7. EXPERIMENTAL STUDY USING THE 'DOBBIN' AS THE "CARRIER"

The previous experiments provided a new matrix suitable for extended exposure to rumen mechanics in the form of paraffin wax, but the iron bar core boluses were not eroding sufficiently to release drug at a consistently high enough level to prevent the output of viable nematode eggs and produce effective vermicidal activity.

The following study was designed to monitor the rate of erosion using the 'Dobbin' as the "carrier" for a paraffin wax matrix.

7.1. Experimental data

Fourteen 'Dobbins' were loaded with a matrix of paraffin wax, iron powder and thiophanate in the ratio of 25 : 25 : 50 (Plate 18). The iron powder was added to increase the density and provide an abrasive surface.

PLATE 18 : PRE-DOSE LOADED 'DOBBINS'. Experiment 7.

All metal 'Dobbins' were used with the exception of one pair which consisted of metal rods with nylon flanges. The loaded 'Dobbin' weights ranged from 24.72 gms (metal rod-nylon flanges) to 35.38 gms (all metal) with average densities of 1.8 and 2.59 respectively.

One day following infection with a mixed suspension of larvae containing H.contortus, O.circumcincta, T.colubriformis and N.spathiger, 8 lambs were each dosed with two 'Dobbins'. Three lambs were retained as untreated, infected controls.

Faecal samples were collected at intervals throughout the experiment for assessment of nematode egg counts and egg viability and to monitor the excreted drug by the plate assay.

After the first rumenotomy to assess the erosion rate at 30, 33 or 36 days following dosing, the 'Dobbins' were replaced into the rumen for a further 40, 37 or 34 days respectively. At this first stage, one lamb, along with one control, was slaughtered to make a preliminary assessment of the anthelmintic activity. All the remaining lambs were killed at the end of the complete medication period of 70 days and a final assessment of the anthelmintic activity was made.

7.2. Results

One metal rod-nylon flanged 'Dobbin' was regurgitated 8 days after dosing having released 60 mg thiophanate per day while retained.

The drug release rates achieved from these 'Dobbins' are summarised in Table 27.

The amount of drug released dropped after the initial 30 day retention period in all cases. Each 'Dobbin' in the paired group exhibited an increased release rate, an average of 51.2 and 41.8 mg thiophanate per day over the 0 - 30 and 0 - 70 day periods respectively, compared to the single release rate of 18.75 and 17.05 mg over the same time scale.

TABLE 27 : Summary of the drug release rates achieved using the 'Dobbin' as the "carrier" for a paraffin wax matrix. Experiment 7.

Lamb No.	'Dobbin'		Recovery + 30/33/36 days				Recovery + 70 days				+ 30/33/36 - + 70 days		
	No.	Weight (gms)	Weight (gms)	Loss (gms)	Mg/day	Mg thiophanate per day	Weight (gms)	Loss (gms)	Mg/day	Mg thiophanate per day	Loss (gms)	Mg/day	Mg thiophanate per day
432	3	24.72	Regurgitated + 8 days*										
	5	24.92	22.99	1.93	58.5	29.2	22.06	2.86	40.8	20.4	0.93	25.1	12.6
152	6	35.04	31.91	3.13	94.8	47.4	29.50	5.54	79.1	39.6	2.41	65.1	32.6
	7	35.38	32.11	3.27	99.1	49.5	29.52	5.86	83.7	41.8	2.59	70.0	35.0
442	8	34.0	30.58	3.42	103.6	51.8	28.31	5.69	81.28	40.6	2.27	61.4	30.7
	9	33.57	29.86	3.71	112.4	56.2	27.48	6.09	87.0	43.5	2.38	64.3	32.1
248	10	33.74	29.92	3.82	106.1	53.1	Lamb killed						
	11	33.47	29.44	4.03	111.9	55.97							
363	12	33.91	30.77	3.14	95.1	47.6	27.92	5.99	85.57	42.8	2.85	77.0	38.5
	13	34.04	30.85	3.19	96.7	48.3	28.04	6.0	85.7	42.8	2.81	75.9	37.9
156	14	34.37	31.40	2.97	90.0	45.0	28.85	5.52	78.8	39.4	2.55	68.9	34.4
	16	34.11	** No results										
246	17	34.55	33.53	1.02	34.0	17.0	32.14	2.41	34.4	17.2	1.39	34.7	17.4
240	21	34.79	33.56	1.23	41.0	20.5	32.22	2.57	36.7	18.3	1.34	33.5	16.7

* Wt. = 23.76 gms. Loss = 0.96 gms. 120 mg per day 60 mg thiophanate per day.

