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Antibiotic granules for reconstitution as syrups: product uniformity and stability dependent upon reconstitution procedure

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Summary

The penicillin content and stability of diluted antibiotic syrups, prepared according to the manufacturers' recommendations and other, non-approved, methods have been investigated. Methods which involve portioning the granules before reconstitution are hazardous and may result in preparations which range from very little antibiotic content to a double strength preparation. The choice of diluent controls the stability of the preparation. Phenoxymethylpenicillin syrups become less stable as the sucrose content increases. This is not always true with ampicillin syrups where the system is more complex. Although syrups prepared according to the manufacturers' instructions are not always the most stable, the effect of different diluents on the stability of syrups, especially suspensions, suggests that syrups should always be reconstituted and diluted according to the directions provided with the product.

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Introduction

Oral liquid penicillin formulations are widely prescribed as a means of increasing patient acceptability. Penicillins are generally too labile for an adequate shelf-life to be assigned to a liquid preparation by a manufacturer. Such preparations are formulated as granules for reconstitution, incorporate a sugar base (usually sucrose) and require the addition of a fixed volume of water. The reconstituted syrup may be in the form of a solution, e.g. phenoxymethylpenicillin (penicillin V), or a suspension, e.g. ampicillin. A 7- or 14-day expiry date is normal on such preparations.

The stability profile of penicillins (Hou and Poole, 1971; Blaha et al., 1976; Bundgaard, 1980; Baltzer et al., 1979; Irwin et al., 1984a, b and c) is influenced by pH, buffer salts, buffer concentration, ionic strength (Tsuji et al., 1978; Hou and Poole, 1969a and b; Tomlinson et al., 1980; Finholt et al., 1968) carbohydrates (Simberkoff et al., 1970; Lynn, 1972; Hem et al., 1973; Bundgaard and Larsen, 1978a and b; Landersjo et al., 1977) and solubility (when suspensions are formulated). The excipients in the granules thus have a profound effect on the stability of the reconstituted preparation, although the shelf-life of well-formulated products is satisfactory (Jaffe et al., 1976; Allen and Lo, 1979; Grogon et al., 1979; Kitazawa et al., 1976; Hempenstall et al., 1983). These studies, however, assume that the product is dispensed in accordance with the manufacturers' recommendations. When dilutions of products are required, there is scope for procedural variations. These may lead to an incorrect composition of the vehicle, causing possible stability problems, or, in extreme cases, the antibiotic content of the preparation may vary widely from that required.

To study these problems we have examined the drug content and stability of phenoxymethylpenicillin and ampicillin syrups, prepared by different procedures from commercial granules.

Materials and methods

Antibiotic granules

Two brands of phenoxymethylpenicillin granules (PVA and PVB) and three brands of ampicillin granules (AMC, AMD and AME), all with a labelled penicillin content of 125 mg per 5 ml when reconstituted, were purchased. The unreconstituted granules were separated into two fractions of equal weight. Each half was then reconstituted to 100 ml by adding the appropriate diluent. The volume of the diluent was calculated as follows:

Water:	$x + 0.5\,(100 - x)$ ml	(1)
Water:syrup:	0.5x ml of water and 50 ml of Syrup B.P.	(2)
Syrup:	$x + 0.5\,(100 - x)$ ml	(3)

where x is the volume of water added to the preparation to produce 100 ml of a full-strength preparation, following the manufacturers' instructions.

Syrups containing 62.5 mg per 5 ml phenoxymethylpenicillin and 125 mg per 5 ml (ampicillin) were diluted as recommended by the manufacturer and were used as controls.

High-performance liquid chromatography

Chromatography was undertaken with a system constructed from an Altex 100A constant-flow solvent metering pump, a Rheodyne 7120 injection valve fitted with a 20-μl loop, a Shandon column (10 cm $\times$ 4.6 mm i.d.) packed with Hypersil-ODS (5 μm) and a Pye LC3 variable wavelength UV monitor.

Phenoxymethylpenicillin was chromatographed with a mobile phase consisting of 28% acetonitrile in a pH 6 phosphate buffer (1.32 g $Na_2HPO_4 \cdot 2H_2O$ and 8.07 g KH_2PO_4 per litre) delivered at 1 ml/min under a pressure of approximately 600 p.s.i. Detection was at 271 nm (0.16 AUFS) and retention times of 2.2 min (phenoxymethylpenicillin) and 3.6 min (phenol) were obtained.

Ampicillin was chromatographed with a mobile phase consisting of 10% acetonitrile in the pH 6 phosphate buffer delivered at 1 ml/min under a pressure of 800 p.s.i. Detection was at 250 nm (0.08 AUFS) and retention times of 3.5 min (ampicillin) 4.6 min (caffeine) were obtained.

