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Compatibility Analysis of A Novel Antidepressant with Different Excipients in Solid Dosage Forms and in Some Binary Mixtures

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The present paper compared thermodynamic data on a novel antidepressant's (venlafaxine hydrochloride) melting and vapourization processes with those found for several solid binary mixtures and in some commercially available venlafaxine hydrochloride based dosage forms. No universally accepted protocol is available for evaluating the compatibility of drug with different excipients. Some of the reported methods have poor predictive values and few of them are labour intensive and time consuming. Differential scanning calorimetry was used to assess the compatibility between venlafaxine hydrochloride and some excipients in several of more commercially available pharmaceutical formulations and in solid binary mixtures. This technique allows a rapid evaluation of possible incompatibilities by revealing changes in appearance, shift or disappearance of melting or other exothermic processes and/or variations in the corresponding enthalpies of reaction. By the comparison of thermal, thermodynamic and kinetic values for pure venlafaxine hydrochloride and venlafaxine hydrochloride containing in dosage forms and in binary mixtures only slight differences were observed with the opadry yellow and one formulation (D-3) formulation. Differential scanning calorimetry traces of pure venlafaxine hydrochloride showed a sharp endothermic peak at 217 ºC corresponding to its melting point. In case of binary mixtures and formulations containing large amount of excipients showed a slight change in endoth-ermic peak. Present study had demonstrated the successful utilization of technique of differential scanning calorimetry to assess the compatibility of venlafaxine hydrochloride with the excipients. Based on the results of differential scanning calorimetry majority of excipients showed compatibility with venlafaxine hydrochloride except opadry yellow. So these excipients can be used to develop novel formulation of venlafaxine hydrochloride.

Key Words: Compatibility analysis, Venlafaxine hydrochloride.

INTRODUCTION

The possible compatibility assessment between active component *i.e.* venlafaxine hydrochloride and different excipients along with the evaluation of thermal stability are crucial part of normal study prior to final formulation

setting of a solid dosage form[1]. Excipients are to facilitate administration and release of an active component as well as to protect it from environment. Excipients can be defined as pharmaceutically inert substances but physical and chemical interaction with an active component are possible[2]. Drug-excipient interaction study at an early stage of product development is an important exercise in the development of a stable dosage form. There was no universally accepted protocol for evaluating the compatibility of drug with different excipients. Some of reported methods have poor predictive values and few of them were labour intensive and time consuming. Differential scanning calorimetry (DSC) had been proposed as a rapid method for evaluating the drug-excipient interaction[3-5]. DSC allows a rapid evaluation of possible incompatibilities by revealing changes in the appearance, shift or disappearance of melting or other exothermic processes and/or disappearance of melting or other exothermic processes and/or variation in corresponding enthalpies of reaction[6-9]. In present study, the possible interaction between venlafaxine hydrochloride and excipients microcrystalline cellulose (AVICEL) PH 112 (M1), lactose (Pharmatose 200M & K40)-(L), DCL-11 and DCL-21 (DL-1 & DL-2), hydroxy propyl methyl cellulose (HPMC) (H), pregelatinized starch (P), magnesium stearate (M2), talc (T), colloidal silicon dioxide (Aerosil) (A), opadry yellow (O) and ethyl cellulose (E) in several of more commercially available pharmaceutical formulations (D-1 to D-5) and in solid binary mixtures. All the excipients contained in the examined dosage forms have been evaluated. Venlafaxine hydrochloride having the molecular weight 313.78 and pKa 9.4. Chemically unrelated to tricyclic, tetracyclic or other currently available antidepressants and to other drugs used to treat anxiety disorders. For thermal analysis of drug and drug-excipient mixtures a differential scanning calorimeter (DSC Shimadzu-60TA) was used. Individual samples (drug and excipients) as well as physical mixtures and formulations containing drug and selected excipients were weighed directly in the pierced DSC aluminium pan and scanned in the temperature range of 25-300 ºC at the heating rate of 10 ºC/min under an atmosphere of dry nitrogen. DSC traces of pure venlafaxine hydrochloride showed a sharp endothermic peak at 217 ± 5 ºC corresponding to its melting point. In case of binary mixtures and formulations containing large amount of excipients showed a slight change in endothermic peak. Present study had demonstrated the successful utilization of technique of DSC to assess the compatibility of venlafaxine hydrochloride with the excipients. Based on the results of DSC majority of excipients showed compatibility with venlafaxine hydrochloride except opadry yellow.

