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COMMUNICATION

Drug Adjuvant Interaction Study Using DSC Supported by Isothermal Method

A. Balasubramaniam[1,*] and G. M. Panpalia[2]

[1] *Vel's College of Pharmacy, Old Pallavaram, Chennai-117, India*
[2] *Department of Pharmaceutics, Birla Institute of Technology, Ranchi, India*

ABSTRACT

Extensive work has been done in the field of drug adjuvant interaction studies using differential scanning calorimetry (DSC), but conclusive interpretive techniques could not be reached since very few workers supplemented their work by conventional isothermal stability testing methods. This work compared the drug adjuvant thermogram with results obtained from isothermal stability studies and used it to reiterate the results of the drug adjuvant thermograms. In the formulation of ascorbic acid in a cosmetic preparation, the various adjuvants were tested for interactions first by the isothermal stability testing technique, which was followed by DSC scanning of the drug adjuvant. The results of the two methods were compared and correlated.

Key Words: *Drug adjuvant interaction; DSC.*

INTRODUCTION

Utilizing thermal methods like differential thermal analysis (DTA) and the more recent differential scanning calorimetry (DSC), it is possible to obtain significant data rapidly, and the method has been suggested for routine screening of potential drug-excipient interaction at the preformulatory level (1–3). Of a series of reports (2–15) that suggest the use of thermal analysis for rapid prediction of chemical interactions between drugs and formulation adjuvants, only five studies have confirmed thermal interactions with routine stability testing involving chemical analysis (1–3,7,10,). It is therefore necessary that a large amount of data be generated before thermal analysis becomes a powerful tool for investigating drug-excipient interactions.

The present work thus investigated the interactions of ascorbic acid with some ingredients and adjuvants of cosmetic formulations through DSC supplemented with isothermal stability testing.

* Corresponding author. E-mail: basu68@yahoo.com

EXPERIMENTAL

Materials

Materials used were L(+)ascorbic acid GR, disodium editate GR, thiourea ER, glutathione (reduced) GR, citric acid LR, stearic acid LR, stearyl alcohol LR, zinc oxide LR, kaolin LR, and bentonite LR. We accurately weighed 6 g each of the drug and excipient. Each excipient-drug admixture was then prepared by incorporating 5% by weight of moisture introduced slowly while triturating until a free-flowing powder was obtained. After removing about 0.5 g for the initial analysis, the rest was divided in two almost equal parts and placed in 2 × 5 ml capacity (normal volume) glass vials, sealed, and placed in a hot air oven at 50°C and at ambient temperature. A control sample of the pure drug, prepared exactly in the same manner, was subjected to analogous storage conditions. Samples were withdrawn at predetermined time intervals in quantities sufficient for analysis of the drug content, and the vials containing the rest of the samples, after resealing, were replaced in their respective ovens.

Methods

Chemical Analysis of Vitamin C Content

The drug and drug-adjuvant admixture samples were analyzed individually for their chemical contents in 0.1 N HCl at 243 nm against an 0.1 N HCl blank on a Beckman UV-Vis spectrophotometer.

Thermal Analysis

The drug-excipient mixture was prepared in a 1:1 ratio, and after placing it in suitable containers, it was stored in a desiccator until analysis. The thermal analysis was conducted on a pressure differential scanning calorimeter (DSC) 1993 (Polymer Laboratories, England). The sample was scanned at a heating rate of 20°C min^{-1} from ambient temperature to 200°C .

RESULTS AND DISCUSSION

The data on the isothermal stability of vitamin C at 50°C alone and in combination with cosmetic adjuvants, including drug stabilizers like Na_2EDTA (chelating agent), glutathione, and thiourea as antioxidants and citric acid (antioxidant synergist), ingredients of cosmetic value like stearic acid, stearyl alcohol, bentonite, kaolin, and zinc oxide were studied and ranked according to increased interaction (Table 1). At this storage temperature of 50°C, vitamin C (in the solid state with 5% added moisture) underwent considerable drug loss, nearly 30% in 45 days. The observed instability may thus be attributed to the presence of 5% free water (16,17). In the presence of the cosmetic adjuvants of the present investigation, the drug stability by the end of 45 days at 50°C varied largely, from as high as 80% to as low as 55%. While materials like stearic acid gave a protection of 10%, stearyl alcohol and citric acid increased protection 7%, and thiourea improved the stability by 2%–3%. Zinc oxide and kaolin did not interfere; bentonite, glutathione, and (surprisingly) Na_2EDTA deteriorated the drug stability.

