RESEARCH PAPER

Received 16 September 1994
Indian J.Pharm. Sci., 1996, 58(1) pp 22-24

Preformulation Compatability Study Between Metoprolol Tartrate and Tablet Excipients Using Differential Scanning Calorimetry (DSC)

E.K. Iyer and H.P. Tipnis*.
The Bombay College of Pharmacy and The Research Society
of Bombay College of Pharmacy. Kalina, Santacruz (East), Bombay 400 098.

Differential scanning calorimetry (DSC) was employed as a tool to investigate the physico-chemical compatability between metoprolol tartrate and a number of commonly used excipients. Metoprolol was found to be compatable with microcrystalline cellulose (Avicel PH 101®), Eudragit® and colloidal silicon dioxide (Aerosil®). Although metoprolol showed interactions with stearic acid, magnesium stearate, lactose, sodium carboxymethyl starch / sodium starch glycollate (Primojel®), Indian CRP 234 and starch, one cannot conclusively state that interaction incompatabilities will occur on storage at room temperature.

EXCIPIENTS can affect the stability of drugs by chemical or physical interaction thus posing a threat to the drug's stability[1] or bioavailability[2]. DSC is a fast and reliable method to screen any drug-excipient interaction as compared to the time consuming conventional method of accelerated stability studies. Other techniques used for the detection of potential interaction or incompatability include accelerated storage stability testing[3], TLC[4], IR[4] and various thermal analytical techniques[5-8]. DSC backed up by short time stress tests has been highly recommended to get a better indication of drug-excipient compatability[9]. Compatability study between oxprenolol[10], bisoprolol[11], and betaxolol[12] with excipients using DSC have been reported. Varying ratios[9] of drug to excipient have been recommended for binders, lubricants, colorants, disintegrants etc.. The present study utilised a 1:1 ratio of drug : excipient to maximise the likelihood of interaction and to avoid any endotherm masking phenomena due to a higher ratios. An interaction in DSC is concluded by elimination of exothermic or endothermic peak(s), by appeareance of new peak(s), changes in peak shape and its onset, peak temperature / melting point and relative peak area or enthalpy.

* For reprints.

EXPERIMENTAL

Materials : The following excipients and metoprolol tartrate were used; starch, stearic acid, magnesium stearate, lactose, microcrystalline cellulose (Avicel PH 101®), sodium starch glycollate / sodium carboxymethyl starch (Primojel®), Indion CRP 234, colloidal silicon dioxide (Aerosil®) and Eudragit®. (RS 100).

Instrumentation : Differential Scanning Calorimeter (Shimadzu Thermal Analyzer, DT 40) equipped with a monitor and a computerized Thermal Analysis System 40-1 : Printer (Chromatopac C-R6A) were used. The instrument was calibrated with standard indium and operated at an ampere range of 8mj/sec.

Differential Scanning Calorimetry : Thermograms of (in replicates) individual excipients, metoprolol tartrate, as well as 1:1 physical mixtures of metoprolol and excipients were obtained. Samples (2-4 mg) in weight were sealed hermetically in flat bottomed aluminium cells (pans). These samples

