ORIGINAL ARTICLE

Modafinil-excipient compatibility study using differential scanning calorimetry

Derar Omari, Assayed Sallam[1], Hasan Al-Hmoud, Iyad Rashid[2]

Department of Pharmaceutical Technology and Pharmaceutics, Faculty of Pharmacy, Yarmouk University, Irbid, [1]TQ-Co for Pharm. Manufacturing, [2]Jordan Pharmaceutical Manufacturing Co., Amman, Jordan

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ABSTRACT

Drug excipient compatibility studies are considered important in successful formulation of drug products. Suggested methods for this purpose are thermal techniques under isothermal or nonisothermal conditions. In this study, modafinil, a wakefulness-promoting drug, was investigated under nonisothermal conditions using differential scanning calorimetry. Four different heating rates, 5, 10, 15, and 20°C/min, were performed for modafinil pure material and its physical mixtures with magnesium stearate (MgSt) or Gelucire 48/16. Activation energy (Ea) was calculated from the straight line of plotting a function of heating rate versus temperature and found that modafinil-Gelucire physical mixture increased Ea. This indicates drug-excipient interaction, supported by evidence from Fourier transform infrared spectroscopy and nuclear magnetic resonance spectroscopy. No significant interaction was detected with MgSt.

Key words: Differential scanning calorimetry, excipient compatibility, modafinil, thermal studies

INTRODUCTION

The successful formulation of a stable and effective solid dosage form depends on a careful selection of the excipients. Selection is based on their functionality and compatibility with active pharmaceutical ingredient (API).[1] Drug-excipient compatibility studies are of great importance in the preformulation and development processes of drug dosage forms.[2-5] In order to evaluate the excipient effect over the solid-state decomposition, thermal studies under isothermal and nonisothermal conditions are conducted.[6,7] Under isothermal kinetics, parameters are determined using Arrhenius equation, while under nonisothermal conditions, parameters are determined by methods of Kissinger-Akahira-Sunose, Ozawa-Flynn-Wall, American society for testing and materials (ASTM) E698, and others.[8] The Kinetics Committee of the International Confederation for Thermal Analysis and Calorimetry[9] recommended the use of more accurate equation of Kissinger-Akahira–Sunose as modified by Starink:[10]

$$\ln\frac{\beta}{T^{1.92}} = Const - 1.0008\left(\frac{E}{RT}\right) \quad \text{..... eqn (1)}$$

Where β is heating rate (°C/min) and T is absolute temperature corresponding to peak maximum of the temperatures of differential scanning calorimetry (DSC) curves obtained at various heating rates. E is the activation energy (Ea) (KJ/mol) and R is gas constant (0.00831KJ/Kmol). The main purposes of such studies are to determine Arrhenius parameters, assess the degradation mechanism, help in storage condition selection, and study of drug-excipient compatibility.[11] In general, as Ea increased, thermal stability increased. Furthermore, drug

Address for correspondence:
Dr. Derar Omari,
Faculty of Pharmacy, Yarmouk University, Irbid, Jordan.
E-mail: derar.m@yu.edu.jo

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stability could be affected, positively or negatively, by the excipients in the formulation.[7,12]

Thermal techniques such as DSC, differential thermal analysis, thermogravimetry, and others, are well known methods in studying drug properties. They can give beneficial information on stability of drug in its pure form as well as a dosage form. One such piece of information is drug-excipient compatibility which may significantly changes the physicochemical properties of drug as well as its absorption and therapeutic activity.[13] DSC is a thermal method that determines the temperature and heat flow during material transitions as a function of time and temperature. It is a highly efficient technique to assess physical properties of drug, its compatibility with other materials, and stability of the components in the final dosage form. DSC is very helpful in the evaluation of possible incompatibilities by indicating curve changes such as appearance, disappearance, or shift in the endothermic or exothermic peaks and variations in the heat flow values.[13,14]