EXPERIMENTAL

Venlafaxine hydrochloride, microcrystalline cellulose (AVICEL) PH 112 (M1), lactose (Pharmatose 200M & K40)-(L), DCL-11 and DCL-21 (DL-1 & DL-2), hydroxy propyl methyl cellulose (HPMC) (H), pregelatinized starch (P), magnesium stearate (M2), talc (T), colloidal silicon dioxide (Aerosil) (A), opadry yellow (O), ethyl cellulose (E) were supplied by Ranbaxy Research Laboratory. All the compounds were used as received without further purification. The composition of the pharmaceutical dosage forms tested denoted as DF1-DF5. Physical binary mixtures of venlafaxine hydrochloride and microcrystalline cellulose (AVICEL) PH 112 (M1), lactose (Pharmatose 200 M & K40)-(L), DCL-11 and DCL-21 (DL-1 and DL-2), hydroxy propyl methyl cellulose (HPMC) (H), pregelatinized starch (P), magnesium stearate (M2), talc (T), colloidal silicon dioxide (Aerosil) (A), opadry yellow (O) excipients were prepared in suitable proportions by gentle mixing them in an agate mortar with a spatula at room temperature.

The DSC measurements of the individual components as well as of mixed systems of venlafaxine hydrochloride and excipients were carried out on a Shimadzu DSC TA 60 differential scanning calorimeter with a thermal analyzer. Instrument calibration was performed using very pure standards. To this end, indium, gallium, lead, tin, naphthalene, benzoic acid samples were used in the present work as their temperatures and enthalpies of melting are well known. Both for pure venlafaxine hydrochloride and D1-D5 dosage forms at least three rising temperature experiments were carried out in a temperature range from room temperature to 673 K while for all pure excipients, the scanning temperature range was from room temperature to 873 K. Heating rate was used 10 K/min during this study and at least three runs were performed for each heating rate. An aluminium crucible was used to contain the sample and an identical empty aluminium crucible was used as reference material. A small sample weighing 4-6 mg, enough to uniformly cover the base of the crucible, was weighed out and placed in argon filled dry box to avoid oxidation of the sample. The simultaneous DSC system was fluxed with the purge gas stream. In this way the gases given off during the thermal heating process experiment were continuously removed. Taking into account the sensitivity of the DSC equipment, the vapourization of venlafaxine hydrochloride (both in pure and in contained D1-D5 dosage form samples and also in binary mixtures) begins to be detectable after the completion of melting. The rate of vapourization process ($d\alpha/dt$) as well as in the case of other thermally stimulated reaction is expressed as a function of temperature by the basic kinetic equation.

$$d\alpha/dt = K\ vap\ (T)f(\alpha)$$

t = time, T = temperature, α = extent of conversion, $f(\alpha)$ = reaction model expressed by different mathematical expressions in relation with the mechanism of transformation[10-12].

RESULTS AND DISCUSSION

The DSC curves of D-1 to D-5 formulations containing venlafaxine hydrochloride sample along with those of pure venlafaxine hydrochloride are displayed in Figs.1-5 while in Fig. 6 the DSC curves of all binary mixtures of venlafaxine hydrochloride with different excipients contained in studied dosage forms are compared with those of pure venlafaxine hydrochloride. The trend of DSC curves in Figs. 1-5 is almost identical for the entire examined binary mixture samples except binary mixture containing opadry yellow sample. From the area of corresponding DSC peaks enthalpies related to melting and subsequent vapourization dH_{fus} and dH_{vap} were determined, respectively for both pure venlafaxine hydrochloride contained in considered dosage form at the heating rate of 10 K/min. The results are shown in Table-2. By the comparison of thermodynamic and kinetic data for pure venlafaxine hydrochloride and for venlafaxine hydrochloride contained in dosage forms tested. A difference had been observed for binary mixtures containing opady yellow probably because of mass loss up to 600 K. The higher the value of dH_{fus} for opady yellow is probably due to inter-