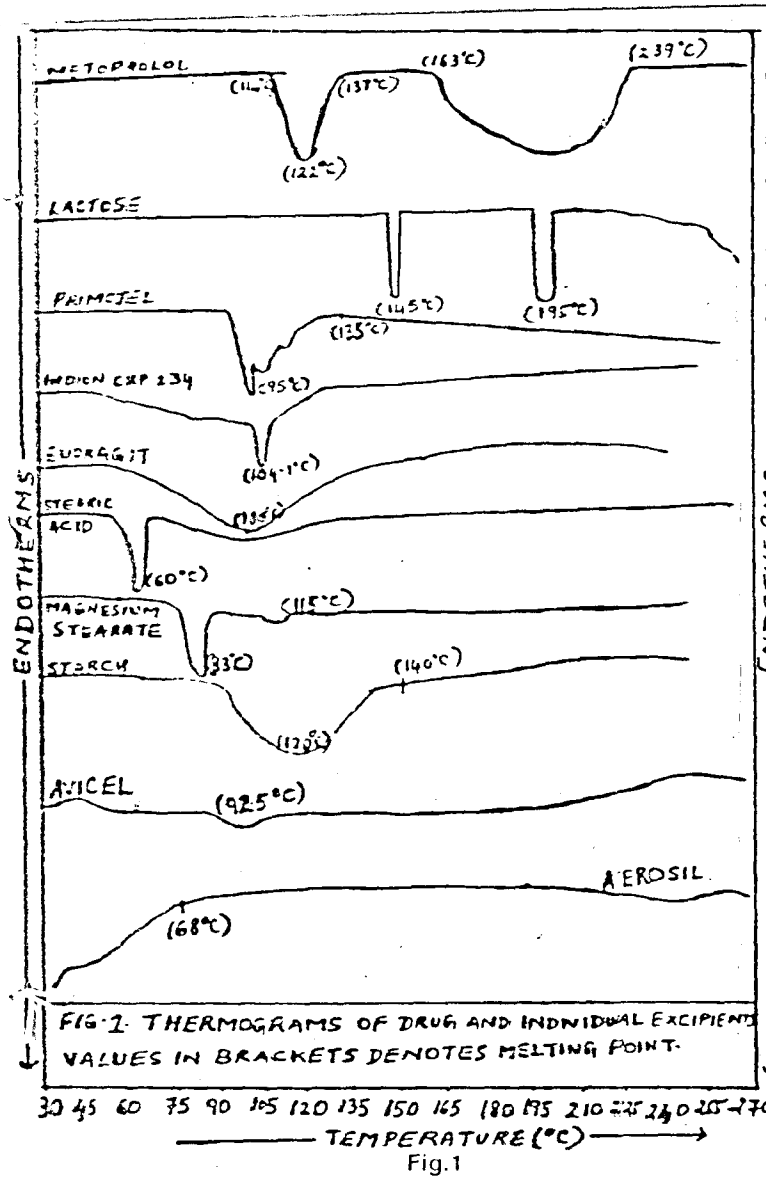

FIG. 1. THERMOGRAMS OF DRUG AND INDIVIDUAL EXCIPIENTS. VALUES IN BRACKETS DENOTES MELTING POINT.

Fig.1

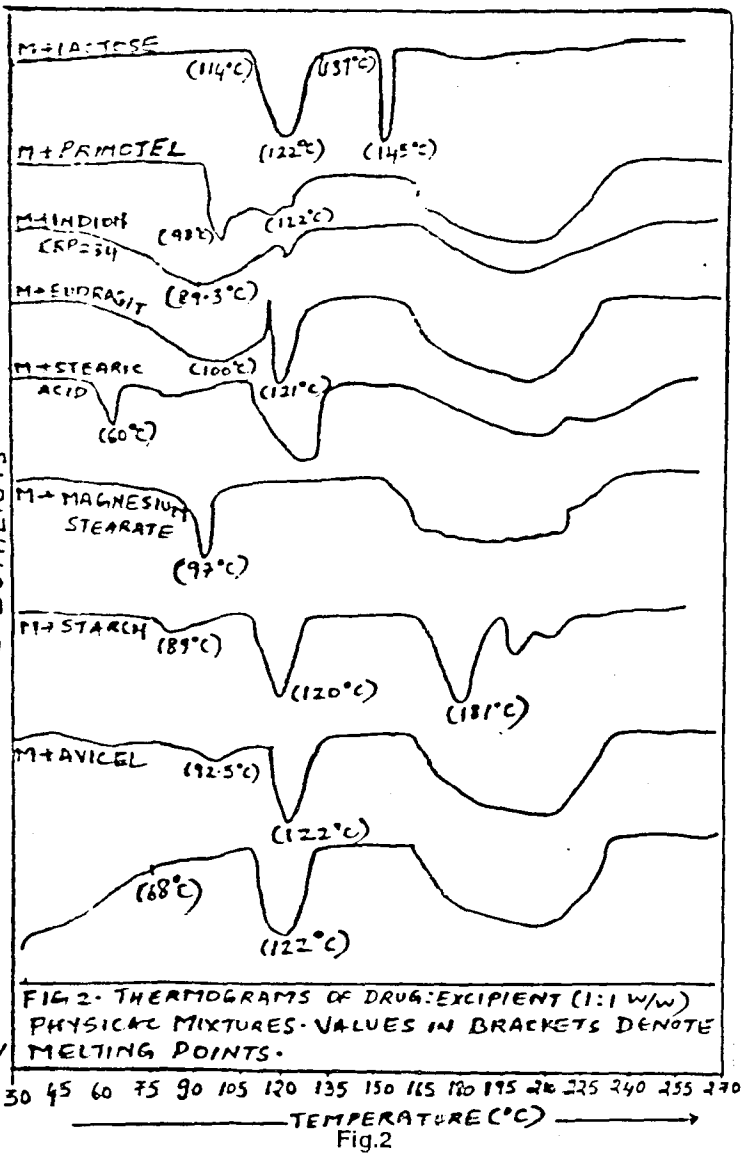

FIG 2. THERMOGRAMS OF DRUG:EXCIPIENT (1:1 W/W) PHYSICAL MIXTURES. VALUES IN BRACKETS DENOTE MELTING POINTS.

Fig.2

were then heated over a temperature range of 28 - 250°C in an atmosphere of nitrogen (50ml/min) at a constant rate of 10°C per minute, with alumina being the reference standard.