Analyses

Approximately 1 g of syrup, accurately weighed, was transferred to a volumetric flask (25 ml). Internal standard (5 ml) was pipetted into the flask and water was added to volume. 20 μl of this solution was rapidly injected onto the HPLC column. The internal standards were:

phenoxymethylpenicillin —phenol (0.5 mg/ml) in water
ampicillin —caffeine citrate (0.5 mg/ml) in water.

Quantification was achieved by interpolation onto calibration lines prepared from standards of the penicillins.

The stability of the syrups was assessed by storage at 25°C and measurement of the residual concentration of penicillin over a period of time. The ampicillin preparations were shaken occasionally to improve the homogeneity of the suspension.

The concentration of ampicillin in solution in the supernatant liquid was also determined. A homogeneous sample was centrifuged at 3000 rpm for 30 min, the solution filtered through a millipore filter (0.8 μm) and the filtrate (approximately 1 g) assayed as before. pH values were measured at 25°C using a Radiometer (Copenhagen) PHM 64 Research pH meter.

Calculations

First-order rate data were analyzed using:

$$C_t = C_0 \cdot \exp(-k_1 \cdot t)$$

$$t_{10\%} = 0.1054/k_1$$

$$\text{shelf-life} = \frac{\ln(C_0/11.25)}{k_1}$$

where C_0 is the initial concentration (mg/ml) of penicillin; C_t is the concentration at time t (h); k_1 is the first-order degradation rate constant (h^{-1}).

Zero-order rate data were analyzed using:

$$C_t = C_0 - k_0 \cdot t$$

$$t_{10\%} = C_0/10 \cdot k_0$$

$$\text{shelf-life} = (C_0 - 11.25)/k_0$$

where C_0 is the initial concentration (mg/ml) of penicillin; C_t is the concentration at time t (h); k_0 is the zero-order degradation rate constant ($mg \cdot ml^{-1} \cdot h^{-1}$).

Variation of degradation rates were analyzed using the Arrhenius equation

$$\ln k_T = \ln A - \frac{E}{RT}$$

where k_T is the degradation rate constant at a temperature of T (K); E is the activation energy (J/mol); and A is the pre-exponential factor (h^{-1}). Shelf-lives refer to the time taken for the concentration of penicillin to fall to 90% of the labelled claim unless otherwise noted.

Results and Discussion

Penicillin syrups are normally reconstituted by the addition of a measured volume of water, sufficient to produce 100 ml of the final preparation. Dilutions, to produce a half-strength preparation, should be made by the addition of equal volumes of Syrup BP to the full-strength product. An alternative procedure is to divide the granules into two lots, by weight or by eye, and to make the half-weight granules up to 100 ml. These half-strength preparations are not made to the manufacturers' specification and are only equivalent to the correctly made dilution if:

(a) the granules are homogenous so that the division of the contents produces two identical lots; and

(b) the correct diluent is used. This is not water (Eqn. 1), which produced a vehicle containing too little sucrose, nor Syrup BP (Eqn. 3) which gives a vehicle containing too much sucrose. The true diluent is a diluted form of Syrup BP, the composition of which depends upon the volume of water needed for reconstitution of the original granules and may be calculated from Eqn. 2.

Penicillin content of diluted syrups

Quantitative analysis of the syrups was undertaken by HPLC (Fig. 1). Table 1 contains typical results for the phenoxymethylpenicillin content of diluted syrups. These were prepared from the top and bottom portions of various batches of

