RESEARCH PAPER

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Application of Differential Scanning Calorimetry (DSC) to Preformulation Compatibility Studies Between Chloroquine Phosphate and Tablet Excipients

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DSC was employed as a means to investigate the physicochemical compatibility between chloroquine phosphate (CQP) and a number of commonly used excipients. CQP was found to be compatible with microcrystalline cellulose (MCC), starch, polyvinyl pyrrolidone (PVP K-30), sodium starch glycolate (SSG), magnesium stearate, talc, hydroxypropyl methyl cellulose (HPMC), polyethylene glycol (PEG-4000) and titanium dioxide (Ti02). Gelatin was found to interact with CQP. Methyl and propyl paraben showed interaction in the 1:1 ratio. However, when studied at a 1:100 ratio, no significant interaction was observed. Although gelatin was found to interact with CQP, one cannot conclusively state that this incompatibility will be encountered on storage at room temperature.

COMPATIBILITY of the active ingredient (drug) with the other ingredients is one of the major factor amongst others, affecting the stability[1] of the formulation which in turn may have a bearing on the bioavailability of the drug[2].

Although it is mandatory to carry out stability studies which may extend over a period of weeks to several months, DSC has been utilised as a tool for rapid evaluation of interaction of drugs with excipients in preformulation stability studies[3,4]. Though it seems unlikely that DSC may phase out the classical stability programme entailing long term observations, it can prove to be a guide to serious incompatibility problems and may prove to be a guiding beacon in the pursuit of a successful formulation.

Besides DSC, the other techniques used for the determination of interactions and/or incompatibility include accelerated stability testing[5], diffuse reflectance spectroscopy[6], TLC[7], IR[7] and various other thermal techniques[3,8-10].

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To maximise the likelihood of an interaction, 1:1 mixtures of drug and excipients have been utilised rather than the 'realistic ratios' proposed for classical compatibility studies[11]. Interactions in the samples have been derived or deduced from DSC[12,13] by changes in thermal events such as elimination of an endothermic peak or exothermic peak. Changes in peak shape, peak onset or peak maximum temperature and relative peak heights are also considered[13].

The objective of the present study was to evaluate CQP excipient compatibility using DSC. The results of the study will be useful in the development of a formulation of CQP.

EXPERIMENTAL

Materials :

The following materials, with sources mentioned in parenthesis were used in the study: CQP (IPCA Laboratories Ltd., Bombay), MCC (FMC International, Food and Pharmaceuticals Division, Ireland), Starch (Universal Starch Chemicals, Bombay), Talc

(Pharmalink, Bombay), PVP K-30 (BASF, India) SSG (Sheetal Chemicals, Naroda), Magnesium stearate (Amuh Pharma, Bombay), Propyl paraben (Salicylates and Chemicals, Hyderabad), Methyl paraben (Salicylates and Chemicals, Hyderabad), Gelatin (Rallis India, Bombay), HPMC (Dow Chemicals, U.S.A.), Ti02 (Stregis Bates, Malaysia) and PEG 4000 (SMZF Chemicals, Bombay).

Instrumentation :

Differential Scanning Calorimeter (Shimadzu Thermal Analyser, DT40) equipped with a monitor and a computerised 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. The Indium used was of 99.9% purity. The melting point obtained for Indium was 155°C which was 1.5°C lower than the reported value for Indium (156.5°C). Therefore to obtain a correct temperature, 1.5°C was added to the value read from the recorder. The enthalpy changes were calculated automatically by the computerised analyser.

Procedure :

Thermograms (in replicates) or individual excipients, CQP as well as 1:1 physical mixtures of chloroquine phosphate and excipients were obtained.

Samples (2-4 mg) in weight were sealed hermetically in flat bottomed aluminium cells (pans). These samples were then heated over a temperature of 30-300°C in an atmosphere of nitrogen (50 ml/min) at a constant rate of 10°C per minute using α - alumina (alumina -standard material for D.S.C. supplied by Shimadzu Corporation.) as a reference standard. Amount of α- alumina used was about twice the amount of the samples used.

