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POLYMORPHIC CHARACTERIZATION OF TRAMADOL HYDROCHLORIDE USING DIFFERENTIAL SCANNING CALORIMETRY

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ABSTRACT

The importance of polymorphism study for regulatory consideration in the pharmaceutical industry is increasing day by day. Polymorphism is defined as the ability of a compound to exist in different crystalline forms in which the molecules have different arrangements in the crystal lattice. Polymorphism is wide spread phenomena observed for most of the drug substances. Different Polymorphs exhibit different mechanical, thermal, physical & chemical properties, such as compressibility, melting point, crystal habit, color, density, dissolution rate & solubility. Polymorphism has great influence on the bioavailability, hygroscopicity, stability, filtration & tableting. Polymorphism can be evidenced by using a variety of experimental techniques ranging from optical microscopy to more sophisticated methods of analysis such as DSC, hot stage polarizing microscopy, x-ray powder diffraction etc.

KEYWORDS: Compressibility, melting point, crystal habit, color, density, dissolution rate & solubility.

INTRODUCTION

- Regulatory Perspective of Polymorphs
- Bio-Availability & Formulation Perspectives of Polymorphs
- Formulation Perspectives.

There was a wide spread issue of patentability application of Gleveec (Imatinib Mesylate) and its Beta crystalline form. As in India the product patents are no more encouraged as well

as an invariant modification of final product which doesn't impose significant change in biological properties are not patentable as per Indian patent law. Few drugs have significant change in bio-availability properties with respect to variation in polymorphic structures. (Imatinib Mesylate) Molecules in α and β polymorphic forms exhibit significant conformational differences due to their different intra- and intermolecular interactions, which stabilize their molecular conformations and affect their physicochemical properties such as bulk density, melting point, solubility, stability, and processability. The manufacturing process of a drug tablet included granulation, compression, coating, and drying may cause polymorphic conversions.[13] Biological activity variation may also can be invariant with respect to binding properties on to the receptor. Increase or decreasing in biological activity along with reduction in toxicity, increasing specificity of pharmacophore towards the binding site may reduce toxicity.

Tramodol

PubChem CID: 33741

(1R,2R)-2-[(dimethylamino)methyl]-1-(3-methoxyphenyl)cyclohexan-1-ol. Tramadol is a racemic mixture (R & S). It has some mu-opioid receptor action. Tramadolol also inhibits the reuptake of norepinephrine (NE) and serotonin (5 HT) and produces secondary effects on alpha2 adrenergic receptors in pain pathways. One isomer has greater effect on 5 HT reuptake and greater affinity for mu-opiate receptors. The other isomer is more potent for NE reuptake and less active for inhibiting 5 HT reuptake. Traditional habit forming and behavioral drugs.

Experimentation (Preparation of Polymorphs)

Tramadol was procured as a gift sample from Research Centre in Vadodadara. All the other chemicals were purchased from Sigma Aldrich and TCI Chemicals. DSC instrument was Make of Metler Toledo at KLE University College of Pharmacy Belagavi. The Tramadol hydrochloride was dissolved in different solvents like 1, 4 – dioxan, chloroform, diethyl ether to from the polymorphs.

Polymorphic Characterization of Differential Scanning Calorimetry

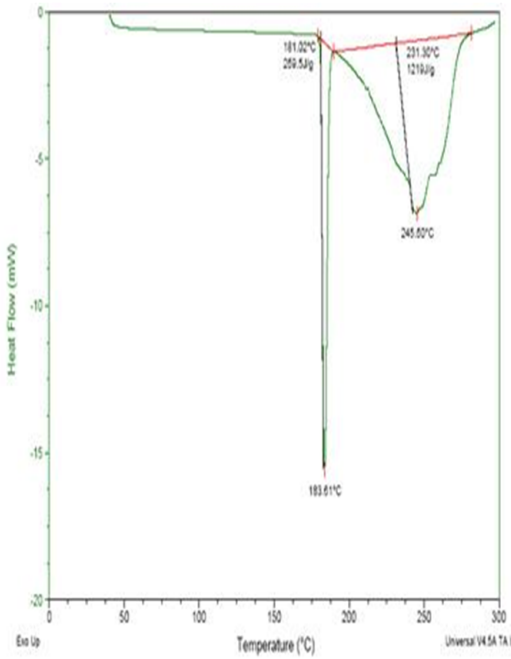
Analytical techniques, such as DSC have proven suitable for the analysis and quantification of polymorphic mixtures and stability of API's and purity is tested using DSC as a routine practice in most of the R&D centre's and API units in most of the reputed companies. Intercovertabilty of one polymorph to the other either during pre-formulation aspects or during formulation aspects can be accessed using fundamental DSC technique.

