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COMMUNICATION

STABILITY OF ASCORBIC ACID-ZINC SULPHATE TABLETS

Anil K.Singla* and Alka Nagrath**
Department of Pharmaceutical Sciences,
Panjab University, Chandigarh 160 014 (India)

ABSTRACT

Microencapsulation using ethylcellulose and embedding in stearic acid or polyethylene glycol 6000 have been employed to protect ascorbic acid from metallic ion catalysed oxidation in tablets containing zinc sulphate. It is observed that presence of Zn^{+2} in the tablets do not affect stability of ascorbic acid even at accelerated storage conditions provided the moisture content is controlled.

INTRODUCTION

Ascorbic acid (1-3) and zinc salts (4-8) are used in different clinical ailments. Recently, we have reported that concomitant administration of zinc sulphate and ascorbic acid produced anti-inflammatory activity against carrageenan-induced paw oedema comparable to indomethacin; the gastric irritability was low (9). Bivalent metal ions catalyse oxidation of ascorbic acid (10). The present study was undertaken to develop a stable tablet dosage form containing ascorbic acid and zinc sulphate. Various techniques such as non-aqueous binder (ethylcellulose) for wet granulation, microencapsulation using ethylcellulose, embedding in stearic acid or polyethylene glycol (11) were employed.

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*Two whom all correspondence to be addressed.
**Present address: Hamdard College of Pharmacy, Hamdard Nagar, Madangir, New Delhi (India).

MATERIALS AND METHODS

MATERIALS

Ascorbic acid, Indian P. (Jayant Vitamins Ltd., Ratlam), ethylcellulose (BDH, England), Stearic acid (Riedel-De Haen, Seelze-Hannover), Polyethylene glycol 6000 (Sisco Research Labs.) and zinc sulphate (S.Merck, Baroda) after drying at 100°C for 4 hr and powdered having moisture content (14.56% w/w) were used in the study.

METHODS

Granulation: Granules of ascorbic acid and zinc sulphate, previously dried at 100°C and powdered, along with diluents, were prepared separately employing ethanolic solution of ethylcellulose (5% w/w) by wet granulation process.

Microencapsulation: Coacervation-phase separation, induced by thermal change, was employed using toluene as the vehicle and ethylcellulose as the coating agent with a core to coating material ratio of 2:1. Ethylcellulose (40 g) was dissolved in toluene (2 l) with heating upto 70°C, thereafter ascorbic acid (80 g) was dispersed in the solution which was kept stirring at 100 rpm. The system was slowly cooled to room temperature, and then to 10°C for 30 min. During this process a phase separation occurred. The supernatant of the system with dispersed microcapsules was decanted, washed with toluene, and dried in vacuum for 24 hr.

Embedding: In a melt of stearic acid (10 g), ascorbic acid(90g was dispersed intimately by agitating. On cooling the mass was screened through a stainless steel screen (22 mesh size) and dried in the air. The granules employing stearic acid at different concentrations (15,25% w/w) with appropriate quantities of the drug which yielded 100 g of the final embedded product in each case were prepared under the same conditions. Ascorbic acid and zinc sulphate granules were also prepared separately with polyethylene glycol 6000 (5,10, and 20% w/w) in a similar fashion.

Preparation and Evaluation of Tablets: Tablets of each formulation (Table 1) containing equivalent to ascorbic acid (0.5g)

