvents substantially bipyramidal crystals (Form II) are obtained.

Further, another patent state that Form II is a more stable polymorphic form and used for the preparation of pharmaceutical drug products. It also discloses that Form I crystals are less stable and in certain pharmaceutical unit operations such as milling / granulation may cause conversion of Form I to Form II, which is an undesirable characteristic to manufacture a solid dosage form and thus is not favored for the pharmaceutical formulation. It also suggested that Form II crystals can be obtained by grinding or milling of Form I, also Form II has been prepared by slurring Form I in solvents such as Mentholated spirit. All these indicate the instability of Form I known in prior art. However, Lamivudine Form I crystals do not convert into Form II, during the preparation of solid pharmaceutical dosage forms as well as during storage at 80ºC for 72 hours. The comparative studies were done with FT-Raman spectroscopy by using different chemo metric models with combination of different path length types. The results as well as the advantages of the FT-Raman spectroscopy method relative to other analytical techniques were discussed for Lamivudine drug substance. The present study demonstrates that FT-Raman spectroscopy can be used as a fast and

efficient technique that is very suitable for the identification and quantification of polymorphic forms of Lamivudine drug substance according to regulatory requirements.

SCOPE OF THE STUDY:

Lamivudine polymorph Form I and Form II can be distinguished easily by polarized light microscope, DSC, XRPD, FT-IR and FT-Raman spectroscopic methods due to the differences in their particle shape, melting points, 2θ values, IR and Raman spectral bands respectively. In this present study, we have developed FT-Raman spectroscopy methods with proper chemo metric models suitable for the quantification of low levels of Lamivudine Form II content in polymorphic mixtures of Lamivudine Form I. We also found that the intensity of characteristic bands are proportional to the amount of Form I and Form II for the different polymorphic mixtures of Form II in Form I. The constructed many calibration curves are linear in the range of from 1 to 20% (w/w) of Form II in Form I. From the many calibration curves, partial least squares models using characteristic peak regions with 1st derivative spectra were finalized based on the values of correlation coefficient, RMSEC and distribution of residuals for the quantification of Form II in polymorphic mixtures with Form I. Based on our LOD and LOQ study and curves of relative standard deviation as the function of concentration in Raman chemo metric methods, it was confirmed that PLS models of characteristic ranges of the first derivative spectrum after preprocessing operations mean centering and MSC or normalization of spectra were suitable to quantify levels down to 3.0% and to detect less than 1.5% of Lamivudine Form II in polymorphic mixtures containing Form I and Form II.

RESULT:

Before the preparation of polymorphic mixtures, the reference standards of Lamivudine polymorph Form I and Form II were well characterized by using above mentioned analytical instruments and from the results both polymorphs of Lamivudine were considered to be 100% pure. As can be observed from the powder x-ray diffraction patterns, Form I and Form II of Lamivudine are highly crystalline since no broad halo pattern synonymous with amorphous material can be observed. The diffraction patterns are unique to each form and are comparable with those found in the literature. X-ray powder diffraction pattern of Lamivudine Form I shows characteristic peaks at 2θ values of 15.5°, 18.9° and shows no peak at 2θ values of 14.4°, 17.6°, 20.7°, 21.6° and 26.6°, which are characteristic of Form II of Lamivudine.

Multivariate data analysis was carried out by Thermo Nicolet TQ Analyst software. Classical least squares and Partial least squares models were tested with different path length correction parameters and over the different spectral ranges. The results were compared using root mean squared errors of calibration (RMSEC), linear correlation coefficients and root mean squared errors of prediction (RMSEP) values, as well as the relative difference between the predicted concentration and the nominal one for the indication of model accuracy, and relative standard deviation of multiple measurements assessing calibration model precision.

REFERENCES:

Britain HG (2002). Polymorphism: Pharmaceutical Aspect, Encyclopedia of Pharmaceutical Technology. Marcel Dekker Publication, New York 2002, pp. 2239- 2249.

Aguiar AJ, Krc J, Kinkel AW, Samyn JC : Effect of polymorphism on the absorption of chloramphenicol from chloramphenicol palmitate. J Pharm Science, pp. 847-853.

Aguiar AJ, Zelmer JE. Dissolution behavior of polymorphs of chloramphenicol palmitate and mefanamic acid. J Pharm Sci., pp. 983-987.

S. Byrn, R. Pfeiffer, M. Ganey, C. Hoiberg, G. Poochikian. Pharmaceutical Solids: A Strategic Approach to Regulatory Considerations. Pharm. Res.

A.S. Raw, M.S. Furness, D.S. Gill, R.C. Adams, F.O. Holcombe Jr., L.X. Yu. Regulatory considerations of pharmaceutical solid polymorphism in Abbreviated New Drug Applications (ANDAS). Adv. Drug. Deliv. Rev., pp. 397-414.

Food and Drug Administration, Center for Drug Evaluation and Research, Guidance for Industry, ANDAs: Pharmaceutical Solid Polymorphism: Chemistry, Manufacturing and Controls Information.

J. Lucas, P. Burgess. When Form Equals Substance: The Value of Form Screening in Product Life-Cycle Management. Pharma Voice, pp. 54-57.

H.G. Brittain (Ed), Polymorphism in Pharmaceutical Solids, 95, Marcel Dekker, New York.

J. Bernstein, Polymorphism of Molecular Crystals, Clarendon, Oxford.

Bugay D.E. Characterization of the Solid- State: spectroscopic techniques. Adv. Drug. Deliv. Rev., pp. 43-65.

Giron D.A. Thermal analysis and calorimetric methods in the characterization of

polymorphs and solvates. Thermochim. Act 248.

Findlay W.P,. Bugay D.E. Utilization of Fourier transform-Raman spectroscopy for the study of pharmaceutical crystal forms. J. Pharm, Biomed. Anal.

Auer M.E,. Griesser U.J, Sawatzki J. Formulations by near infrared FT-Raman spectroscopy. J. Mol. Struct.

Zoltan N, Adam D, Gyorgy P. Quantifying low levels of polymorphic impurity in clopidogrel bisulfate by vibrational spectroscopy and chemometrics. J. Pharm, Biomed. Anal.

Deeley C.M, Spragg R.A, Threlfall T.L. Acomparison of Fourier transform infrared and near- infrared Fourier transform Raman spectroscopy for quantitative measurements: An application in polymorphism.

Corresponding Author

Salinder Singh*

Research Scholar of Himalayan University, Itanagar, Arunachal Pradesh, India