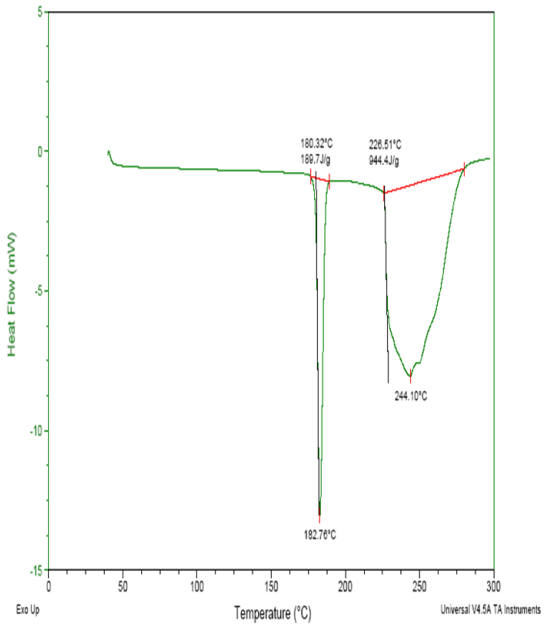
Calibration of DSC

Differential Scanning Calorimetry applied at heating rate of 10 °C / min with a closed aluminum pan system in stream of N_2 gas from 30-250 °C. Temperature and heat flow of DSC system were calibrated by a standard indium reference sample. The determined data of indium in this DSC system were 156.5 °C and 3.293 KJ / mol which were very close to that of the literature temperature at 156.6 °C and enthalpy value of 3.296 KJ/ mol for indium DSC calibration standard respectively.

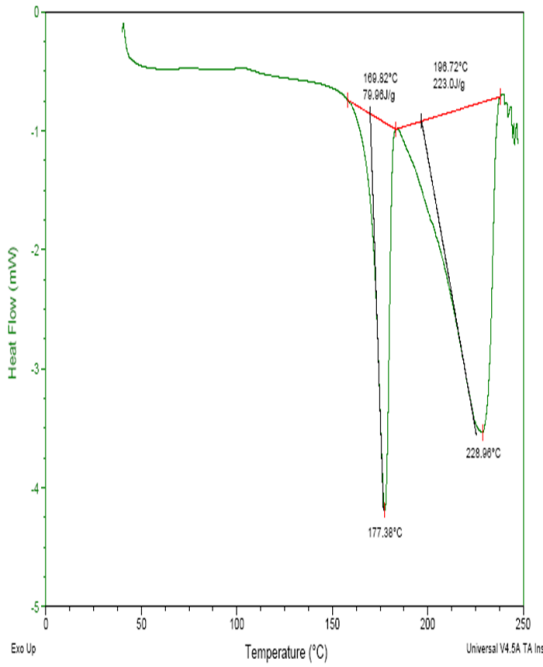
EXPERIMENTAL

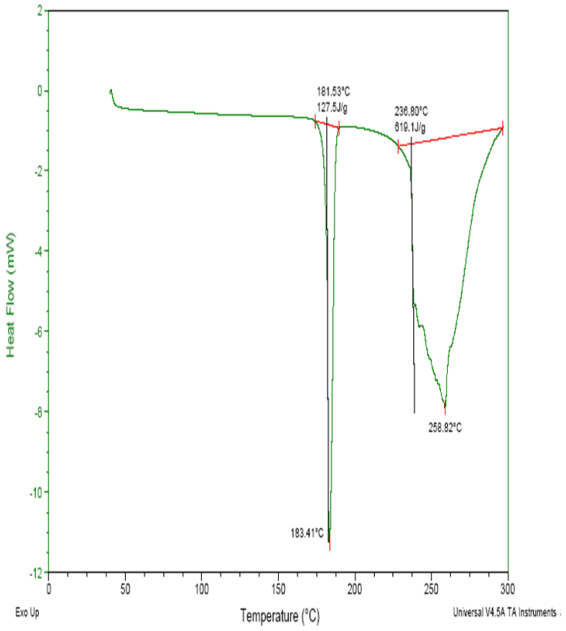
Differential scanning calorimetry (DSC) measures the loss or gain of heat result in form physical or chemical changes within a sample as a function of temperature.





(DSC Thermogram of Tramadol hydrochloride) (Tramadol hydrochloride- chloroform)





(Tramadol hydrochloride – 1,4-dioxan) (Tramadol hydrochloride- diethyl ether)

M. P. of Tramadol hydrochloride Polymorph.

Sr. No.	Sample Name	Solvent used for crystallization	Melting point (°C)
1	Tramadol hydrochloride	-	183.61
2	Tramadol hydrochloride	Chloroform	182.76
3	Tramadol hydrochloride	1,4- Dioxan	177.38
4	Tramadol hydrochloride	Diethyl ether	183.41

RESULTS AND DISCUSSIONS

DSC thermogram of pure Tramadol hydrochloride indicates their endothermic peak was appearing at 183.61 °C. There was no change in the endothermic peaks of diethyl ether and chloroform polymorph. In case of 1,4 – dioxan the sharp endothermic peak appear at 177.38°C so there is difference of 5 °C between standard and 1,4 –dioxan polymorph. From the above discussion we can conclude that it could be identified as 1, 4 –dioxan gives its one of the polymorphic forms. It is necessary to carry out extensive studies further. Therefore utmost care should be taken in avoiding 1.4-dioxane as a solvent in any of the synthetic scheme in preparation of tramadol.

Orthogonal alternate analysis

Further our study should be confirmed by alternate modern analytical instruments say PXRD, ATR-FTIR, near-infrared spectroscopy (NIR), diffuse reflectance infrared spectroscopy (DRIFTS), Raman spectroscopy, solid state 13C NMR spectroscopy etc.

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