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STABILITY OF AMINOPHYLLINE

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ABSTRACT

The stability of aminophylline was studied in the presence of four tablet excipients (cellulose, math, glucose and lactase) and nine intravenous fluids (inter for injection, dextrose. 10%, normal saline, dextrose normal saline 5%, Rugger lactate, Ringer, aminoplasmal 5%, apofuadin 10%, total parenteral nutrition solution TINS). Tea percent mixtures of the powder drug with the excipients were kept at 5°C, room temperature (27± 3°C), 4S °C and in direct sunlight for 30 days The degradation of the drug incrusts with increase in temperature and on spouse to sunlight. The degradation is puticsla4 intense in the presence of glucose sad lactose and change in colour from whim to yellow occurs in such mixtures. At 45 °C and in sunlight both pure drug and its mixtures change colour dining the storage period. In intravenous fluids, the drug (1 g/L) is stable and physically compatible for 2 days at 5°C, 27±3°C and 45 °C except in lipofundin 10% and TPNS ahem the drug is stable for only 12 hours at 45°C Yellow tinge appears in the admixture contains dextrose after 2 days at room temperature and at 45°C.

INTRODUCTION

Aminophylline is a salt of theophylline and ethylenediamine. It has a number of pharmacological actions including bronchodilation, central nervous system stimulation, myocardial stimulation and diuresis. The dosage forms of the drug include tablets, oral solution and injections (Swinyard, 1985; Rall, 1985). Aminophylline can be assayed by chemical methods (B.P., 1988; *U.S.P., 1975)* and instrumental methods (Elasyed *et al*, 1979; Cotgreave and Caldwell, 1983; Soviar *et al*, 1984).

In moist air, aminophylline powder gradually loses ethylenediamine and absorbs carbon dioxide with the liberation of theophylline (Martindale, 1989). Poor and Magdolanad (1980) studied the stability of aminophylline. They found that light (especially in the presence of oxygen and high pH) stimulates the degradation of aminophyline tablets and solutions. The photostability of the drug was studied by Ishiguro *et al. (1980).* According to this study, photooxidation results in the formation of 1,3 dimethyl allantoin, N,N'-dimethyl oxamide and ammonia as main degradation products. Aminophylline suppositories on storage decompose resulting in the formation of monoamides and diamides of *athylenediamine.* After 60 weeks, there was a marked decease in ethylenediamine contents of suppositories (Vandopic and Smith, 1981). The stability of aminophylline injection was studied in three parcateralnutrition solutions by Niemicc *et al* (1983). Aminophylline was stable for up to two days at room

temperature and ordinary room light. Parker (1970) showed that aminophylline dextrose admixture was stable for two days over a pH range of 3.5 to 8.6.

In the present study, the stability of aminophylline was studied in the presence of tablet excipients cellulose, glucose, lactose and starch. The aim was to study the effect of temperature and sunlight on the aminophylline mixtures. The effect of nine intravenous (I/V) fluids on the storage stability of the drug at various temperatures was also studied.

MATERIALS AND METHODS

The chemicals were of Alt. grade. CPOrdnv, glucose, lactose and aminophyflice $(C_7H_8N_4O_2)_2$. $C_2H_4(NH_2)_2$. $2H_2O$ were of B.P. grade. Dextrose infusion 10%, normal saline, aminoplasmal 5% (amino acid solution), lipofundin 10% (fat solution), Ringer infusion, Ringer lactate were obtained from B. Braun, West Germany. Dextrose normal saline 5% was from Otsuka Pharmaceutical Co. Ltd., Japan and water for injection was from Orient Lab. Lahore. Total parenteral nutrition solution TPNS was made by mixing aminoplasmal 5%, lipofundin 10% and dextrose 10% in the ratio of 2:3:5.

(a) Powder Mixtures

Ten percent aminophylline powder mixtures were formed with cellulose, glucose, lactose and starch. These were kept under the following conditions:

(i) Refrigerator 5°C,
(ii) Room temperature 27±3°C,
(iii) Oven 45°C
and (iv) Direct sunlight

Pure aminophylline and its powder mixtures were placed in two well stoppered amber coloured glass bottles at the above mentioned temperatures and in direct sunlight for 30 days. In the latter case, samples were also placed in two colourless well stoppered glass bottle.