Isothermal stability studies were also carried out at near ambient storage of 30°C. Although the stability in each case was comparatively higher than at 50°C, the same pattern of results were followed. In both instances, the drug alone and the drug in combination with excipients appear to follow zero-order and first-order decomposition with exactly the same precision.

Ranking of the adjuvants with respect to increased interaction in terms of percentage drug remaining (considering the absence of interaction as cent per cent content) at the end of 45 days at 30°C is also presented in Table 1. The ranking in terms of degradation rate constants are also made. At 50°C, the ranking in terms of percentage drug remaining at 45 days fully coordinates with that based on K values. There was a minor change in ranking at 30°C when compared on this basis.

Thermogram Interpretation

The drug ascorbic acid produces (Figs. 1–9, in which D + A drug + adjuvant, A = adjuvant, and D = drug) a single, almost sharp, endotherm characteristic of its melting. This fusion endotherm, which ranges from 170°C to 197°C, rises slowly from 170°C to 180°C, with a peak maximum of 190.05°C. Ascorbic acid is reported to melt at 190°C with decomposition (13). Out of these nine adjuvants, only four (i.e., stearic acid, citric acid, stearyl alcohol, and thiourea) produced the distinct endotherms; except for citric acid, which exhibited two endothermic peaks, the rest gave only one endotherm. With stearic acid, stearyl alcohol, kaolin, zinc oxide, and bentonite, the lone endotherm of the drug was largely preserved. While with stearic acid and stearyl alcohol, this endotherm shifted to a slightly higher temperature (192.3°C and 193.3°C, respectively), zinc oxide produced a marginal downward shift to 187.50°C, whereas

Table 1

Influence of Cosmetic Adjuvants on Relative Stability of Ascorbic Acid After 45 Days Storage at Room Temperature (RT) and 50°C and Quantification of First-Order Decomposition Rate Constant

		50°C				RT			
SI No.	Material	Relative Stability	r	$K \times 10^3$	K Ranking	Relative Stability	r	$K \times 10^3$	K Ranking
	Pure drug	100 (70.93)	0.9695 ($P < .001$)	7.46	C	100 (84.44)	0.9674 ($P < .001$)	3.38	C
1	Stearic acid	112.43	0.9933 ($P < .001$)	4.74	1	109.29	0.9668 ($P < .001$)	1.69	1
2	Citric acid	108.00	0.9783 ($P < .001$)	5.25	2	106.76	0.9557 ($P < .01$)	2.229	2
3	Stearyl alcohol	107.40	0.9749 ($P < .001$)	5.33	3	105.50	0.9855 ($P < .001$)	2.236	3
4	Thiourea	103.18	0.9991 ($P < .001$)	6.92	4	102.07	0.9950 ($P < .001$)	3.108	4
5	Kaolin	100.00	0.9920 ($P < .001$)	7.17	5	98.96	0.9635 ($P < .01$)	3.7	6
6	Zinc oxide	97.26	0.9829 ($P < .001$)	7.33	6	101.06	0.9612 ($P < .001$)	3.13	5
7	Bentonite	89.03	0.9521 ($P < .001$)	8.26	7	93.68	0.9899 ($P < .001$)	5.13	7
8	Glutathione	68.18	0.9729 ($P < .001$)	11.12	8	—	—	—	—
9	Na_2EDTA	78.18	0.9787 ($P < .001$)	12.22	9	75.97	0.9927 ($P < .001$)	9.73	8

r correlation coefficient with 6 degrees of freedom at 50°C and 5 degrees of freedom at 30°C; C, control (pure drug in the same state).

kaolin and bentonite produced practically no shift in the endotherm.

In the opinion of Gerber and Lotter (12), if the shift of a function endotherm characteristic of the drug to a higher temperature is treated as an incompatibility, then vitamin C should not be as stable with stearic acid and stearyl alcohol as with kaolin and bentonite, for which the drug melting endotherm was essentially preserved without any shift. In contrast, these are among the few excipients (stearic acid, citric acid, stearyl alcohol) affording extra protection to the bare drug. In the science of polymorphism, the energetic form is the one that has a low melting point and low heat of fusion. A quantitative

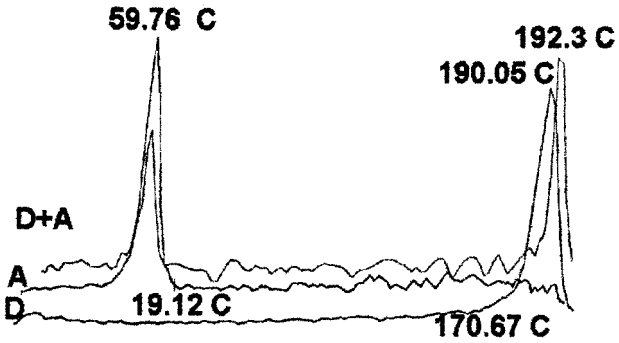

Figure 1. D, ascorbic acid; A, stearic acid; D+A, admixture of ascorbic acid and stearic acid.