RESULTS AND DISCUSSION

DSC thermograms of individual excipients, CQP and 1:1 CQP- excipients physical mixtures were obtained and compared. Figures 1 to 12 show curve A as thermogram of CQP, curve B as thermogram of individual excipients under study and curve C which is the thermogram of CQP and the excipient mix in 1:1 proportion. The thermogram of CQP (**Fig. 1-A**) showed a peak with an onset at 175.6°C, with a slight shoulder at 188.0°C, followed by a sharp peak at 200.3°C and recovery at 208.5°C. No additional peaks are seen.

DSC studies can yield more data than studies on compatibility undertaken by DTA, as the quantities of heat required to complete a transition can be measured accurately[13]. Thus, change in enthalpy of fusion, as a result of incompatibility on mixing a drug with an excipient can be measured. The significance of measuring enthalpy lies in the fact that incompatibilities which manifest themselves only as changes in enthalpy of fusion and which may be overlooked by the inspection techniques detailed earlier, can be detected in this way[13]. This approach has been used successfully in several studies wherein conventional inspection techniques failed to detect incompatibilities[14,15,16,17].

Thermogram of CQP and MCC mix (**Fig. 1-C**) showed no change in peak characteristics for CQP thereby ruling out the possibility of an interaction with MCC. This was corroborated by the fact that there was no change in enthalpy.

Thermogram of CQP and starch mix (**Fig 2-C**), showed a slight change in the shape of peak when compared with thermogram B. However there was no significant change in enthalpy.

Thermogram of CQP and PVP mix (Fig. 3-C) showed a sharper peak for PVP K-30 with an onset at 113.0°C, a maxima at 129.4°C and recovery at 162.1°C in comparison with thermogram of PVP K-30 (Fig. 3-B) which showed a peak having an onset at 106.0°C, peak maxima at 129.8°C and recovery at 172.5°C. However no change in enthalpy whatsoevet was noted. Thermograms of physical mixes of CQP with

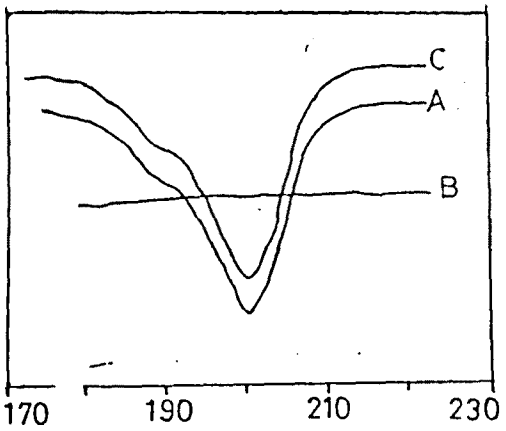

Fig.1: Thermograms of CQP(A), MCC(B) and 1:1 Physical mixture (C).

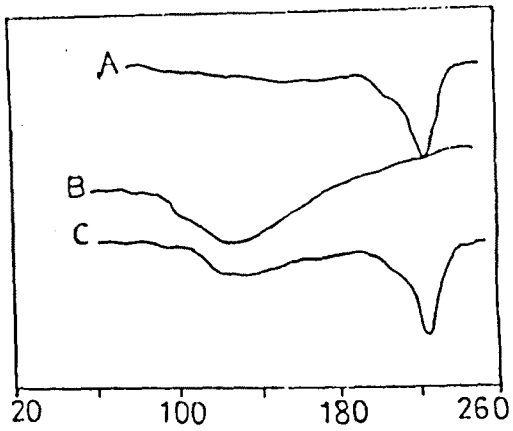

Fig.2: Thermograms of CQP(A), Starch(B) and 1:1 Physical mixture (C).

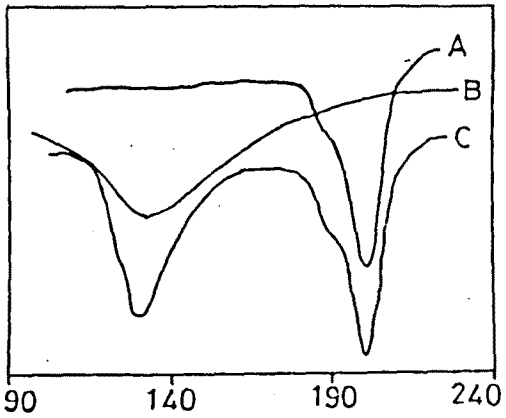

Fig.3: Thermograms of CQP(A), PVP-K 30(B) and 1:1 Physical mixture (C).