(b) Parenteral Fluids

Ten grams of aminophylline was dissolved in distilled water and made up the volume to one litre by distilled water. This stock solution was kept in the dar.

Ten millilitre of the stock solution was diluted to 110 ml by Í/V fluids and two amber coloured glass bottles containing each admixture and Í/V fluids were kept at 5°C, room temperature and at 45°C for three days.

(c) Aminophylline Assay

Aminophylline has a wavelength of maximum absorbance at 275 nm in N/100 NaOH (Beckett and Stenlake, 1986). Beer's law was linear in the concentration range 0.5-10ug/ml (See Fig. 1).

Powder mixture or admixture equivalent to 80 mg of aminoplylline was weighed accurately and dissolved in 200 ml N/100 NaOH. 5m1 of this solution was diluted to 250 ml with N/100 NaOH. Aborbance was measured at 275 nm in 1 cm quartz cell against N/100 NaOH as blank using Hitachi UV-Visible Spectrophotometer Model 2000U. Aminophylline contents were calculated from Beer's law plot. The % recovery was found by the formula

$$\%\text{Recovery} = \frac{\text{Amount Found}}{\text{Amount taken}} \times 100 = \frac{\mu g/ml\ \text{Found}}{8 \mu g/ml} \times 100$$

RESULTS AND DISCUSSION

The results of stability studies of pure aminophylline and as 10% powder mixture with an excipient are presented in Table 1. The drug appears to be stable at 5°C and at room temperature during the storage period of 30 days. However, about 10% drug is lost in the presence of glucose and lactose at these temperatures. Higher temperature i.e. 45°C causes considerable degradation and the loss of aminophylline is about 6% in the presence and absence of cellulose and starch during the storage period. During the same period at 45°C in presence of glucose and lactase about 15% drug is lost. The change of colour from white to yellow (a sign of physical incompatability) occurs in mixtures with glucose and lactose at all temperatures. At 45°C, colour change takes place in all mixtures and in pure aminophylline during the storage period. From the results it appears that the drug should be stored at lower temperatures such as room temperature and glucose and lactose should not be used as excipients during the manufacture of aminophylline tablets.

The effect of sunlight (average temperature 38°C) on aminophylline and as 10% powder mixture with an excipient was studied. A typical set of results is shown in Table 2. The loss of drug was found to be almost same in amber and colourless glass *bottles.* On the basis of the results, it is suggested that probably the spectral region involved in the degradation of the drug is other than UV region (250-400 nm). On exposure to swdlgbt, the colour change occurs in pure aminophylliae and its powder mixtures during the storage period. Therefore, aminophylline should be protected from sunlight and this is also suggested by British Pharmacopoeia (1988). Farther degradation of aminophylline was more in mixtures with glucose and lactose.