TABLE 1

Summary of Different Ascorbic Acid with Zinc Sulphate Tablet Formulations

Raw material	Formulation, mg per tablet												
	A	B	C	D	E	F	G	H	I	J	K	L	M
Ascorbic acid	500.00	500.0	500.0	500.0	500.0								500.0
Ascorbic acid, embedded in PEG						526.3*	555.56**						
Ascorbic acid, embedded in stearic acid								555.6**	588.2[a]	625.0[c]			
Ascorbic acid, microencapsulated with ethylcellulose											510.0*		
Coated ascorbic acid(commercial)												500.0	
Zinc sulphate	100.0	100.0				100.0	100.0	100.0	100.0	100.0	100.0	100.0	
Zinc sulphate, embedded in PEG			105.3*	111.0**	125.0[b]								
Starch, (0.5%)	3.75	3.75	3.75	3.75	3.75	3.75	3.75	3.75	3.75	3.75	3.75	3.75	3.75
Lactose, anhydrous		114.38											
Calcium sulphate, anhydrous	114.38		109,08	103.38	89.38	88.08	58.82	58.82	26.18	4.38	104.38	114.38	214.38
Stearic acid,(1.75%)	13.12	13.12	13.12	13.12	13.12	13.12	13.12	13.12	13.12	13.12	13.12	13.12	13.12
Talc, (2.5%)	18.75	18.75	18.75	18.75	18.75	18.75	18.75	18.75	18.75	18.75	18.75	18.75	18.75

*Includes 5% embedded/coated material; **Includes 10% embedded/coated material;
[a]15%, [b]20%, [c]25% embedded/coated material.

and zinc sulphate (0.1 g) per tablet were made using 12.5 mm standard concave punch on a single punch machine. Product assay and tests for content uniformity and disintegration were performed on each product according to compendial standards (12,13). Dissolution profiles were determined for each product on six individual tablets using a pH 1.5, HCl medium (900 ml). Tests were performed using the USP XVIII (14) dissolution apparatus (rotating basket method) at 100 rpm and a temperature of 37±0.5°C. At various time intervals, aliquots (5 ml) were withdrawn and replaced by the fresh medium and analysed by 2,6-dichlorophenolindophenol method (13).

Stability Testing: Selected samples were stored for 80 days at 47, 57 and 67°C, and under accelerated test conditions used to store the samples were 6 days at 25° and 79.5% relative humidity. The variations in temperature were ± 1°. All tablets were stored in the absence of light. The ascorbic acid concentrations were determined by the 2,6-dichlorophenolindophenol method (13).

RESULTS AND DISCUSSION

Stability studies conducted on the products, after storing at 79.5% RH/25±1°C for 6 days, showed the maximum stability of the drug in the formulations made either with stearic acid (H-J), or with microcapsules (K), or commercially coated ascorbic acid (L) while the others exhibited deterioration of 22-35% w/w ascorbic acid content. An apparent first-order decomposition rate constant (k) calculated from the slope of the linear data on a log of concentration-versus-time plot (Fig.1) for the selected products was, J & L, $6x10^{-3}$; A, $2x10^{-2}$ and G, $5.4x10^{-2}$ day^{-1}. The presence of hydrophilic polythylene glycol in the latter (G, $t_{\frac{1}{2}}$ = 12.8 day) may be attributed to enhanced hydrolytic degradation of ascorbic acid when compared to others (J, $t_{\frac{1}{2}}$=115.5 days determined by the rates of 0.693 and k). The magnitude of the catalytic effect of Zn^{+2} on the oxidation of the drug, however, is dependent on the water binding capacity.

Results (Table 2) of the stability studies on all the formulations after storage at 47,57 and 67±1°C (except formulations