RESULTS AND DISCUSSION

DSC thermograms of individual excipients, metoprolol tartrate and 1:1 drug-excipient physical mixtures were obtained and compared. **Figure 1** shows the thermograms for metoprolol and all the individual excipients and **Figure 2** corresponds to the thermograms of the 1:1 w/w physical mixture respectively. The values shown in the parantheses indicate the peak melting temperature.

Trace 1 of **Fig. 1** is that of metoprolol tartrate with two peaks. The first peak is that of metoprolol with an onset at 114.1°C, followed by melting at 122.1°C and recovery at 137.1°C while the second broad shallow peak is for tartaric acid with an onset at 163.8°C followed by a shallow peak at 219.1°C and recovery at 239.3°C.

Trace 1 of **Fig. 2** shows no major changes in onset, melting or recovery as compared to trace 1 of Figure 1 for metoprolol tartrate combining the features of both the drug and the excipient. The endotherms for lactose at 145°C is seen while the endotherm at 195°C merges with the tartaric acid part. Calculation of enthalpy of metoprolol reveals a significant difference by about 25 mj/mg, thus suggesting a probable interaction. Also the browning reaction of lactose with amino group containing drugs (β blocker class) is well documented[13].

Trace 2 of figure 2 shows a change in the peak onset, peak shape, recovery and enthalpy thus suggesting a probable incompatability.

Trace 3 of Figure 2 shows appearance of a broad shallow endotherm at 89.3°C. Trace 3 of Figure 1 shows the endotherm for Indion CRP 234 with a broad transition peak at 104.1°C. The characteristic features of both the components are not reproduced in trace C (1 : 1 mixture of metoprolol and Indion CRP 234).

Trace 4 of Figure 2 shows no characteristic changes in peak shape, melting or recovery thus combining the characteristics of traces 1 and 4 of figures 1. The slight enthalpy change seen may be due to differences in mixture geometry.

Trace 5 of Figure 2 shows an endotherm at 60°C corresponding to the melting of stearic acid with changes in the peak onset and recovery for the drug and an enthalpy variation of 20 mj/mg thus suggesting a probable interaction.

Trace 6 of Figure 2 portrays a clear cut incompatability of metoprolol with magnesium stearate. There is a total distortion of the characteristic endotherms for the drug and the individual excipient alongwith major changes in the onset, melting and recovery.

Trace 7 of Figure 2 shows a break in the onset endotherm as compared to that of the individual excipient (Trace 8, Figure 1) and the enthalpy of metoprolol nearly doubles thus suggesting a probable interaction.

Traces 8 and 9 of Figure 2 shows reproducibility of the endotherms for the drug and excipient combinations (Avicel and Aerosil) without any major changes in peak shape, onset or enthalpy.

CONCLUSION:

The incompatabilities of metoprolol tartrate with stearic acid, magnesium stearate, starch, lactose, Indion CRP 234 and Primojel® were thus obtained using DSC. It was found to be compatable with Avicel PH 101®, Eudragit and Aerosil®

. It has been warned[14,15] against accepting incompatabilities thus derived as detrimental but DSC serves as an invaluable tool in avoiding excipients with interaction potential.

ACKNOWLEDGEMENTS

The authors wish to thank Cipla Limited for supply of pure sample of metoprolol tartrate.

REFERENCES

1. Li Wan Pao A. and Mrose,P.V., **Int. J.Pharm.**, 1984, 18, 287.
2. Levy,G. and Reuning R.H., **J.Pharm.Sci.**, 1964, **53**, 1472.
3. Carstensen,J.T, Johnson,J.B, Valentine,W. Vance J.J. **J.Pharm.Sci.**, 1964, **53**, 1050.
4. Kassem A.A. Zaki S.A. Mursi N.M. and Tayel S.A, **Pharm.Ind.**, 1979, **41**, 1020.
5. Jacobson H. and Reier G., **J.Pharm.Sci.**, 1969, **58**, 631.
6. Lee K.C. and Hersey J.A. **Aust. J.Pharm.Sci.**, 1977, **6**, 1.
7. El-Shattaway H.H, **Drug Dev.Ind.Pharm.**, 1984, **10**, 491.
8. Botha S.A, Lotter A.P. and du Preez J.L., **Drug Dev. Ind. Pharm.**, 1986, **12**, 811.
9. Van Dooren, **Drug Dev. Ind. Pharma.**, 1983, **9**, 943.
10. Botha S.A, and Lotter A.P, **Drug Dev. Ind. Pharma.**, 1989, **15**, 1843.
11. Iyer E.K. and Tipnis H.P, **Indian Drugs.**, 1995, **32**, 25.
12. Erram S.V.,and Tipnis H.P, **Indian Drugs.**, 1993, **30**, 61.
13. Duvali R.N, Koshi K.T. and Dashiell E.E., **J.Pharm.Sci.**, 1965, **54**, 1196.
14. Hardy M.J.,**Anal. Proc.**, 1982, **19**, 556.
15. Smith A, **Anal. Proc.**, 1982, **19**, 559.