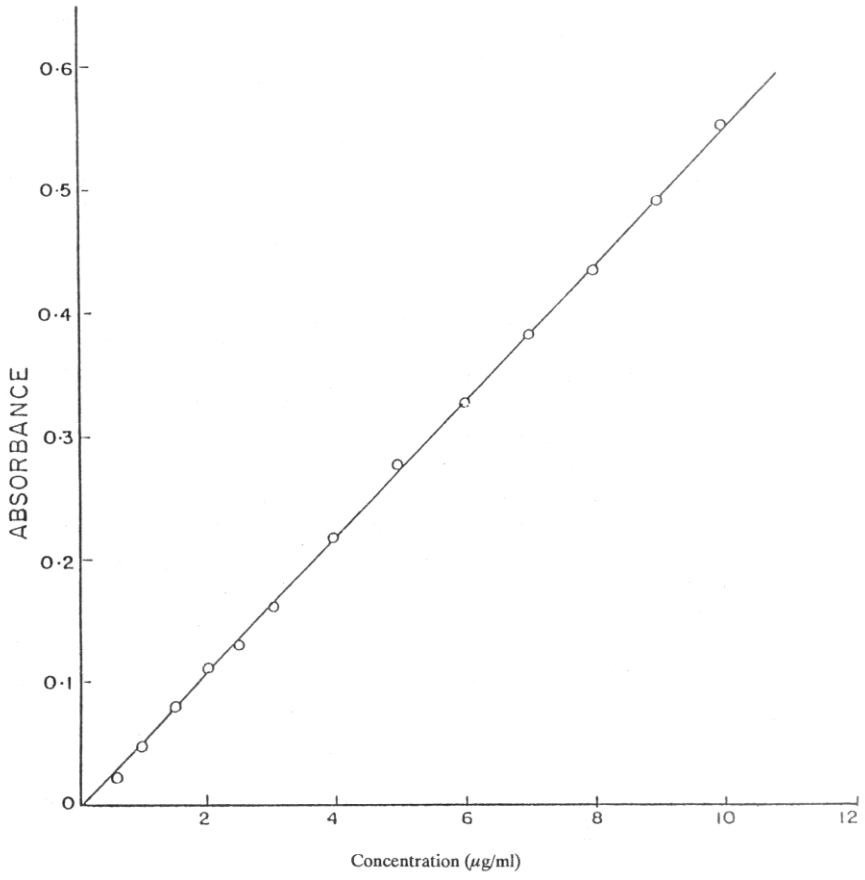
ABSORBANCE
0·6
0·5
0·4
0·3
0·2
0·1
0
2
4
6
8
10
12
Concentration (μg/ml)

Table 1

Percentage recovery* of aminophylline powder in the presence of excipients at different temperatures

Storage time (days)	Pure Am.			Am. with Cellulose			Am. with Starch			Am. with Cellulose			Am. with Lactose		
	RF	RT	HT	RF	RT	HT	RF	RT	HT	RF	RT	HT	RF	RT	HT
0.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0
1.5	100.0	100.0	99.8	100.0	100.0	99.8	100.0	100.0	99.8	100.0	99.8	99.5	100.0	99.5	99.4
3.5	100.0	100.0	99.6	100.0	100.0	99.6	100.0	100.0	99.6	100.0	99.6	98.9	99.8	99.3	98.6
6.5	100.0	100.0	99.3	100.0	100.0	98.9	100.0	100.0	99.0	100.0	99.0	98.0	98.9	98.0	98.2
12.5	100.0	100.0	98.6	100.0	100.0	98.4	100.0	100.0	98.0	99.8	95.0	97.0	98.3	97.4	96.3
24.5	100.0	100.0	97.1	100.0	100.0	96.7	100.0	100.0	96.3	98.3	93.4	91.4	95.4	94.5	92.3
30.0	100.0	100.0	95.3	100.0	100.0	94.4	100.0	100.0	94.3	95.3	89.9	86.5	93.6	89.6	84.6

*Average of two samples; RF = 5°C, RT = 27±3°C, HT = 45°C; Am. Aminophylline

Table 2

Percentage recovery* of aminophylline in the presence of excipients in sun-light (Average temperature 38°C)

Storage Time (Days)	Pure Am.	Am. with Cellulose	Am. with Starch	Am. with Glucose	Am. with Lactose
0.0	100.0	100.0	100.0	100.0	100.0
3.5	99.0	99.0	99.0	98.6	98.4
6.5	98.4	98.4	98.4	97.3	96.8
20.5	95.5	95.3	95.2	90.3	89.0
24.5	94.5	94.2	94.2	88.9	87.3
30.0	89.6	88.2	88.3	84.2	81.9
30.0+	89.9	89.2	88.9	84.9	81.9

*Average of two samples; + In colourless glass bottles; Am. Aminophylline

Table 3

Stability study of aminophylline in water for injection, 10% dextrose, normal saline and 5% dextrose normal saline