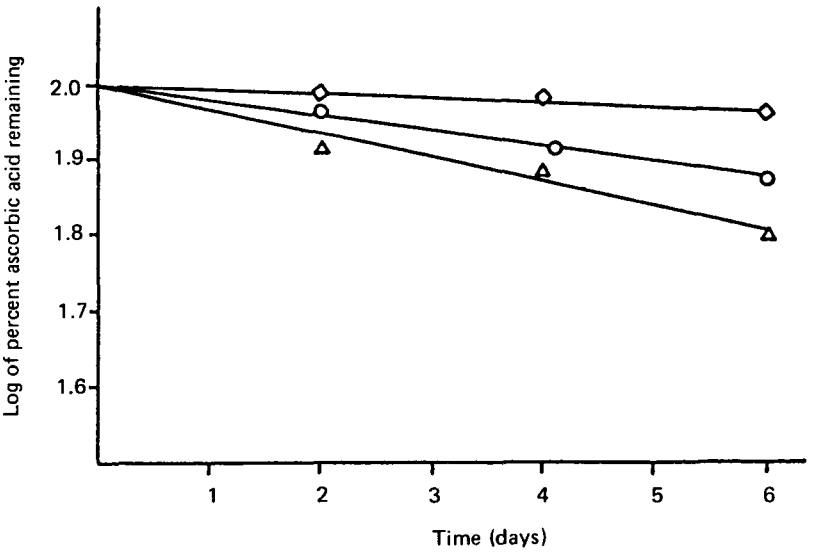

FIGURE 1

Log of per cent ascorbic acid remaining versus time of tablet formulations under 79.5% R.H. at 25±1°C storage; A, O—O; G, Δ—Δ ; J&L, □—□ .

TABLE 2

Per cent of Ascorbic Acid in Tablets Stored for 80 Days at Different Temperatures (°)±1°C

Formulation	47°	57°	67°	Formulation	47°	57°	67°
A	100.00	98.0	96.0	B	97.3	95.32	95.31
C	97.0	96.74	96.6	D	98.0	98.68	98.12
E	98.45	98.11	98.0	F	93.45	91.41	86.6
G	94.56	93.36	83.26	H	99.0	-	-
I	99.21	-	-	J	99.34	-	-
K	-	97.91	97.31	L	99.7	98.0	97.42
M	97.41	95.42	94.21				

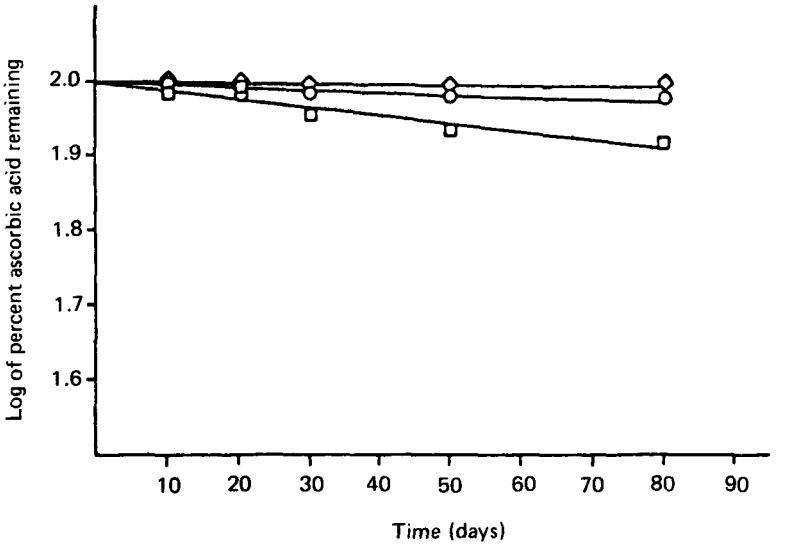

FIGURE 2

Log of percent ascorbic acid remaining versus time of tablet formulations under 67±1°c storage; A and M, O——O; D, ◇—◇; G, □—□ .

H-J) for 80 days showed that the presence of Zn^{+2} in the tablets (moisture content < 2.8% w/w) did not promote the degradation of ascorbic acid even at high temperature (67°) storage conditions (Fig 2). The decomposition rate constants at 67±1°C for selective products, A, 1.43×10^{-4}; D, 6.22×10^{-4}; G, 1.5×10^{-3} and M, 1.0×10^{-4} day^{-1} also showed that the stability of the drug in the products containing Zn^{+2} ion was comparable to that of having no zinc salt (M) indicating the decomposition is not affected by Zn^{+2} present in the tablets. Various workers (10,15) also reported that Zn^{+2} had least catalytic degradative property on the oxidation of the drug as compared to Cu^{+2} and Fe^{+2} in solutions.