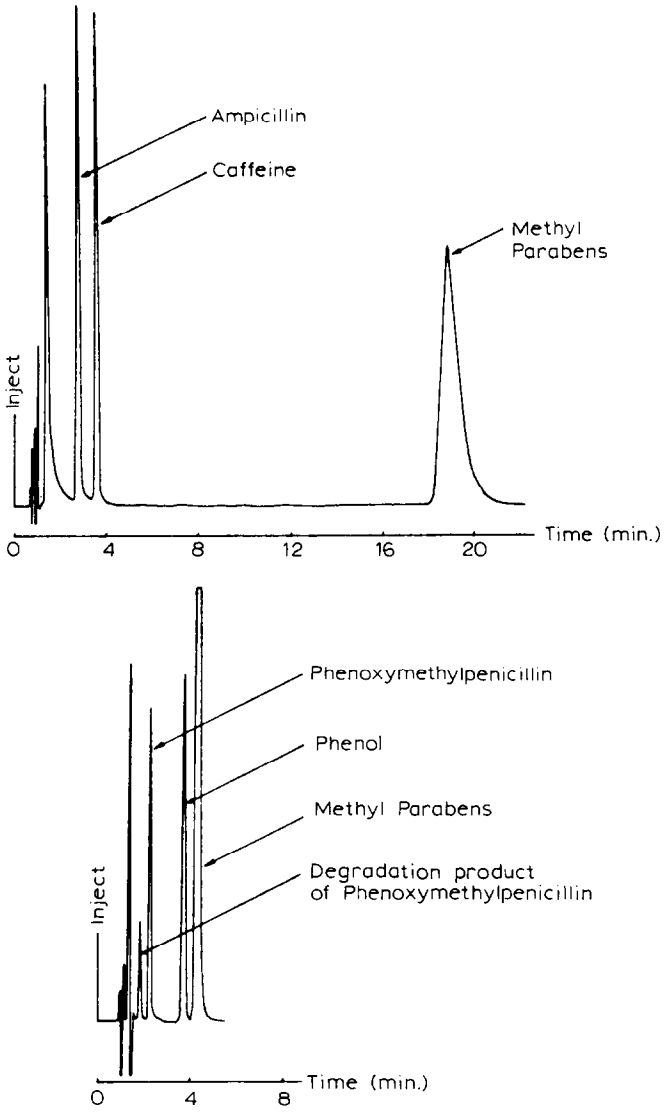

Fig. 1. HPLC of ampicillin and phenoxymethylpenicillin syrups.

granules, separated by weight, as may occur in general practice dispensing. All preparations are 1 : 1 dilutions of 125 mg/5 ml full-strength syrups and the values quoted are those found in a recommended 5-ml dose, nominally 62.5 mg.

It is apparent that significant segregation of the granule components has occurred. The extreme example is PVA-4 in which the syrup prepared from the top layer has 89.9% of the nominal penicillin content while that from the bottom layer contains 130.2% of expected level. The Pharmaceutical Codex (1979) refers to the B.P.C.

TABLE 1

PHENOXYMETHYLPENICILLIN CONTENT OF DILUTED SYRUPS PREPARED FROM TOP AND BOTTOM FRACTIONS OF GRANULES: PRODUCTS A AND B

Sample number	Concentration (mg/5 ml) of phenoxymethylpenicillin in syrup prepared from:		Percentage of labelled content (%)
	Top	Bottom	
PVA-1	61.1	77.7	110.0
PVA-2	67.3	68.2	108.4
PVA-3	62.3	70.4	106.2
PVA-4	56.2	81.4	110.1
PVA-5	68.4	72.7	112.9
PVA-6	69.7	73.1	114.2
Mean	64.2	73.9	110.5
CV (%)	8.09	6.56	2.65
CL	5.45	5.09	3.07
PVB-1	62.5	63.0	100.4
PVB-2	61.0	60.2	97.0
Mean	61.8	61.6	98.7
CV	1.72	3.21	2.44

CV, coefficient of variation; CL, 95% confidence limits.

(1973) for a standard concerning phenoxymethylpenicillin syrups, in which the content of total penicillins in the preparation should be 100–125% of the prescribed or stated concentration of phenoxymethylpenicillin. Assuming phenoxymethylpenicillin is the only penicillin present in the preparation, syrups PVA-1, PVA-3, PVA-4 (because of segregation of the penicillin in the granules) and PVB-2 (because of low penicillin content) fail this standard. Although the homogeneity of samples PVB-1 and PVB-2 was good, the lack of overage in the samples provides less tolerance of segregation.

Results from ampicillin syrups can be found in Table 2. The samples of product C that were analyzed in this study show a high degree of segregation of the antibiotic within the granules. This was so marked that in three cases (AMC-2, AMC-3 and AMC-6) almost all of the penicillin was located in one-half of the granules. Preparations made by an inappropriate method may thus contain almost no penicillin or up to double the recommended dose. The Pharmaceutical Codex (1979) refers to the B.P.C. (1973) for a standard concerning ampicillin syrups, in which the content of ampicillin in the preparation should be 90–120% of the prescribed or stated concentration. Syrups AMC-1, AMC-2, AMC-3, AMC-5, AMC-6, AMC-7, AMC-11, AMC-12 and AMC-13, when prepared by separation of the dry granules before reconstitution, do not conform to this requirement. The total ampicillin content in the whole syrup, however, is well within the required range. Ampicillin products D and E show no significant segregation of the penicillin and all comply with the official standard.