Fourier transform infrared (FTIR) is also used to study the behavior of solid state APIs as well as a screening tool of their compatibility with other additives. This capability is based on changes in the chemical group upon interaction. Thus, a comparison between the new group location, after interaction, and that of the pure material, can be performed. Any change in the band location, referred as "shift," peak intensity reduction, or new peak appearance may indicate API-excipient interaction.[15]

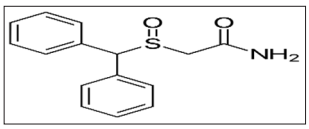

Figure 1: Modafinil chemical structure

Modafinil, is (*d*,l-2-[(diphenylmethyl) sulfinyl] acetamide) [Figure 1], a synthetic non-amphetamine stimulant used as a wakefulness enhancing drug. It is a 50:50 racemic mixtures of the R- and S-enantiomers and contains a chiral center at the Sulphur atom.[16] It is an off-white solid, crystalline in nature, and is water insoluble but slightly soluble in other organic solvents like methyl alcohol and acetone.[17] Modafinil enantiomers are pharmacologically equal in mice. However, their pharmacokinetic behavior is different, in human as well as other species tested.[18-20] A latest review was published on its use in treating the fatigue and neurocognitive deficits of long COVID.[21]

Magnesium stearate (MgSt) is the most frequently used lubricant in tablet compression due to its exceptional properties.[22] However, there are many published articles concerning its incompatibility with pharmaceutical ingredients due to its hydrophobic nature, the presence of the positively charged magnesium ion, and its strong surface energetic behavior.[23-25] Gelucire 48/16 is a member of the Gelucire family, is a mixture of mono, di, and triglycerides with PEG esters of fatty acids, working as nonionic surfactants and used in lipid-based formulations to increase solubility and bioavailability of poorly soluble drugs.[26] However, there is a lack of research data regarding their compatibility behavior toward drugs.[27,28]

Drug-excipient interaction studies are a regulatory-must in the development process of drug products as mentioned previously. Furthermore, to authors' knowledge, there were no thermal studies regarding modafinil and/or modafinil-excipient compatibility. Therefore, the objective of this article was to study the thermal behavior of modafinil and its mixtures with the selected excipients, MgSt, and Gelucire, under nonisothermal methods through multiple scans using DSC at different heating rates. The main target is to calculate Ea, using equation (1), as an

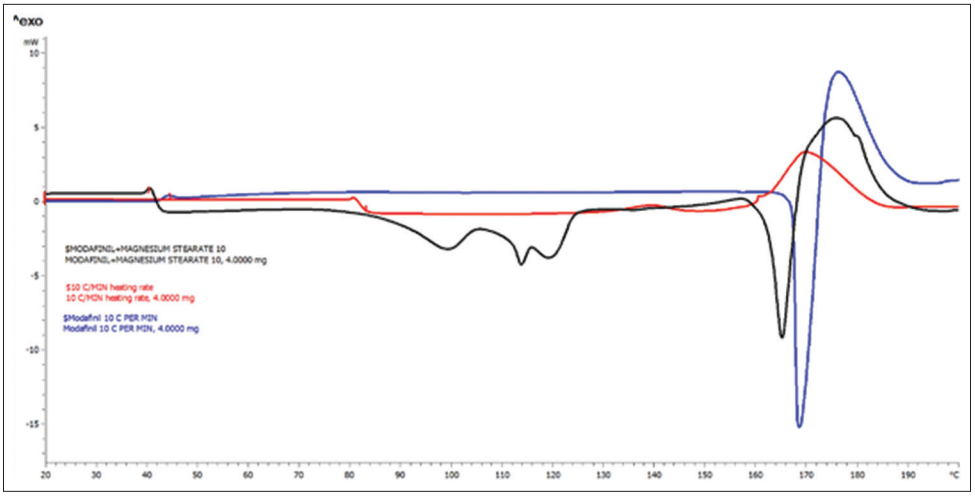

Figure 2: DSC curves of (all done at 10°C/min heating rate): .....Pure Modafinil .....Modafinil and MgSt 1:1 physical mix .....Modafinil and Gelucire 1:1 physical mix. MgSt: Magnesium stearate, DSC: Differential scanning calorimetry

indicator of incompatibilities. FTIR and nuclear magnetic resonance (NMR) spectroscopies will be used as supportive characterizing techniques.