** One flange separated, load lost, all 'Dobbin' parts recovered after first retention period. Empty 'Dobbin' replaced.

The lambs used in this trial ranged in bodyweight from 37.0 to 55.0 kg so the total daily dosage of thiophanate actually received ranged from 0.44 mg per kg for a single dosing to 2.63 mg per kg bodyweight for a pair over the first 30 days then dropping to an average of 0.4 and 1.7 mg per kg for the single and paired dosings respectively over the complete 70 day medication period. Plate 19 illustrates the difference in surface erosion caused by dosing in pairs.

The mean nematode faecal egg count (Fig.13) remained low in both treated groups (pairs and singles) throughout the medication period, the higher drug release rate from the paired 'Dobbins' being reflected in the lower egg count and a markedly lower egg hatch (Fig.14). Very little effect was apparent on the viability of the nematode eggs passed by the single 'Dobbin' treated sheep. This observation was verified by the plate assay results which did not detect drug in the majority of the faecal samples as the level was too low. Zones of drug activity were, however, measured from all the faecal samples collected from the paired treated sheep throughout the medication period, but the sizes were very erratic (Fig. 15).

The worm burdens at the end of the 70 day medication period are summarised in Table 28.

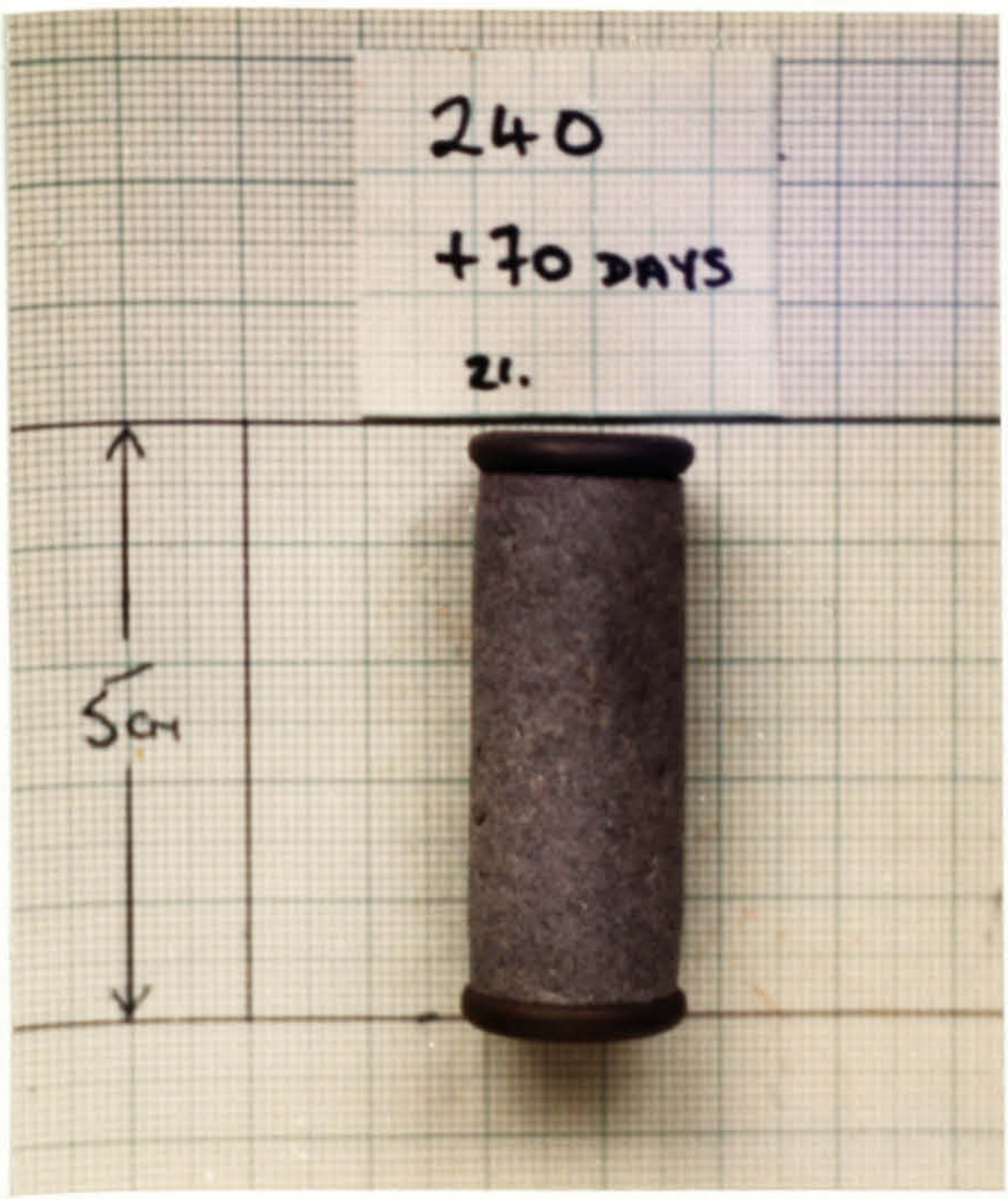
With the exception of lamb 156, a complete vermicidal effect was not achieved with the matrix tested, but a higher percentage worm reduction was apparent from the lambs treated with two 'Dobbins'. On microscopic examination of the remaining worms, ovaries were devoid of eggs in many females but no actual structural damage to the reproductive system was apparent.