TABLE 2

AMPICILLIN CONTENT OF DILUTED SYRUPS PREPARED FROM TOP AND BOTTOM FRACTIONS OF GRANULES: PRODUCTS C, D AND E

Sample number	Concentration (mg/5 ml) of ampicillin in syrup prepared from:		Percentage of labelled content (%)
	Top	Bottom	
AMC-1	52.9	71.7	99.7
AMC-2	125.1	1.8	101.5
AMC-3	128.2	< 0.5	103.0
AMC-4	66.3	60.1	101.1
AMC-5	51.8	69.9	97.4
AMC-6	< 0.5	121.1	97.3
AMC-7	100.3	21.0	97.0
AMC-8	58.0	70.0	102.4
AMC-9	57.0	65.5	98.0
AMC-10	58.0	70.0	102.4
AMC-11	55.5	71.5	101.6
AMC-12	54.5	71.0	100.4
AMC-13	45.5	75.5	96.8
Mean	65.7	59.2	99.9
CV (%)	52.2	55.9	2.31
CL	20.7	20.0	1.39
AMD-1	62.4	59.9	97.8
AMD-2	59.1	60.6	95.8
AMD-3	60.2	59.5	95.8
AMD-4	60.5	59.1	95.7
AMD-5	60.2	59.5	95.8
AMD-6	60.9	61.7	98.1
AMD-7	62.9	64.4	101.8
AMD-8	61.8	61.6	98.7
AMD-9	60.2	66.0	101.0
Mean	60.9	61.4	97.8
CV (%)	2.00	3.89	2.38
CL	0.94	1.84	1.79
AME-1	61.1	60.9	97.6
AME-2	61.1	65.2	101.0
mean	61.1	63.1	99.3
CV (%)	–	4.82	2.42

CV, coefficient of variation; CL, 95% confidence limits.

From the results for phenoxymethylpenicillin and ampicillin syrups presented above, it is clear that the practice of separation of the dry granules before reconstitution is to be deprecated.

TABLE 3

FIRST-ORDER DEGRADATION RATES OF DILUTED PHENOXYMETHYLPENICILLIN SYRUPS: PRODUCTS A AND B

Sample	Temp. (°C)	First-order rate constant ($h^{-1} \times 10^{-3}$) (± 95% CL) for syrup prepared with:			$t_{20\%}$ * (days)	Shelf-life * (days)	Initial pH
		Water	Water/ Syrup BP	Syrup BP			
PVA-1 (Top)	25	0.862 (0.144)			10.8	4.9	5.95
PVA-1 (Bot)	25	0.859 (0.097)			10.8	15.6	5.98
PVA-2 (Top)	25		1.067 (0.190)		8.7	7.2	5.92
PVA-2 (Bot)	25		1.130 (0.192)		8.2	7.1	5.91
PVA-3 (Top)	25			1.061 (0.140)	8.8	4.0	5.85
PVA-3 (Bot)	25			1.044 (0.095)	8.9	9.0	5.83
PVA-4 (Top)	40	3.481 (0.278)			2.7	0	5.55
PVA-4 (Bot)	40	3.458 (0.296)			2.7	4.5	5.54
PVA-5 (Top)	40		5.161 (0.187)		1.8	1.6	5.52
PVA-5 (Bot)	40		4.966 (0.215)		1.9	2.2	5.53
PVA-6 (Top)	40			5.490 (0.293)	1.7	1.6	–
PVA-6 (Bot)	40			5.449 (0.328)	1.7	2.0	–
PVB-1 (Top)	25	1.007 (0.057)			9.2	4.4	5.33
PVB-1 (Bot)	25	1.019 (0.093)			9.1	4.6	5.32
PVB-2 (Top)	25		1.203 (0.145)		7.7	2.8	5.20
PVB-2 (Bot)	25		1.183 (0.163)		7.9	2.4	5.16

* Time for phenoxymethylpenicillin content to fall to 80% of original value.
** Time for phenoxymethylpenicillin content to fall to 90% of labelled claim.

Penicillin stability in diluted syrups

The shelf-life is assigned to a reconstituted product on the assumption that reconstitution is in accordance with the manufacturers' directions. Diluted products may have a different stability profile due to the changes in concentrations of the excipients (buffers, ionic strength, sugars) and the effects may be enhanced by the diluent chosen (water, Syrup BP, diluted Syrup BP).

Phenoxymethylpenicillin

Table 3 records stability data for phenoxymethylpenicillin syrups prepared using three different diluents; and Table 4 contains comparative data from an undiluted commercial preparation containing 62.5 mg/5 ml of phenoxymethylpenicillin.

The B.P.C. standard for phenoxymethylpenicillin syrup states that, after 7 days storage at 15°C, the concentration of total penicillins in the stored syrup should not be less than 80% of the concentration found in the freshly prepared syrup. Using the Arrhenius parameters calculated for syrups PVA 9–11, in Table 4, a rate constant of 2.94×10^{-4} h^{-1} is obtained for storage at 15°C which represents a shelf-life of 31.6 days to reach 80% of the initial concentration.