MATERIALS AND METHODS

Materials

Modafinil (USP, Batch No 1602003257 by Alembic, polymorph I) and Gelucire 48/16 are kind gift from TQPharma, Amman, Jordan. MgSt is purchased from local vendors in Amman, Jordan.

Methods

Samples preparation

Physical mixtures of 1:1 w/w modafinil/excipients powders (40 mesh size) were prepared by mixing in a mortar and pestle for 5 min and filled in amber glass vials. This ratio (1:1 w/w) is usually selected in compatibility studies to increase interaction possibilities.[29]

Differential scanning calorimetry

The DSC thermograms of modafinil and its physical mixtures were recorded in a differential scanning calorimeter (DSC 821; Mettler Toledo AG, Giessen, Germany) in nitrogen (flow rate: 50 mL min^{-1}), at a heating rate of 10°C/min in the range of 20°C–220°C. For nonisothermal experiments, the heating rates performed were 5, 10, 15, and 20°C/min in the same range. A 4.0 mg (±0.1) mass was weighed in a hermetically sealed aluminum crucible. The DSC was calibrated by indium.

Fourier transform infrared

FTIR spectra were obtained using FTIR spectrometer (Bruker, Billerica, MA, USA) with potassium bromide (KBr) pellets. The samples were scanned from 4000 cm^{-1} to 400 cm^{-1}. Spectra for drug, excipients, and physical mixtures were recorded.

Nuclear magnetic resonance

Proton (H1) NMR spectra of modafinil and its physical mixtures with MgSt and Gelucire were obtained on NMR spectrometer (Bruker 400MHz Avance III, USA). Dimethylsulfoxide (DMSO) or CDCl3 were used as the solvent and tetramethylsilane was used as the internal standard.

RESULTS AND DISCUSSION

The DSC curves of modafinil alone or modafinil/excipients mixtures are shown in Figure 2. Modafinil possessed a sharp melting peak at 170°C followed by degradation. Thus, modafinil is considered thermally stable before melting and no any event was observed before this point. DSC curves of drug with excipients showed significant changes in the melting endotherms and degradation exotherms. Physical mixture of modafinil-MgSt showed multiple endothermic peaks in the range of 100°C–130°C, which is related mainly to MgSt. Modafinil melting point showed a shift down about 5°C to 165°C, which may indicate a kind of interaction. However, such variation could be attributed to decrease in material purity upon mixing rather than to incompatibilities.[30]

DSC curve of modafinil with Gelucire physical mixture showed a lowering in the DSC line corresponding to some type of transition due to a complex formation (say, solid dispersion) between drug and excipient since Gelucire melted at about