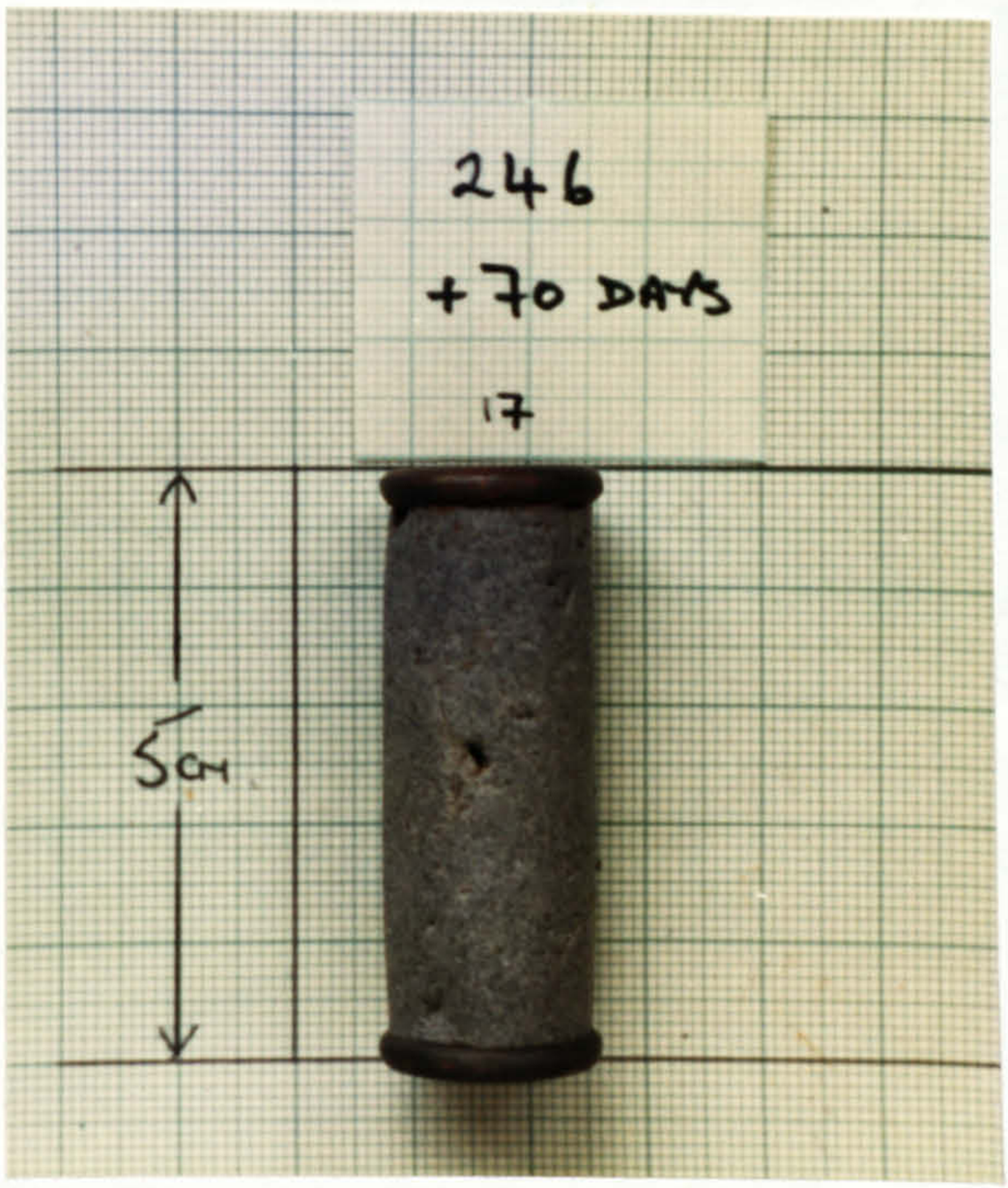
7.3. Discussion

A hundred per cent retention was achieved with the loaded, all metal 'Dobbin' but