This is well within the limits of the standard (7.0 days). Even at 25°C, the

TABLE 4

FIRST-ORDER DEGRADATION RATES OF UNDILUTED PHENOXYMETHYLPENICILLIN SYRUPS (62.5 mg/5 ml): PRODUCT A

Sample	Temp. (°C)	First-order rate constant ($h^{-1} \times 10^{-3}$) (±95% CL) for phenoxymethylpenicillin syrups prepared according manufact. instruct.	$t_{20\%}$ (days)	Shelf-life (days)	Initial pH
PVA-7 *	25	0.914 (±0.147)	10.2	9.0	5.92
PVA-8 *	40	4.612 (±0.277)	2.0	2.9	–
PVA-9 **	25	0.911 (±0.061)	10.2	8.6	5.73
PVA-10 **	40	4.032 (±0.289)	2.3	2.0	5.73
PVA-11 **	50	11.56 (±0.071)	0.8	0.8	5.80

* Batch 1; ** Batch 2—the rate constants for Batch 2 were used to calculate the energy of activation and frequency factor for this syrup: activation energy (E) = 80.9 kJ·mol^{-1}; frequency factor (A) = 1.354×10^{11} h^{-1}; correlation coefficient (r) = −0.999.

standard is complied with ($t_{20\%}$ = 10.2 days—Table 4). However, the choice of diluent for the syrups has a significant effect on the degradation rate of phenoxymethylpenicillin. Dilution with water (PVA-1) produces a slightly more stable syrup than the undiluted syrup (PVA-7 and -9), but using water/Syrup BP or Syrup BP increases the degradation rate (PVA-2 and -3). This trend is also seen at 40°C (PVA-4–6 and PVA-8 and -10). It is likely that this difference in stability is due to the level of sucrose in the diluted syrup. When water is used alone, the sucrose level is lower than that of the normal syrup, and this results in a more stable preparation. As the sucrose level increases, the stability decreases, although there is little difference between the syrups prepared with water/Syrup BP and Syrup BP. Recent work has shown that carbohydrates catalyze penicillin degradation by providing a reactive nucleophilic centre which attacks the β-lactam ring (Bundgaard, 1980). Syrups prepared from product B (Table 3) similarly indicate a more stable preparation is obtained if water is used as diluent rather than water/Syrup BP. Here, however, the degradation rates of the diluted syrups are greater than with product A. This is probably explained by the lower pH of the syrups made from product B.

Although diluent selection has been shown to affect the stability of the diluted

TABLE 5

EFFECT OF PHENOXYMETHYLPENICILLIN SEGREGATION ON THE INITIAL pH AND DEGRADATION RATE CONSTANT FOR SYRUP PVA-4

PVA-4	Initial conc. (mg/5 ml)	Initial pH	First-order rate constant ($h^{-1} \times 10^{-3}$)
Top	56.2	5.55	3.481
Bottom	81.4	5.54	3.458

TABLE 6

ZERO-ORDER DEGRADATION RATES OF DILUTED AMPICILLIN SYRUPS AT 25°C: PRODUCT D

Sample	Zero-order rate constant ($mg \cdot ml^{-1} \cdot h^{-1} \times 10^3$) for syrup prepared with diluent:		$t_{10\%}$ (days)	Shelf-life (days)	Initial pH
	Water	Water/Syrup BP			
AMD-6 (Top)	6.92		7.3	5.6	4.50
AMD-6 (Bot)	6.87		7.5	6.6	4.47
AMD-7 (Top)		4.37	12.0	12.7	4.58
AMD-7 (Bot)		4.65	11.5	14.6	4.59
AMD-8 (Top)*	7.57		6.8	6.1	4.42
AMD-8 (Bot)*	7.31		7.0	6.1	4.41
AMD-9 (Top)*		4.43	11.3	7.4	4.59
AMD-9 (Bot)*		5.07	10.8	16.0	4.59
AMD-10*	Control 6.45		16.0	15.0	4.44

* Ampicillin in solution and whole suspension determined.

syrups, none of the diluted syrups, whichever diluent is selected, fail to meet the B.P.C. (1973) standard on stability requirements. This is illustrated in Table 3, where the $t_{20\%} > 7$ days at 20°C for all the diluted syrups.

Segregation of phenoxymethylpenicillin in the dry powder had no significant effect on the degradation rate constant or the initial pH of the diluted syrups, in the samples studied, e.g. PVA-4 (Table 5).