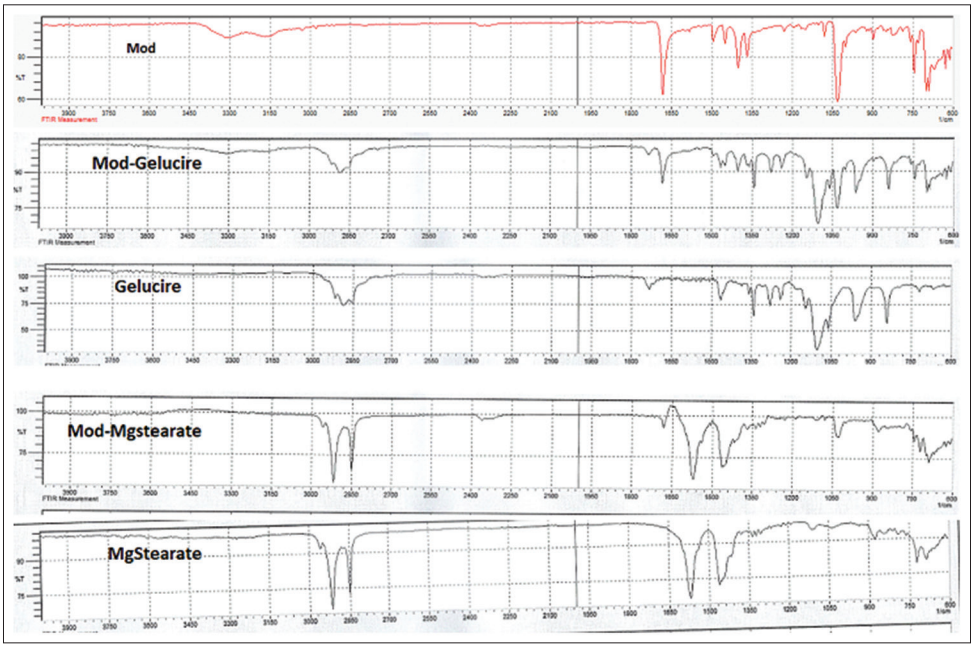

Figure 3: FTIR of modafinil and its physical mixtures with MgSt or Gelucire. MgSt: Magnesium stearate, FTIR: Fourier transform infrared

50°C. No melting endotherm of modafinil observed but only the exotherm of degradation. The disappearance of melting endotherm indicates some type of drug excipient interaction.[31]

FTIR spectra of physical mixtures of modafinil with either Gelucire or MgSt as compared to pure drug [Figure 3] showed no change in the characteristic bands' positions. However, a decrease in peak intensity in modafinil-Gelucire physical mixture's spectrum was observed. This might be due to interaction effect on dipole moment of absorption band, where the greater this effect the more intense is the absorption.[32,33] This evidence supports the interaction hypothesis between modafinil and Gelucire

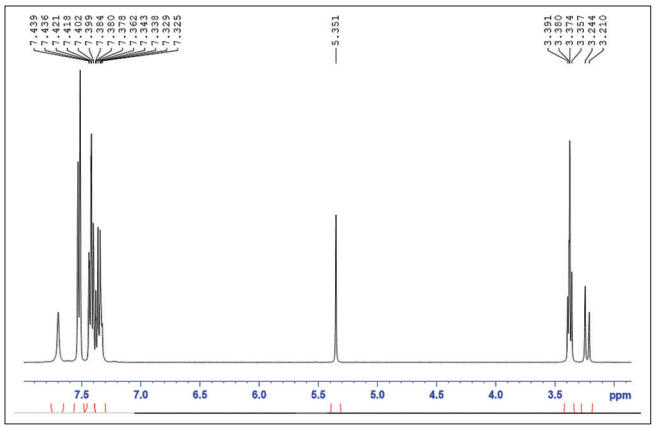

Figure 4: H1-NMR spectrum of Modafinil pure material. NMR: Nuclear magnetic resonance

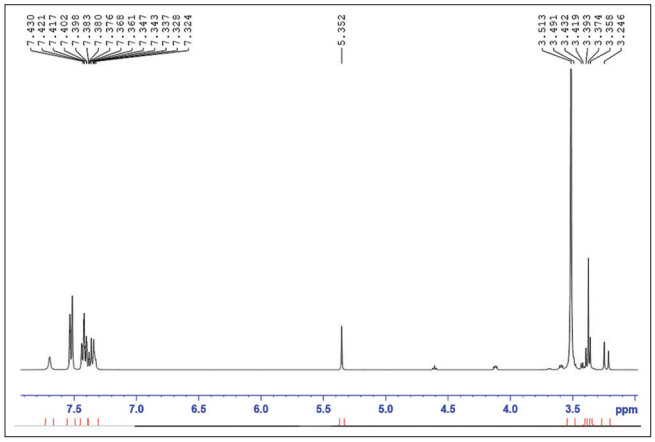

Figure 5: H1-NMR spectrum of Modafinil-Gelucire physical mixture. NMR: Nuclear magnetic resonance