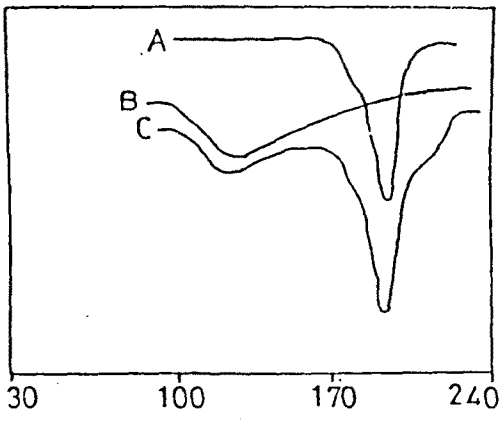

Fig.4: Thermograms of CQP(A), SSG(B) and 1:1 Physical mixture (C).

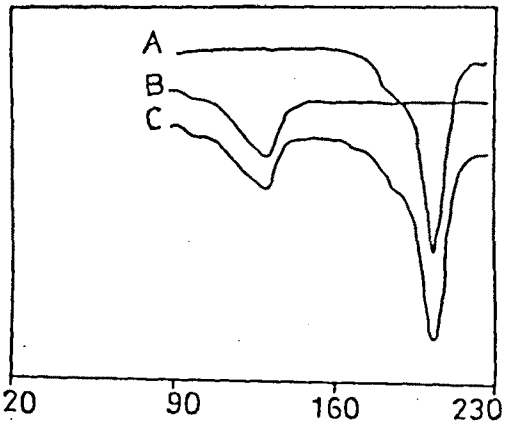

Fig.5: Thermograms of CQP(A), Magnesium stearate(B) and 1:1 Physical mixture (C).

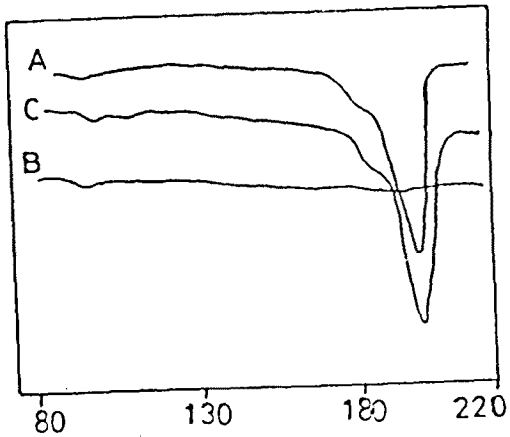

Fig.6: Thermograms of CQP(A), Talc(B) and 1:1 Physical mixture (C).

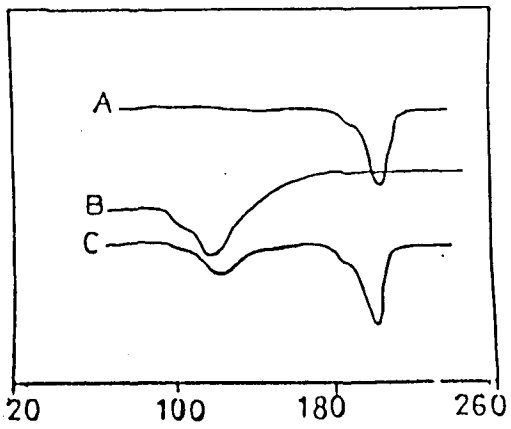

Fig.7: Thermograms of CQP(A), HPMC(B) and 1:1 Physical mixture (C).

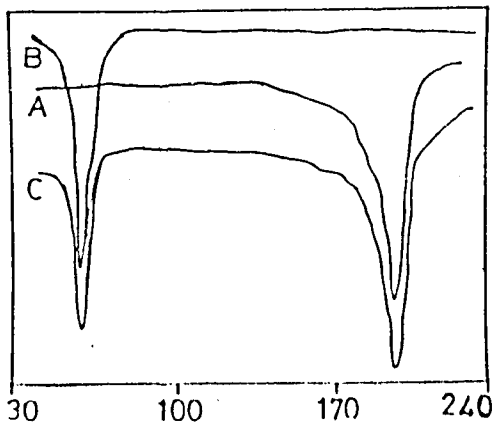

Fig.8: Thermograms of CQP(A), PEG-4000(B) and 1:1 Physical mixture (C).