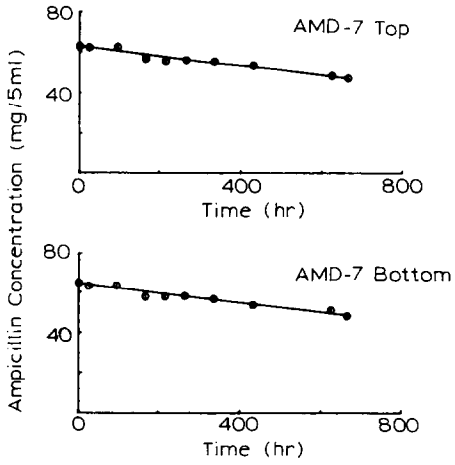

Fig. 2. Zero-order degradation rate profile of ampicillin syrup: Product D.

Ampicillin syrups

Stability data for ampicillin syrup product D indicated zero-order degradation profiles (Fig. 2). Pseudo-zero-order degradation is expected for ampicillin syrups because ampicillin (present as the trihydrate in product D) is not completely soluble in the syrup vehicle. Hence, when ampicillin degrades in solution, it is replaced by further dissolution of solid ampicillin which maintains a constant concentration of the penicillin in the vehicle. Degradation rates for product D diluted syrups (Table 6) show that using water rather than water/Syrup BP as diluent results in a preparation with increased degradation rate and decreased shelf-life.

The B.P.C. standard for ampicillin syrups states that after 7 days storage at 15°C, the concentration of ampicillin in the stored syrup is not less than 90% of the concentration found in the freshly prepared syrup. All of the diluted syrups in Table 6 comply with this standard at 25°C. The shelf-life ($t_{10\%}$) of the preparations was less than 7 days for this syrup diluted with water. Although the temperature of storage was higher than required in the B.P.C. standard, many medicines are stored at or above 25°C, despite cautionary labelling on the containers. Thus choice of diluent is important to the syrup's efficacy.

In contrast to product D, degradation profiles produced from product C were not linear (Fig. 3), suggesting that pseudo-zero-order degradation did not take place. Shelf-life and $t_{10\%}$ measurements were, therefore, made graphically rather than mathematically and results are presented in Table 7.

Syrup AMC-14 was included as a control in the degradation study. Ideally, a syrup of nominal concentration 62.5 mg/5 ml would have been used, but ampicillin syrups of this concentration were not available. Thus, a syrup of nominal concentration, 125 mg/5 ml, was reconstituted as recommended by the manufacturer and stored under the same conditions as the diluted syrups. From Table 7 the stability of diluted product C was totally inadequate for storage at 25°C, 10% of the original

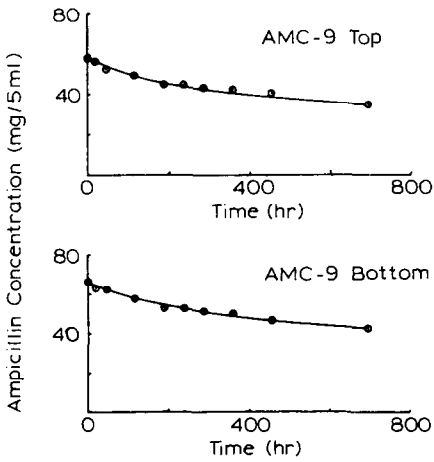

Fig. 3. Non-linear degradation profile of ampicillin syrup: Product C.

TABLE 7

DEGRADATION RATE ESTIMATES FOR DILUTED AMPICILLIN SYRUPS AT 25°C: PRODUCT C.

Sample	Diluent	$t_{10\%}$ (days)	Shelf-life (days)	Initial pH
AMC-8 (Top)	Water	2.3	0.5	5.58
AMC-8 (Bot)	Water	2.9	6.5	5.85
AMC-9 (Top)	Water/Syrup BP	2.0	0.0	5.95
AMC-9 (Bot)	Water/Syrup BP	2.4	5.4	5.92
AMC-14	Control	4.5	7.3	6.16
AMC-12 (Top)*	Water	2.0	0.0	5.98
AMC-12 (Bot)*	Water	2.1	5.1	6.00
AMC-13 (Top)*	Water/Syrup BP	2.2	0.0	6.04
AMC-13 (Bot)*	Water/Syrup BP	3.2	> 10.0	6.13

* Ampicillin in solution and whole suspension determined.

potency being lost in less than 3 days. Stability of the control (AMC-14) was higher although even this product lost 10% of its original potency in 4.5 days.

There was no significant difference in the degradation rates for ampicillin syrups diluted with water or water/Syrup BP ($t_{10\%}$ values). Shelf-life data was varied because of significant segregation of ampicillin in the dry powder before reconstitution (Table 2). Despite this obvious segregation, there was no significant difference between the pH of the two halves of the reconstituted syrup. The increased $t_{10\%}$ value for the control compared to the diluted syrups is probably explained by the increased concentration of ampicillin; a greater proportion of the antibiotic being present as solid in the suspension, hence less available for hydrolytic degradation.