Another supporting evidence for interaction between modafinil and Gelucire is obtained from NMR spectroscopy [Figures 4 and 5]. In modafinil NMR spectrum, a quartet peak at 3.3 ppm due to the 2 hydrogens at C2 and multiplets between 7.3 and 7.5 ppm due to amide hydrogens are observed. In the NMR spectrum of modafinil-Gelucire mixture, a shift of about 0.2 ppm was occurred to the peak of the C2-hydrogens and also became singlet. Such a change could be due to deshielding by an interaction with Gelucire-like hydrogen bonding.

Effect of heating rate on thermal behavior

Figures 6-8 show DSC curves of thermal behavior of modafinil pure and its physical mixtures at various heating rates. As heating rate increased, thermal events shift to higher degrees. This could be explained by that the higher rate decreases heat distribution in the molecules and makes melting or decomposition start at a higher temperature.[34] Table 1 shows melting and decomposition temperatures at different heating rates

Application of equation (1) to decomposition or melting temperatures of modafinil and the two physical mixtures leads to calculation of Ea from the slope of the regression line in Figures 9-11 and shown in Table 1. The Ea values of drug mixture with MgSt were not significantly changed either if melting (Ea = 318.4kj/mol) ($P > 0.05$) or decomposition (Ea = 149.8 Kj/Mol) ($P > 0.05$) were considered and compared with those of pure modafinil (Ea melting = 313.4 Kj/Mol, Ea decomposition = 164.7 Kj/Mol). However, Gelucire physical mixture caused a significant increase in Ea of decomposition (Ea = 205.5. Kj/Mol) ($P < 0.05$) compared to pure drug. It has been reported that the greater the Ea of a material, the more stable it is.[12] This indicates more stabilized modafinil-Gelucire formulation, an event further supports their interaction hypothesis.

CONCLUSIONS

Modafinil pure material and its physical mixtures with

Table 1: Melting and decomposition temperatures and activation energies (Ea) at different hating rates of modafinil pure or its physical mixtures with magnesium stearate and gelucire

Heating rate	Modafinil		Modafinil-MgSt		Modafinil-Gelucire	
	Melting (°C) Av (n=3)±SD	Decomposition (°C) Av (n=3)±SD	Melting (°C) Av (n=3)±SD	Decomposition (°C) Av (n=3)±SD	Melting	Decomposition (°C) Av (n=3)±SD
5	165.28±0.1920	170.22±0.1040	161.94±0.1621	169.81±0.5449	-	165.45±0.0287
10	168.52±0.0205	176.26±0.1887	165.23±0.0125	176.53±0.4100	-	169.97±0.3916
15	170.91±0.8463	181.05±0.9183	167.39±0.2446	180.62±0.4325	-	174.15±1.0588
20	172.60±0.6905	184.74±0.5421	169.02±0.3492	183.94±0.1849	-	176.34±0.6948
Ea (KJ/mol)	313.4	164.7	318.4	149.8	-	205.5