Storage time (hours)	Water for Inj. Admix.		10% Dextrose Admix.		Normal Saline Admix.		5% Dextrose/Normal Saline	
	pH	% recovery*	pH	% recovery*	pH	% recovery*	pH	% recovery*
0-72	5.84		3.52		6.10		5.40	
		At 5°C						
0	8.45	100.0	7.52	100.0	9.10	100.0	8.45	100.0
12	"	100.0	"	.	"	100.0	"	100.0
24	"	100.0	"	.	"	100.0	"	100.0
48	"	100.0	"	.	"	100.0	"	100.0
72	"	100.0	"	100.0	"	99.8	"	99.8
		At 27±3°C						
12	8.45	100.0	7.52	100.0	9.10	100.0	8.45	100.0
24	"	100.0	"	100.0	"	100.0	"	100.0
48	"	100.0	"	99.8	"	99.8	"	100.0
72	"	99.3	"	99.5	"	99.7	"	99.5
		At 45°C						
12	8.45	100.0	7.52	100.0	9.10	100.0	8.45	100.0
24	"	99.8	"	99.8	"	100.0	"	100.0
48	"	99.3	"	99.5	"	99.8	"	99.7
72	"	98.9	"	99.3	"	99.5	"	99.1

* = Without aminophylline + = average of two samples

Table 4

Stability study of aminophylline in ringer lactate, ringer, 5% aminoplasmal, 10% lipofundin and TPNS

Storage time (hours)	Ringer Lactate		Ringer		5% Aminoplasmal		10% lipofundin		TPNS	
	pH	% recovery*	pH	% recovery*	pH	% recovery*	pH	% recovery*	pH	% recovery*
0-72*	6.56		6.10		6.45		5.65		5.35	
		At 5°C								
0	8.77	100.0	9.48	100.0	8.99	100.0	7.95	100.0	6.16	100.0
12	"	100.0	"	100.0	"	100.0	"	100.0	"	99.5
24	"	100.0	"	100.0	"	100.0	"	98.9	"	98.9
48	"	100.0	"	100.0	"	99.7	"	98.9	"	98.8
72	"	99.8	"	99.7	"	99.7	"	98.8	"	97.1
		At 27±3°C								
12	8.77	100.0	9.48	100.0	8.99	100.0	7.95	98.9	6.16	99.0
24	"	100.0	"	100.0	"	99.7	"	98.9	"	98.9
48	"	100.0	"	100.0	"	99.7	"	98.9	"	98.8
72	"	99.8	"	99.7	"	99.5	"	95.4	"	97.2
		At 45°C								
12	8.77	100.0	9.48	100.0	8.99	100.0	7.95	98.9	6.16	98.9
24	"	100.0	"	100.0	"	99.7	"	97.1	"	97.2
48	"	99.8	"	100.00	"	99.5	"	95.4	"	95.4
72	"	99.5	"	99.7	"	99.3	"	93.6	"	93.6

* I/V fluid without aminophylline; + average of two samples

(See also Table 1) and about 15 % drug is lost in such cases and about 10% in the presence and absence of cellulose and starch during the storage period of 30 days.

The data regarding aminophylline stability in nine I/V fluids are presented in Table 3-4. All the admixtures (solutions) containing 1 g/L aminophylline remain clear and their pH remains unchanged during the storage period of 72 hours. The drug is stable in water for injection, 10% dextrose, normal saline, dextrose normal saline, Ringer 'attar, and Ringer for 2 days at 5°C, 27±3 and 45°C. Yellow tinge appears in the admixtures containing dextrose after 48 hours at room temperature and 45°C. This occurs probably due to slight decomposition of dextrose. The present work confirms the previous study in which it was shown that aminophylline 750 mg/L in 5% dextrose was stable for 2 days at 25°C (Boddapati *et al*, 1982). In another study it was shown that aminophylline in concentration of 450 mg/L was stable for 2 days over pH range 3.5-8.6 (Parker, 1970). In lipofundin 10% and TPNS admixtures, the drug is stable for 48, 48, and 12 hours at 5, 27±3 and 45°C respectively. The higher temperature of 45°C causes instability even in 2 days. This study also confirms a previous study in which aminophylline was shown to be physically compatible and chemical stable for at least 24 hours at 4°C and 25°C (Niemiec *et a1*.,1983) in three different parenteral nutrition fluids.

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