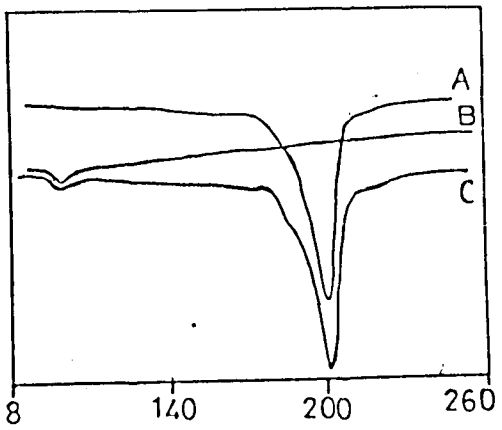

Fig.9: Thermograms of CQP(A), TiO2(B) and 1:1 Physical mixture (C).

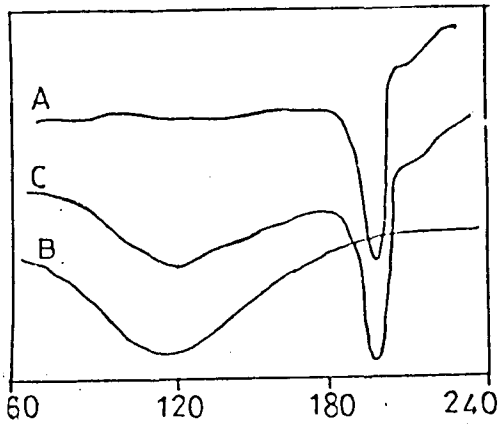

Fig.10: Thermograms of CQP(A), Gelatin(B) and 1:1 Physical mixture (C).

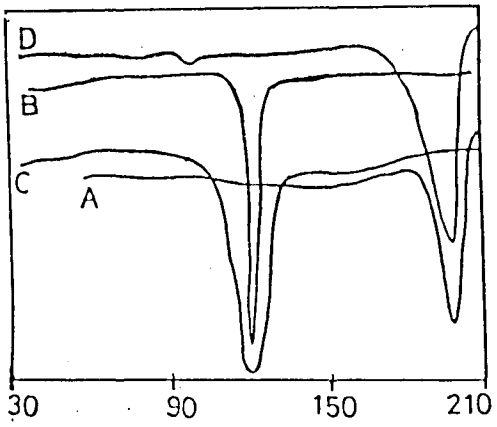

Fig.11: Thermograms of CQP(A), Methyl paraben(B), 1:1 Physical mixture (C) and 100:1 Physical mixture (D).

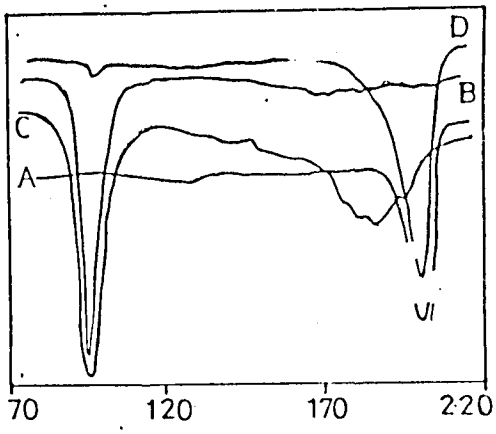

Fig.12: Thermograms of CQP(A), Propyl paraben(B), 1:1 Physical mixture (C) and 100:1 Physical mixture (D).

i) SSG (Fig. 4-C), ii) Magnesium stearate (Fig. 5-C), iii) HPMC (Fig. 6-C), iv) PEG-4000 (Fig. 7-C) and v) Ti02 (Fig. 8-C) showed no change in the peak shape of CQP when compared with thermogram of CQP. No significant change in enthalpy, peak shape or onset was noted in all these cases indicating compatibility of CQP with the above mentioned ingredients.

In Fig. 9-B, a shallow endotherm was noted at 100.9°C in the thermogram of Ti02 which may be attributed to loss of water. Thermogram of CQP-Ti02 mix revealed similar characteristics and in addition, the drug peak at 200.6°C with no change in enthalpy.

Though thermogram of CQP-gelatin mixture (Fig. 10-C) did not apparently show any change of peak characteristics of CQP a significant enthalpy change was observed for CQP (105.97 mJ/sec from curve C i.e. Physical mixture as compared to 60.14 mJ/sec from curve A i.e. Pure sample of CQP) thereby signifying a possible interaction.