MgSt: Magnesium stearate, SD: Standard deviation, Av: Average

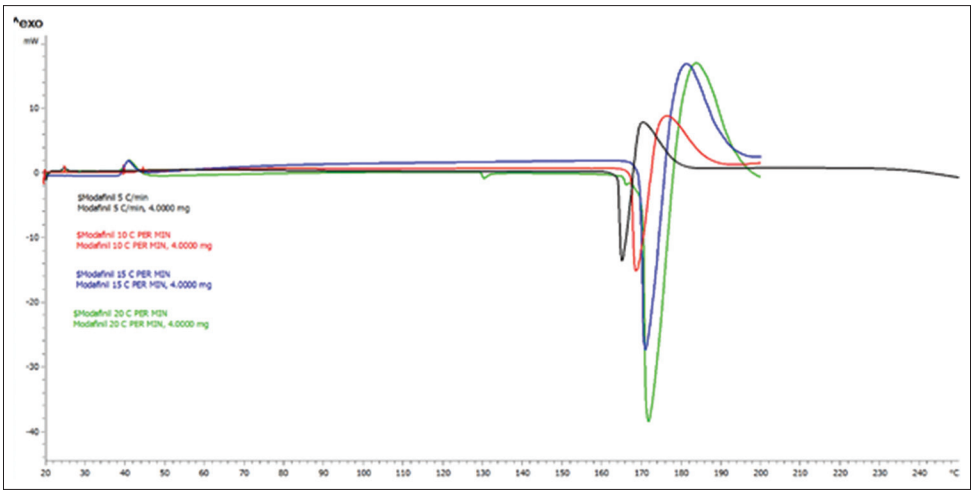

Figure 6: DSC curves of modafinil at various heating rates. DSC: Differential scanning calorimetry

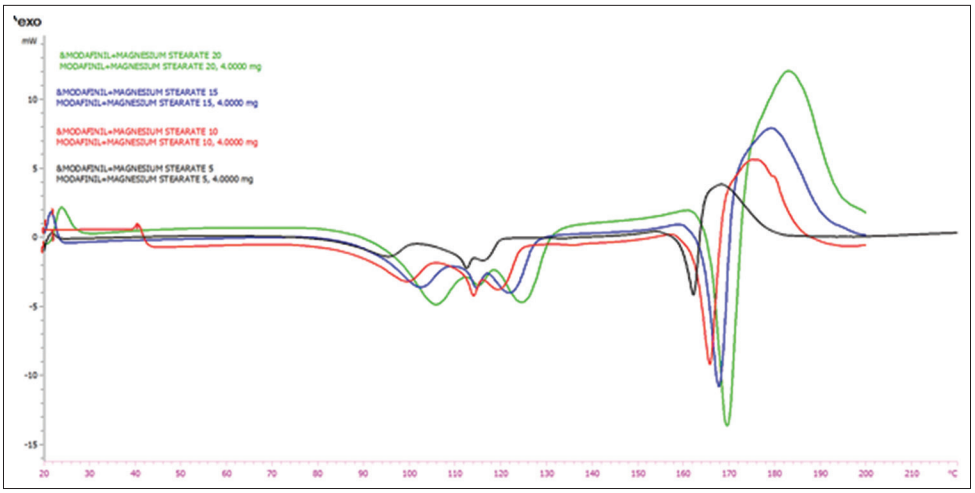

Figure 7: DSC curves of modafinil-MgSt physical mixture at various heating rates, MgSt: Magnesium stearate. DSC: Differential scanning calorimetry