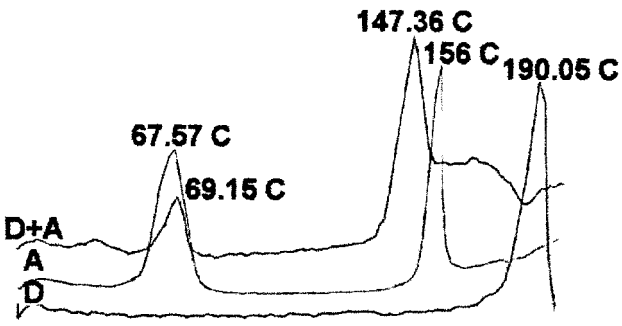

Figure 2. D, ascorbic acid; A, citric acid; D+A, admixture of ascorbic acid and citric acid.

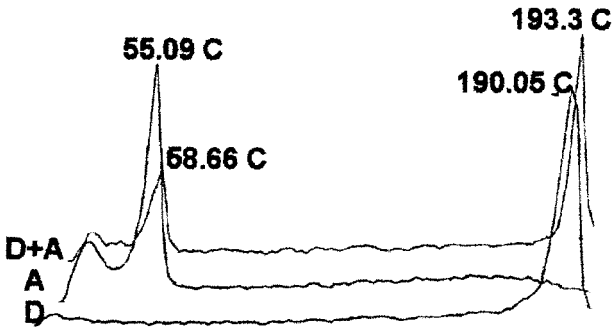

Figure 3. D, ascorbic acid; A, stearyl alcohol; D+A, admixture of ascorbic acid and stearyl alcohol.

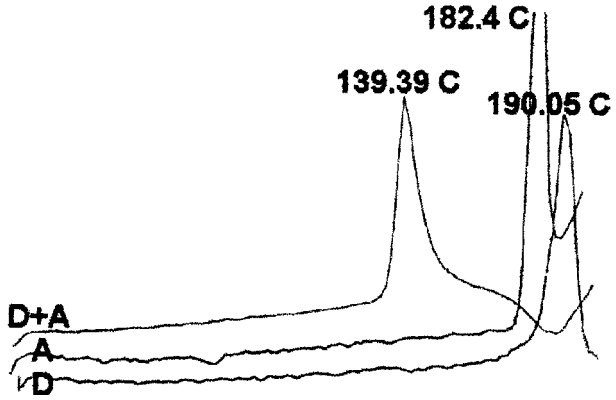

Figure 4. D, ascorbic acid; A, thiourea; D+A, admixture of ascorbic acid and thiourea.

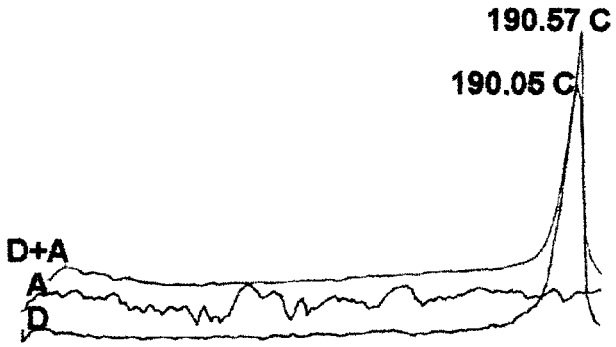

Figure 5. D, ascorbic acid; A, bentonite; D+A, admixture of ascorbic acid and bentonite.

Figure 6. D, ascorbic acid; A, zinc oxide; D+A, admixture of ascorbic acid and zinc oxide.

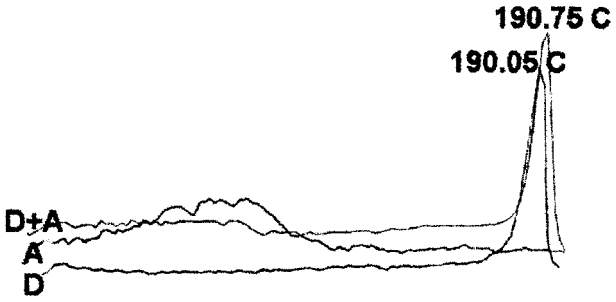

Figure 7. D, ascorbic acid; A, kaolin; D+A, admixture of ascorbic acid and kaolin.