In order to further evaluate the suspension systems, the above experiments were repeated on products C and D with the addition that the concentration of ampicillin in solution was also monitored. Results for product D are in Table 6 and Fig. 4. The pseudo-zero-order degradation rate constants and $t_{10\%}$ values for AMD-8 and AMD-9 were similar to those obtained previously for this product (Table 6). As expected, undiluted product D (AMD-10) had a larger $t_{10\%}$ value than the diluted syrups due to its increased ampicillin content. Shelf-life estimates for the two halves of AMD-9 were not the same because of segregation of ampicillin in the dry powder (Table 2). There was a significant difference between the supernatant concentration in the diluted syrups prepared with water (mean of 26.3 mg/5 ml) and water/Syrup BP (mean of 20.1 mg/5 ml). This partly explains why AMD-8 was less stable than AMD-9 (20.1 mg/5 ml), more ampicillin being in solution, therefore available in a higher concentration for hydrolytic breakdown.

The solubility of ampicillin trihydrate (the form of ampicillin in product D) in water is 35 mg/5 ml at 30°C (Austin et al. 1965) and 40 mg/5 ml at 37°C (Poole et al. 1968). Even allowing for the decreased storage temperature of AMD-8 and AMD-9, these values suggest the ampicillin supernatant concentrations in AMD-8

(26.6 mg/5 ml) and AMD-9 were lower than expected. However, it has been shown that buffer salt concentration affects the solubility of ampicillin (Hou and Poole, 1969b). Additionally, the presence of sucrose will decrease water activity and compound this effect. The difference in solubility between AMD-8 and AMD-9 was not due to pH (4.4 and 4.6, respectively).

Hou and Poole (1969b, 1971) stated that the stability of ampicillin in buffer solutions was highest at or near the isoelectric point, approximately pH 4.85. Earlier,

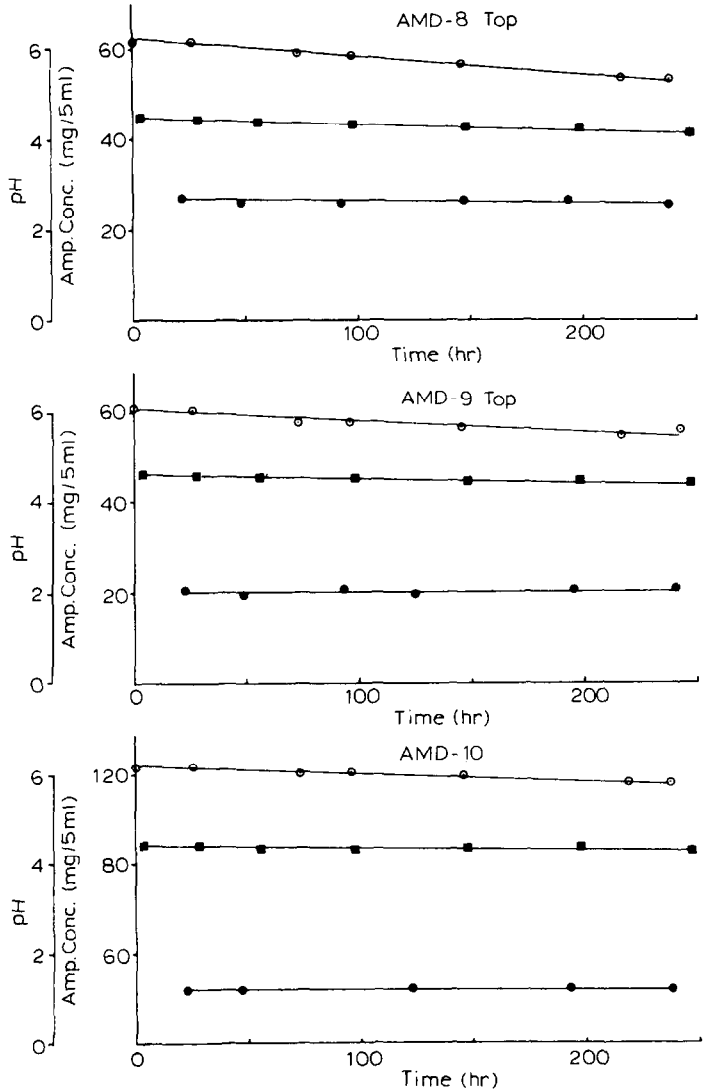

Fig. 4. Change in ampicillin concentration on storage of Product D at 25°C. (⊙, whole syrup; ●, supernatant; ■, pH).

Saccani and Pansera (1968) reported the apparent stability of ampicillin at 27°C in buffer solution to be greatest at pH 4.4. Thus the pH of minimum degradation for ampicillin in diluted syrups is probably 4.4–4.85. The initial pH of diluted product D ranged from 4.41 to 4.59, corresponding to values of maximum stability. During storage, the pH dropped slightly (Fig. 4) but this did not appear to have a significant effect on the rate of degradation.