one of the metal rod-nylon flanged 'Dobbins' with

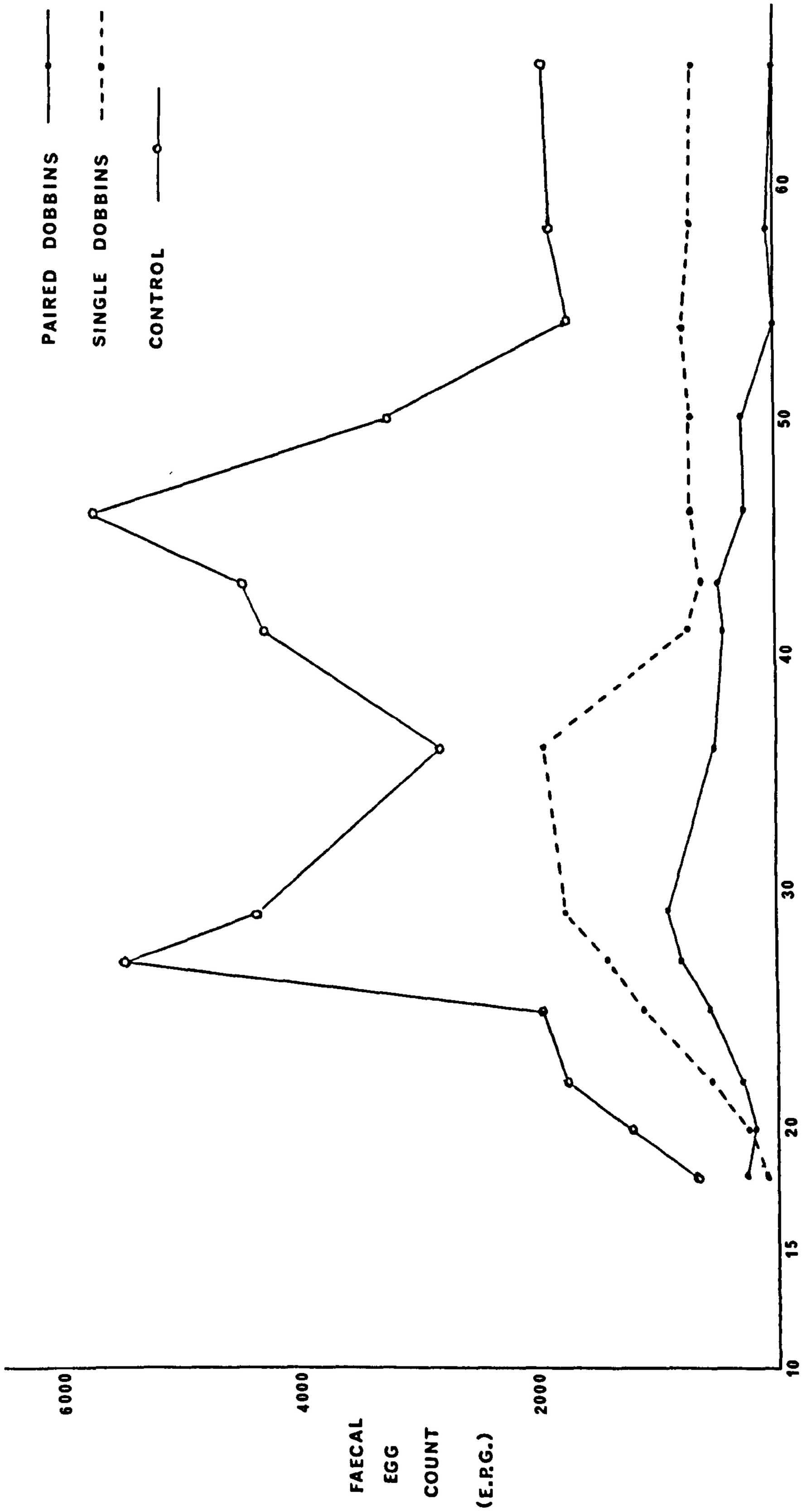
PLATE 19 : 'DOBBIN' RECOVERY. Experiment 7