TABLE-1
% PURITY OF VENLAFAXINE HYDROCHLORIDE IN SOME OF THE EXAMINED COMMERCIAL ANTIDEPRESSANTS

Dosage form	Venlafaxine hydrochloride (% w/w)
D-1	99.2
D-2	99.1
D-3	93.4
D-4	90.5
D-5	98.6

TABLE-2
MOLAR HEATS OF FUSION AND OF VAPOURIZATION BOTH FOR VENLAFAXINE HYDROCHLORIDE AND FOR VENLAFAXINE HYDROCHLORIDE IN THE DOSAGE FORMS TESTED AT HEATING RATE OF 10 K min^{-1}

Compounds	β (K min^{-1})	ΔH_{fus} (kJ mol^{-1})	ΔH_{vap} (kJ mol^{-1})
Venlafaxine hydrochloride	10	21.9 ± 2.1	83.8 ± 2.8
D-1	10	22.8 ± 1.6	84.5 ± 2.4
D-2	10	24.6 ± 1.8	86.7 ± 3.0
D-3	10	23.5 ± 1.9	83.5 ± 2.1
D-4	10	23.0 ± 2.0	88.6 ± 2.4
D-5	10	25.9 ± 2.1	88.4 ± 2.6

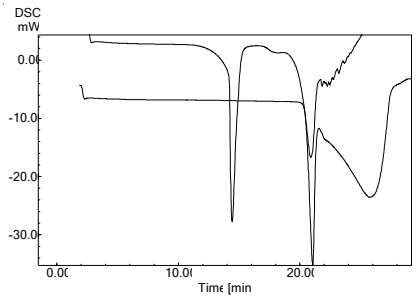

Fig. 1. D-1 and Venlafaxine hydrochloride

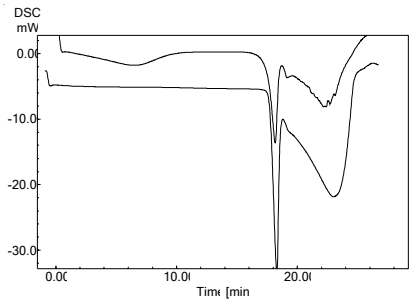

Fig. 2. D-2 and Venlafaxine hydrochloride

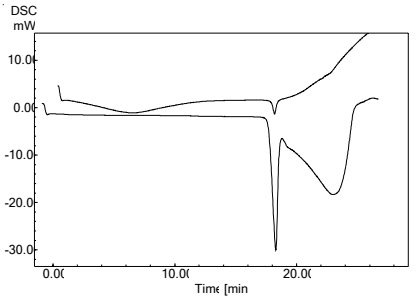

Fig. 3. D-3 and Venlafaxine hydrochloride

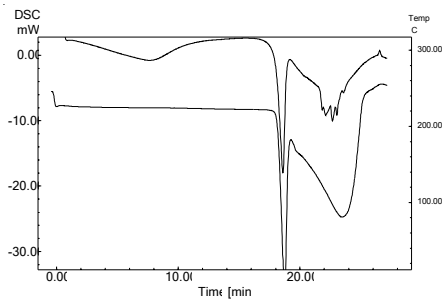

Fig. 4. D-4 and Venlafaxine hydrochloride

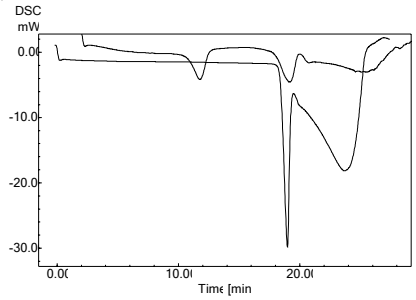

Fig. 5. D-5 and Venlafaxine hydrochloride

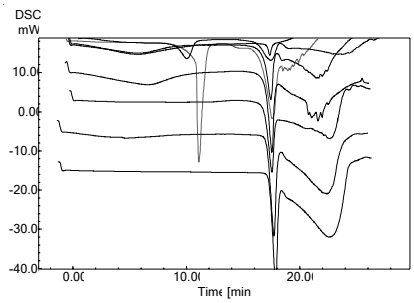

Fig. 6. Final Compatibility of binary mixtures of venlafaxine hydrochloride with different excipients

ference of excipients whose DSC curves of fusion is extremely close to that of venlafaxine hydrochloride. Results obtained by considering all the Figures and Table-2 for all other samples allow to conclude that small quantity of total excipients found in these formulations (5-15 %) does not significantly interfere the thermal behaviour of active component. It is concluded that all the examined excipients were found compatible and can be used to develop a novel formulation except opadry yellow.