Results for product C are in Table 7 and Fig. 5. The $t_{10\%}$ values for AMC-13 and AMC-13 were similar to those obtained previously (Table 7), the high value for AMC-13 (bottom) being explained by the high ampicillin concentration. Shelf-life data was varied because of significant segregation of ampicillin in the dry powder (Table 2). The supernatant concentrations in AMC-12 and AMC-13 were higher than in AMD-8 and AMD-9. This was due to 3 factors: (i) the form of ampicillin; (ii) pH (to a lesser extent); and (iii) the effect of excipients.

Ampicillin is present as the anhydrate in product C. The solubility of the anhydrate is 55 mg/5 ml at 30°C (Austin, 1965) and 50 mg/5 ml at 37°C (Poole et al., 1968), significantly higher than the trihydrate (product D). Hou and Poole

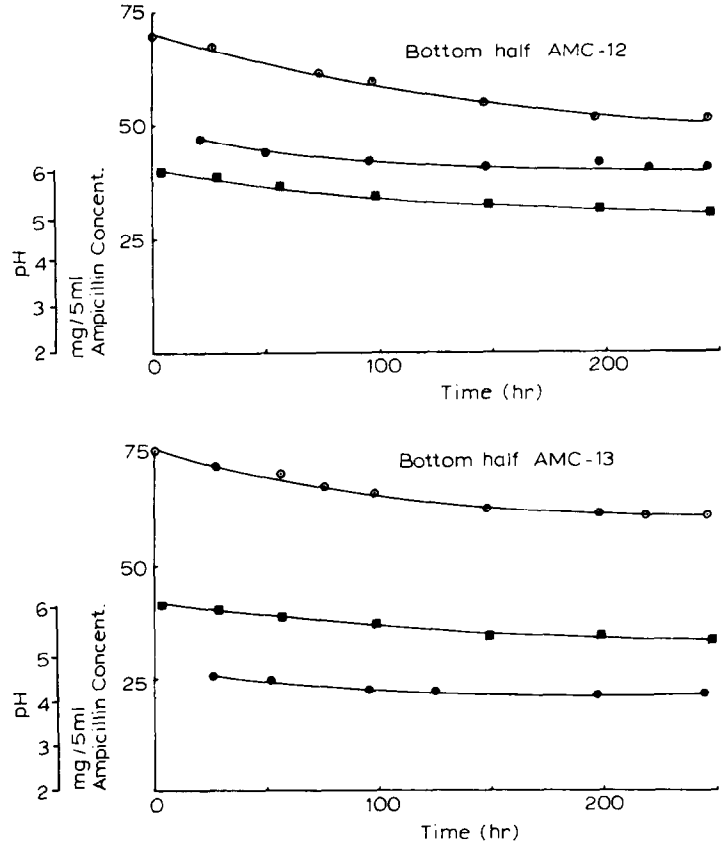

Fig. 5. Change in ampicillin concentration on storage of syrups AMC-12 and AMC-13 at 25°C. (⊙, whole syrup; ●, supernatant; ■, pH).

(1969b) found the minimum solubility of ampicillin occurred at pH 4.9, its isoelectric point, although there was little change in solubility between pH 4 and 6. The initial pH of product C was approximately 6.0, further away from the isoelectric point than product D (initial pH approximately 4.4). As with product D, excipients modify the solubility of ampicillin, illustrated by the difference in supernatant concentration between AMC-12 and AMC-13.

Unlike product D, the supernatant concentrations and the degradation rate constants of product C change with time (Fig. 5). This is due to the change in pH of product C with time. As the diluted syrups degrade, the pH approaches the isoelectric point. This causes: (a) the solubility of ampicillin to decrease; and (b) the stability of ampicillin to increase. These two effects combine to reduce the reaction rate as degradation proceeds and produce the observed profiles in Fig. 5.

Conclusions

The penicillin content and stability of diluted antibiotic syrups depended markedly upon the techniques used to prepare the syrups. When granules were portioned before reconstitution, variations in dosage ranging from almost no antibiotic to a double-strength preparation resulted. The stability of the product was also dependent upon the diluent used. Phenoxymethylpenicillin preparations became less stable when diluted with solutions containing a higher concentration of sugar. The effect of sugar content on the stability of ampicillin preparations was more complex, due to the system being a suspension rather than a solution. One product (product D) was found to be more stable when diluted with water/Syrup BP rather than water. However, the other product (product C) showed little difference in stability for syrups diluted with water or water/Syrup BP, all of the diluted preparations showing a very high rate of degradation at 25°C.

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