Single treatment





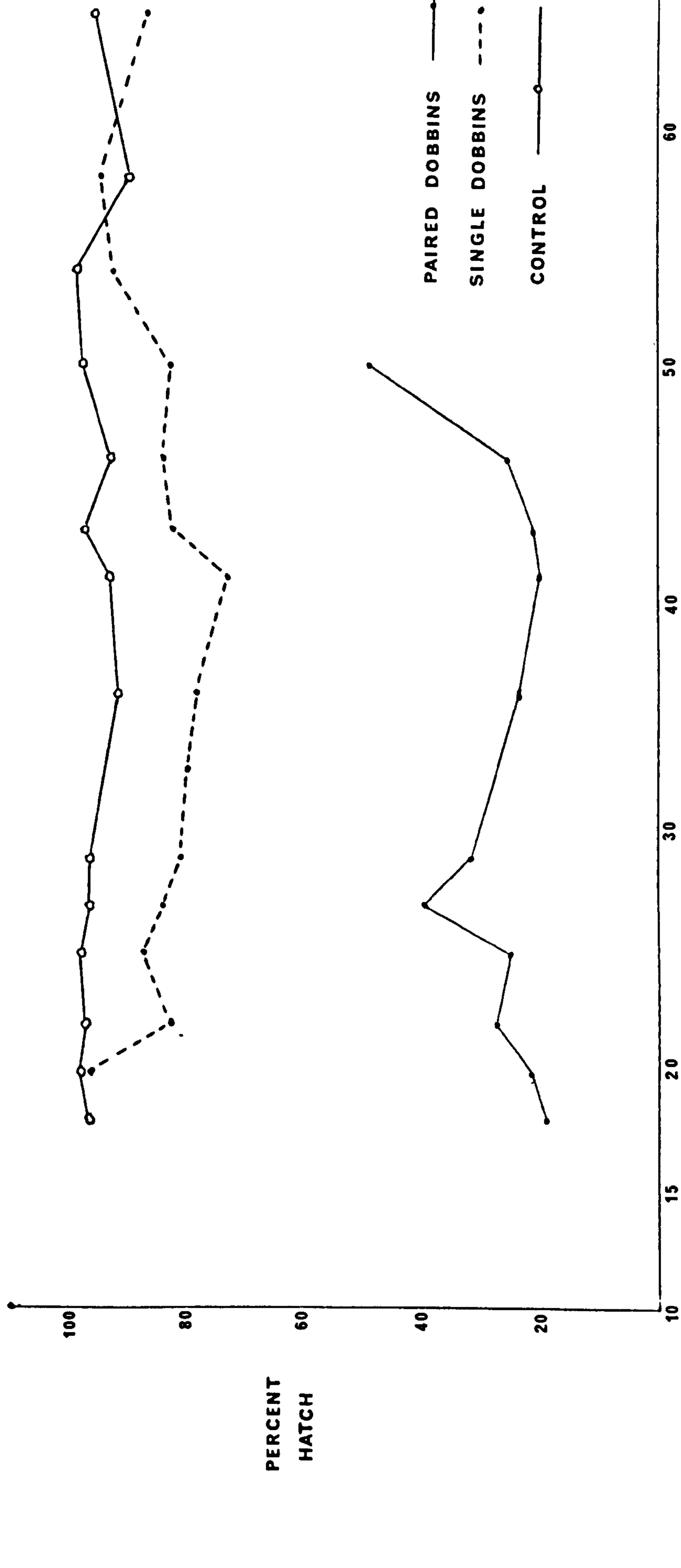
Paired treatment



EXPERIMENT 7.

NEMATODE EGG COUNTS MEAN

FIG. 13



EXPERIMENT 7.

FIG.14

EXPERIMENT 7.

LAMB NOS.
152
156
248
363
442

TWO DOBBINS

EXCRETED DRUG ACTIVITY ZONES MEASURED FROM SHEEP DOSED WITH T

DAYS FOLLOWING TREATMENT

MEAN ZONE DIAMETER (CMS)

0 2·0 4·0 6·0

8 16 24 32 40 48 56 64 72

FIG. 15

TABLE 28 : Anthelmintic activity of thiophanate administered via a slow release ruminal bolus for 70 days. Experiment 7

Treatment	Sheep No.	Worm burden				Per cent efficacy[1].			
		H.c.	O.c.	T.c.	N.s.	H.c.	O.c.	T.c.	N.s.
Single	240	13	2327	2700	1080	97.6	41.3	47.8	77.0
	246	0	2420	2220	2020	100.0	38.9	57.1	57.0
Pair	432[2].	31	3219	2941	1979	94.4	18.8	43.2	57.9
	156[3].	0	20	10	0	100.0	99.5	99.8	100.0
	152	0	1400	80	30	100.0	39.5	98.4	99.4
	248[4].	0	2080	10	0	100.0	47.5	99.8	100.0
	363	0	1620	920	160	100.0	59.1	82.2	96.6
	442	0	1560	1050	110	100.0	60.6	79.7	97.7
Controls	33	400	4880	6800	8400				
	36	986	3734	4133	4267				
	262	670	3280	4602	1438				
	Mean	533.7	3964.7	5178.3	4701.7				

1. $\frac{\text{Mean control worm burden - treated worm burden}}{\text{Mean control worm burden}} \times 100$

2. One 'Dobbin' regurgitated + 8 days

3. One 'Dobbin' lost its load during the first 30 days

4. Killed + 30 days

H.c. = Haemonchus contortus T.c. = Trichostrongylus colubriformis

O.c. = Ostertagia circumcincta N.s. = Nematodirus spathiger

a density of only 1.8 was regurgitated during the first ten days, although the weight was greater than 20 gms. This would confirm the previous observation that a density of equal to or greater than 2.0 is required for complete ruminal retention amongst groups of treated animals.

Compared to the previous results obtained, where no difference in drug release was apparent from each iron bar bolus even when dosed in pairs, the matrix used on the paired 'Dobbins' in this study showed an increase throughout the medication period compared to the single dosed 'Dobbins' (Table 27).

During the latter retention period up to 70 days after dosing, the individual drug release rates measured from the paired 'Dobbins' had not declined as low as those obtained from the single dosed ones.

The presence of the empty 'Dobbin' in lamb 156 appeared to maintain the level of erosion of the remaining loaded 'Dobbin', equivalent to that recorded from each loaded, paired 'Dobbin'.