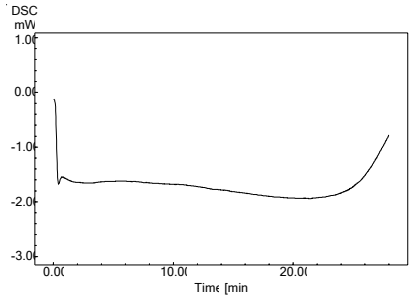

Fig. 6.1. Final compatibility of binary mixtures of venlafaxine hydrochloride with opadry yellow

Conclusion

This compatibility study mainly based on thermo analytical methods is qualitative in nature. The main consideredation was to evaluate the experimental results in order to identify qualitative compatibility indicators obtained from the DSC curves (temperatures, enthalpies). From the above study following conclusions can be drawn: By comparing thermal, thermodynamic data for pure venlafaxine hydrochloride and for venlafaxine hydrochloride contained in dosage forms and in some binary mixtures only slight differences were usually evidenced. The only differences in thermal behaviour between pure venlafaxine hydrochloride and venlafaxine hydrochloride contained in nine of the examined binary mixtures can be ascribed firstly to small mass losses at the higher temperature observed for binary mixture and secondly to the interference due to the simultaneous melting of venlafaxine hydrochloride and opadry yellow. In case of binary mixture containing opadry yellow. For the solid binary mixtures with low content of excipient, a good compatibility was usually observed between venlafaxine hydrochloride and the excipients tested except for binary mixture samples containing opdry yellow. Present study had demonstrated the successful utilization of technique of DSC to assess the compatibility of venlafaxine hydrochloride with the excipients. Based on the results of DSC majority of excipients showed compatibility with venlafaxine hydrochloride except opadry yellow. So these excipients can be used to develop novel formulation of venlafaxine hydrochloride.

REFERENCES

1. A. Marini, V. Berbenni, M. Pegoretti, G. Bruni, P. Cofrancesco, C. Sinistri and M. Villa, *J. Therm. Anal. Calorim.*, **73**, 547 (2003).
2. A.R. Fassihi and P.H.R. Persicaner, *Int. J. Pharm.*, **37**, 167 (1987).
3. M.E. Brown, E.M. Antunes, B.D. Glass, M. Lebete and R.B. Walker, *J. Therm. Anal. Calorim.*, **56**, 1317 (1999).

4. G. Pyramides, J.W. Robinson and S.W. Zito, *J. Pharm. Biomed. Anal.*, **13**, 103 (1995).
5. F. Giordano and G.P. Bettinetti, *J. Pharm. Biomed. Anal.*, **6**, 951 (1988).
6. G. Bruni, L. Amici, V. Berbenni, A. Marini and A. Orlandi, *J. Therm. Anal. Calorim.*, **68**, 561 (2002).
7. P. Mura, A. Manderioli, G. Bramanti, S. Furlanetto and S. Pinzauti, *Int. J. Pharm.*, **119**, 71 (1995).
8. M. Weolowski, *Thermochim. Acta*, **209**, 223 (1992).
9. G.R. Biloyd, D.Q.M. Craig and A. Smith, *J. Pharm. Sci.*, **86**, 991 (1997).
10. G.P. Bettinetti, P. Mura, A. Liguori, G. Bramanti, F. Giordano, *IL Farmaco*, **43**, 331 (1988).
11. M.A. Holgado, M. Fernandez-Arvalo, J.M. Gines, I. Carballo and A.M. Rabasco, *Pharmazie*, **50**, 195 (1995).
12. S.C. Sweetman, Martindale, The Complete Drug Reference, Pharmaceutical Press, edn. 33, pp. 838-843 (2002).

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