Although all the tablets were white and waxy in appearance, those containing stearic acid (➢ 15%) or PEG (≥10%) showed sticking problems during compression. All the products conformed to

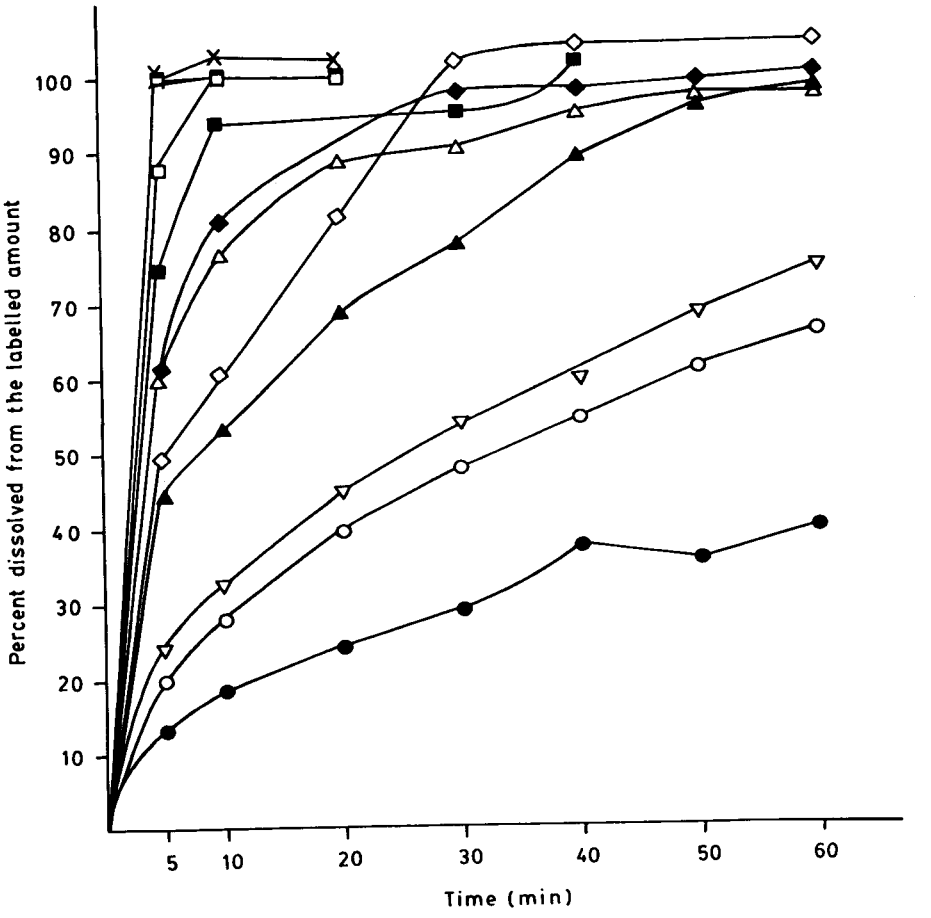

FIGURE 3

Dissolution rate profiles for the different formulations of ascorbic acid with zinc sulphate tablets.

A & B, ; C, ; D,

E, ; F, ; G,

H, ; I, ; J,

K, ; L, ; M,

compendial standards and had a disintegration time in the range from 0.25 - 3.0 min except products I and J where it was 20 and 30 min, respectively. Fig.3 shows that the time for the drug release ($t_{50\%}$ and $t_{90\%}$) from the tablets except those with stearic acid was less than 9 and 60 min, respectively while from the latter (H-J) in 60 min only 39.37 to 74.5% of the drug was released. However $t_{50\%}$ for the product H was 25.64 min.

It is concluded that the tablets of ascorbic acid with zinc sulphate possessing longer shelf-life can be made by utilizing one of the above mentioned techniques if the moisture content is controlled. The variation in drug release from the tablets, however, restricts the use of stearic acid at higher concentrations for embedding the drug.

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