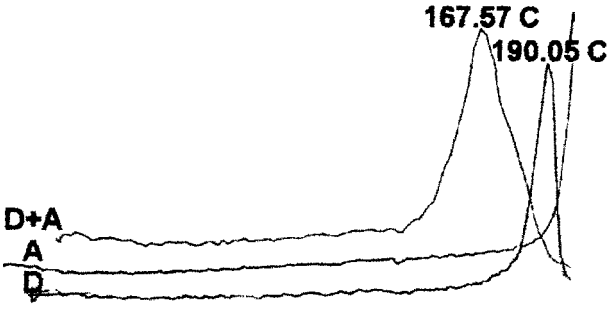

Figure 8. D, ascorbic acid; A, glutathione; D+A, admixture of ascorbic acid and glutathione.

relationship $\Delta EH = K(T_E - a)$ characterizes the linear dependence of the molar heat of fusion on the position of the melting point (18). Higuchi (19), therefore, states, ''It would be difficult to produce rapid absorption of high melting point compounds.''

Just as a higher energetic form would be desirable for drug availability in vivo, a high energetic form may not be suitable form for drug stability. This is evident from the work of Guillory and Higuchi (20) on vitamin A derivatives. The stronger lattice obtained at an increased melting point offers a stabilizing (chemical) effect. Thus, the increase in melting point of vitamin C in the presence of stearic acid and stearyl alcohol could no longer be

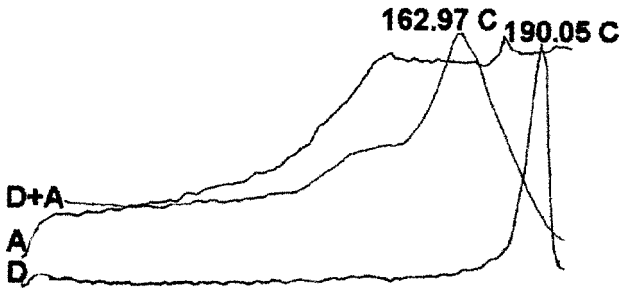

Figure 9. D, ascorbic acid; A, Na_2 EDTA; D+A, admixture of ascorbic acid and Na_2 EDTA.

treated as a possible interaction. In fact, it is likely to act as an indication of improved stability. When the comparison is made between stearic acid and stearyl alcohol, in the stearic acid–vitamin C system, the adjuvant peak was preserved with the same sharpness. But, in the stearyl alcohol–vitamin C system, the stearyl alcohol fusion peak was somewhat broadened. Coupled with the maintenance of the spearlike characteristics of the drug endotherm and its heat of fusion (56.8/mcal/mg, approximately 29.75 × 2, with the multiplication factor 2 standing for the 1 : 1 drug-adjuvant ratio) with stearic acid than in presence of stearyl alcohol ($56.87 \gg 18.4 \times 2$), this strongly makes one believe that stearic acid would act as a better stabilizing agent than stearyl alcohol. A slightly higher melting point (1°C) of vitamin C in combination with stearyl alcohol does not seem to outweigh the above stabilizing effect.

In other systems in which the endotherm of the drug was preserved (kaolin, bentonite, and ZnO), based on the absence of the shift in the thermogram of the drug in kaolin and bentonite, it is expected that vitamin C should be more stable with these adjuvants than with ZnO. But, isothermal stability data (at 45 days for the content at both storage temperatures and for the *K* value) show that not only kaolin (as expected), but also ZnO (unexpectedly) essentially preserved the drug (however, without any extra protection), whereas bentonite somewhat (around 8%–10%) deteriorated the stability of vitamin C. Careful perusal of the drug endotherm in the presence of ZnO and bentonite clearly reveals that, despite the increasing nature of zinc oxide endothermic thermal features, the lone fusion endotherm of the drug is not as broadened as seen with bentonite, which was devoid of such a character. Besides plane features of bentonite above 120°C, the drug endotherm with this adjuvant triggered at a temperature as low as 120°C, thereby making it too broad in comparison with zinc oxide, for which it started rising only at 167°C, also in spite of the opposing effect exerted by the adjuvant.

Thus, the suppression of noncharacteristic thermal features of inorganic adjuvant does not seem to produce chemical interaction. It therefore may be inferred that instances for which the drug melting endotherm is somewhat lowered (here by 2.5°C) broadens the melting endotherm in the sense of its triggering at a lower temperature and contributes more to drug destabilization. The inconsequential effect on drug stability of the somewhat downward shift in melting endotherm was anticipated (6,9,13, 14,21) in the light of the observations that, when two compounds are mixed, the purity of each is obliterated (10,13,14). Furthermore, the heat of fusion in such instances, for which the (melting) endotherm characteristic of the drug is very much broadened, seems not to be of any significance in governing drug-excipient interaction.