The thermograms of CQP-methyl paraben physical mix (Fig. 11-C) and that of CQP-propyl paraben physical mix (Fig. 12-C) showed a complete absence of peak at 200.0°C, which is characteristic of the drug.

As methyl paraben and propyl paraben are used in very low concentrations with the drug, a more realistic mix of 1:100 of methyl paraben: CQP and propyl paraben: CQP were prepared and evaluated.

As seen in thermogram of physical mix of methyl paraben and CQP in 1:100 ratio (Fig. 11-D), the peak for methyl paraben which was noted in thermogram Fig. 11-B, disappeared. This may be attributed to the low concentration of methyl paraben. However no changes in CQP peak or enthalpy were observed for CQP.

Fig. 12-B shows the melting peak of propyl paraben at 100°C. Similarly, the thermogram of propyl paraben and CQP mix in 1:100 proportion, Fig. 12-D revealed presence of a small peak at 100.0°C which may be attributed either to the melting of propyl paraben or to loss of water. At the low concentration of propyl paraben used, it appears less likely that the peak is for melting of propyl paraben. Since there is also a significant difference in enthalpy on comparing curves B and D in Fig. 12 the peak at 100°C is most likely due to loss of water from the mix. However, the peak for CQP and the enthalpy remain unchanged.

CONCLUSIONS

In compatibility studies using DSC, chloroquine phosphate was found to be compatible with MCC, starch, PVP K-30, SSG, Magnesium stearate, talc, HPMC, PEG 4000 and Ti02. Gelatin was found to interact with chloroquine phosphate.

Though methyl paraben and propyl paraben were found to react with CQP in physical mix of 1:1 proportion, when studied as physical mix with more realistic ratio of 1:100, no significant reaction was observed. It has been forewarned[18,19] against accepting such incompatibilities derived as detrimental but DSC serves as an invaluable tool in avoiding excipients which may potentially interact with the drug.

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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. Jacobsen H. and Reier G., **J. Pharm. Sci.**, 1969, 58, 631.

4. Simon T.H., **Paper presented to the Industrial Pharmaceutical Technology section,** APHA, Academy of Pharmaceutical Sciences Las Vegas meeting, April 1967 through Reference 3.

5. Carstensen J.T., Johnson J.B., Valentine W., and Vance J.J. **J. Pharm. Sci.** 1964, 53, 1050.

6. Lach J.L. and Bornstein M., **J. Pharm. Sci.,** 1965, 54, 1730.

7. Kassen A.A., Zaki S.A., Mursi N.M. and Tayel S.A., **Pharm. Ind.**, 1979, 1020.

8. Lee K.C. and Hersey J.C. **Aust. J. Pharm Sci.**, 1977, 6, 6.

9. Shattaway H.H.E., **Drug. Dev. Ind. Pharm.** 1984, 10, 491.

10. Botha S.A., Lotter A.P. and Du Preez J.L., **Drug. Dev. Ind. Pharm.**, 1986, 12, 811.

11. Akers M.J., **Can. J. Pharm.**, 1975, 11, 1.

12. Jacobsen H. and Reier G., **J. Pharm. Sci.,** 1973, 62, 1543.

13. Ford, J.L. and Timmins P., Application of thermal analysis to compatibility studies for solid dosage forms in **Pharmaceutical Thermal Analysis: Techniques and Applications**. Ellis Horwood Ltd., Chichester, 1989 England, 239.

14. El Shattawy, H.H., Kildsig, D.O. and Peck, G.E., **Drug Dev. Ind. Pharm.**, 1982-a, 8, 837.

15. El Shattawy, H,H., Kildsig, D.O. and Peck G.E., **Drug Dev. Ind. Pharm.**, 1982-b, 8, 897.

16. El Shattawy, H.H., Kildsig, D.O. and Peck, G.E., **Drug Dev. Ind. Pharm.**, 1984 10, 1.

17. Jacobson, H. and Gibbs, I., **J. Pharm Sci.,** 1973, 62, 1543.

18. Hardy M.J., **Anal. Proc.**, 1982, 19, 556.

19. Smith A., **Anal. Proc.,** 1982, 19, 559.