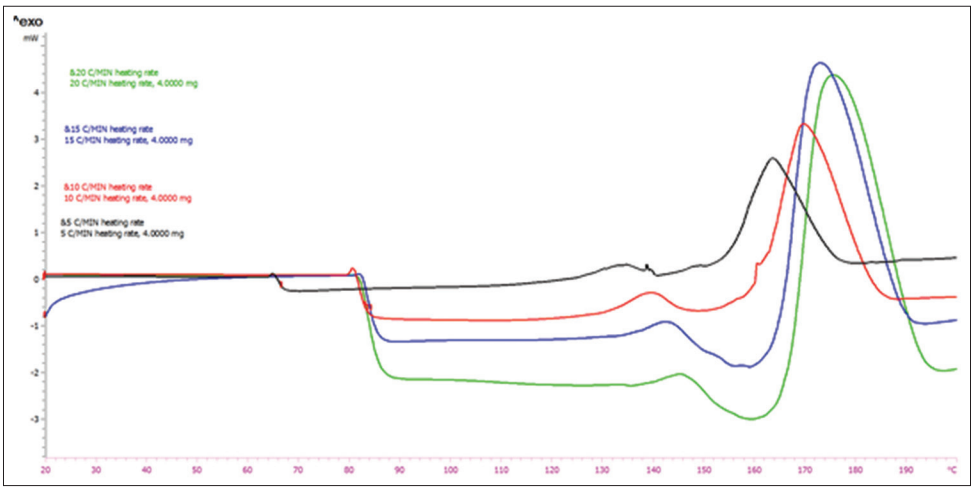

Figure 8: DSC curves of modafinil-Gelucirs physical mixture at various heating rates. DSC: Differential scanning calorimetry

MgSt or Gelucire were thermally characterized using DSC analysis. Several heating rates (5, 10, 15, and 20°C/min) were performed and the Ea was calculated from the regression line of ln $\beta/T^{1.92}$ versus 1/T according to equation (1). Gelucire was found to increase Ea, which means increase in stability of the resulting product. Additional evidence

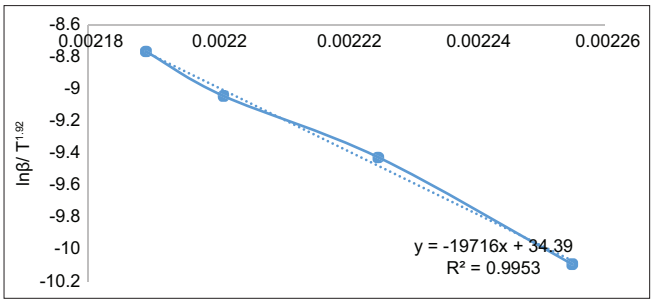

Figure 9: Plot of $\ln\beta/T^{1.92}$ versus 1/T for modafinil at various heating rates

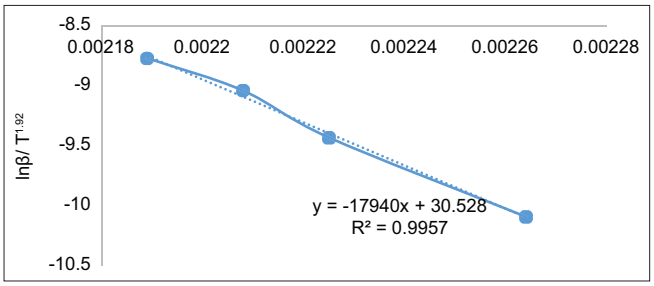

Figure 10: Plot of $\ln\beta/T^{1.92}$ versus 1/T for modafinil- MgSt physical mixture at various heating rates. MgSt: Magnesium stearate

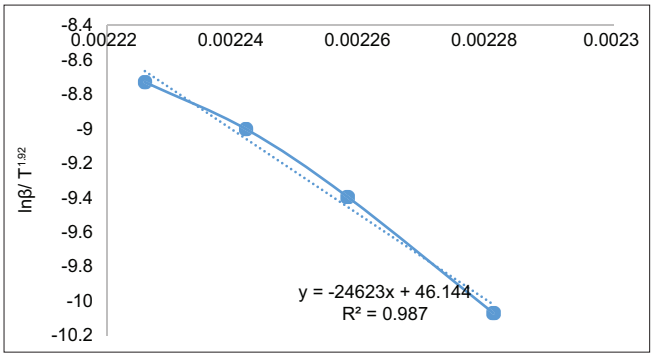

Figure 11: Plot of $\ln\beta/T^{1.92}$ versus 1/T for modafinil- Gelucire physical mixture at various heating rates

supporting this interaction were obtained from FTIR and NMR spectroscopy. No strong evidence on MgSt interaction with modafinil was observed. Therefore, both excipients could be used with modafinil drug without problems.

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Conflicts of interest

There are no conflicts of interest.

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