With the remaining four adjuvants (i.e., citric acid, thiourea, GSH, and Na_2EDTA), for which the drug endotherm was obliterated in the sense of being shifted to a lower degree of melting (peak temperatures with citric acid = 147°C, thiourea = 139°C, GSH = 168°C, and Na_2EDTA = 163°C), only Na_2EDTA and GSH in a 1 : 1 ratio with the drug brought about an adverse effect on vitamin C stability. While Na_2EDTA brought about an additional 25% decomposition in 45 days (at both storage temperatures), GSH caused about 14% extra degradation compared to the drug alone. This is supported by degradation rate constants obtained from all data with these particular adjuvants. In the presence of Na_2EDTA, *K* were about 1.6 and 2.9 times of the drug at 50°C and 30°C, respectively; with GSH, *K* was 1.5 times that of the pure drug or 50°C studied. The extent to which the melting endotherm was lowered fails to explain the chemical incompatibility of vitamin C in the presence of Na_2EDTA and GSH since it was believed that EDTA protects oxidation-susceptible drugs like ascorbic acid by chelating with heavy metal ions. Our observations have shown that, with 100 mg% ascorbic acid solution, more than 0.05% EDTA had a deteriorating effect on drug stability to such an extent that at 0.2% EDTA, the protective effect of chelating agent was fully lost. But, these are the typical cases for which the lowered drug endotherms are excessively broad. In the presence of Na_2EDTA, it is broadest, having spread over from about 100°C to 190°C, whereas with GSH, it is comparatively less broad, ranging from 140°C to 190°C. The broadening of the drug melting endotherm perhaps provides the qualitative explanation to vitamin C incompatibility with Na_2EDTA and GSH. The extent of broadening seems to offer a solution to (relative) deterioration.

The extent of lowering of peak temperature is also likely to contribute. The exact contribution of this factor will remain elusive until many more such occurrences come into light.

The broad endothermic feature of vitamin C in the presence of sodium edetate or glutathione (reduced) indicates the formation of the amorphous adducts, and consequently, it is less chemically stable (22,23) on storage than the drug itself, having basically crystalline characters.

In the presence of citric acid and thiourea, the lone fusion endotherm of the drug seems to have been lost, and a new endotherm is produced in each case. The retention of the spearlike features characteristics of vitamin C in the newly formed endotherm signifies that the fusion endotherm of the drug is substantially shifted to a lower melting point. In spite of this significant lowering, the sharpness of the peak is largely preserved. It is this preservation of the sharpness of the endotherm characteristic of vitamin C that seems to play a major role in the drug stability. The substantial lowering of the endotherm with peak sharpness is indicative of the strong interaction between vitamin C and citric acid/thiourea, leading to the formation of a chemically stable adduct, although it is likely to be physically unstable (24). The protective effect, to some extent, afforded by this compound is presumably due to the formation of the drug-adjuvant crystalline adduct, which helps in taking the drug away from the oxidation-prone environment. Such a protective effect in stoichiometric and nonstoichiometric adducts has been reported previously.

Citric acid and thiourea are two among many adjuvants that exhibit characteristic endotherms. While citric acid itself, used in the monohydrate form, has two endotherms characteristic of dehydration and fusion (m.p. 156°C) (25), the single endotherm associated with thiourea signifies fusion (m.p. 182°C) (26). In the vitamin C–citric acid system, the dehydration endotherm of citric acid, although reduced, largely is still preserved. This, perhaps coupled with less lowering of the drug endotherm, offers an explanation to the somewhat higher stability of vitamin C in the presence of citric acid than in the presence of thiourea.

CONCLUSION

An interesting conclusion was drawn, largely due to the isothermal stability testing done simultaneously, was that obliteration, shift, or broadening of peaks, although indicative of interaction, need not necessarily indicate incompatibility, unlike generally held beliefs. It appears that, as long as the sharp peaks characteristic of the crystalline medicinal agents are preserved, irrespective of whether they retain the original drug endotherm position or not, the so-called thermal interactions do not lead to chemical instability. Shift in peak toward high temperature is a confident indication of drug stability. Induction of the amorphous characteristics in the drug by the adjuvant, evidenced by the broad drug melting endotherm, seems to be enough to warn of chemical instability.

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