The excreted drug monitored from each treated lamb was very erratic throughout the medication period (Fig.15) compared to the steady levels observed from the drug infusion lambs (Fig.2). This would seem to indicate an uneven erosion of the matrix releasing drug in irregular amounts.

The loss of the load from one 'Dobbin' dosed to lamb 156 would account for the rise (from the subsequent breakdown of the loose matrix) and sudden drop in excreted drug. The level of drug released from the remaining 'Dobbin' was insufficient to register on the plate assay after this time. The effective vermicidal activity results from this lamb also confirm this observation.

The excreted drug monitored from lamb 248 prior to its slaughter at the end of the initial retention period produced the largest activity zones recorded (Fig.15). This was in agreement with

the calculated daily dose rate actually received of 2.63 mg thiophanate per kg bodyweight compared to the average of 2.0 mg per kg received by the other paired dosed lambs.

The final worm burden results are comparable to those obtained from the drug infusion experiments in Section A, with the nematode species Ostertagia being the most resistant to the slow release form of anthelmintic medication. This observation agrees with the work reported by Anderson, Laby, Prichard and Hennessy (1980) using the anthelmintic oxfendazole. A graded removal of an established burden of O.circumcincta highlighted the differential susceptibility of adult and immature worms when exposed to a continual low concentration of drug.

It was concluded that a more consistent breakdown of the 'Dobbin' was achieved than with the iron bar core boluses as reflected in the results from the parameters measured. The 'Dobbin' therefore provided a suitable "carrier" for a paraffin wax matrix with improved erosion rates, especially when administered in pairs. The matrix of the load tested, however, did not achieve the required drug release rates.

8. COMPARISON OF THE DRUG RELEASE RATE FROM VARIOUS MATRICES WHEN ADMINISTERED ALONE OR IN PAIRS.

The problem of retention within the reticulo-rumen of sheep had been overcome and a stable "carrier" found which also provided additional weight and density. Further studies now concentrated on the drug release from within the matrix.

The previous experiment indicated that an increase in the erosion rate of a 'Dobbin' could be achieved by dosing in pairs but the release rate from the matrix tested was not at a sufficient level to be effective against gastro-intestinal nematodes.

The following experiment was designed to incorporate various releasing aids within the basic paraffin wax-thiophanate matrix loaded onto 'Dobbins' and to compare the erosion rates when administered as singles or in pairs.

8.1. Matrix formulations

To aid the release of the drug, water soluble leaching agents were incorporated into the matrix. Three types of sugar (granulated*, glucose and sucrose), a salt (Cerebros table salt) and a wetting agent (tragacanth mucilage) were selected. All the substances used were innocuous and acceptable for animal administration.

The percentage combinations used (paraffin wax : thiophanate : releasing agent) were as follows:-

Matrix 1. Salt. 23.1 : 57.7 : 19.2

2. Salt. 20 : 50 : 20 + 10 (iron powder)

3. Granulated sugar. 20.8 : 59.4 : 19.8

4. Granulated sugar. 20 : 50 : 20 + 10 (iron powder)

5. Glucose. 20 : 50 : 1.0 + 29 (iron powder)

* Granulated household sugar - Tate & Lyle

6. Sucrose. 20.8 : 49.5 : 9.9 + 19.8 (iron powder)

7. Tragacanth mucilage. 23.8 : 47.6 : 4.8 + 23.8 (iron powder)

Thiophanate was incorporated at the highest possible level while still maintaining a mouldable mix.

Either all metal or nylon rod-metal flanged 'Dobbins' were used, the latter loaded with the formulations containing iron powder which was incorporated to help provide an abrasive surface.

A plain, control matrix (paraffin wax : thiophanate :: 31.8 : 68.2) was also included for comparison (Matrix No. 8).

The densities ranged from 1.8 to 2.4 and the pre-dose weights from 29.8 to 35.08 gms depending on the 'Dobbin' type and the matrix load.

Either a single 'Dobbin' or a pair loaded with the same matrix were dosed to each lamb. Each matrix was administered as a single and double treatment.

The 'Dobbins' were recovered by rumenotomy at varying time intervals during the medication period and the erosion rates with subsequent drug release rates were calculated.

8.2. Recovery results

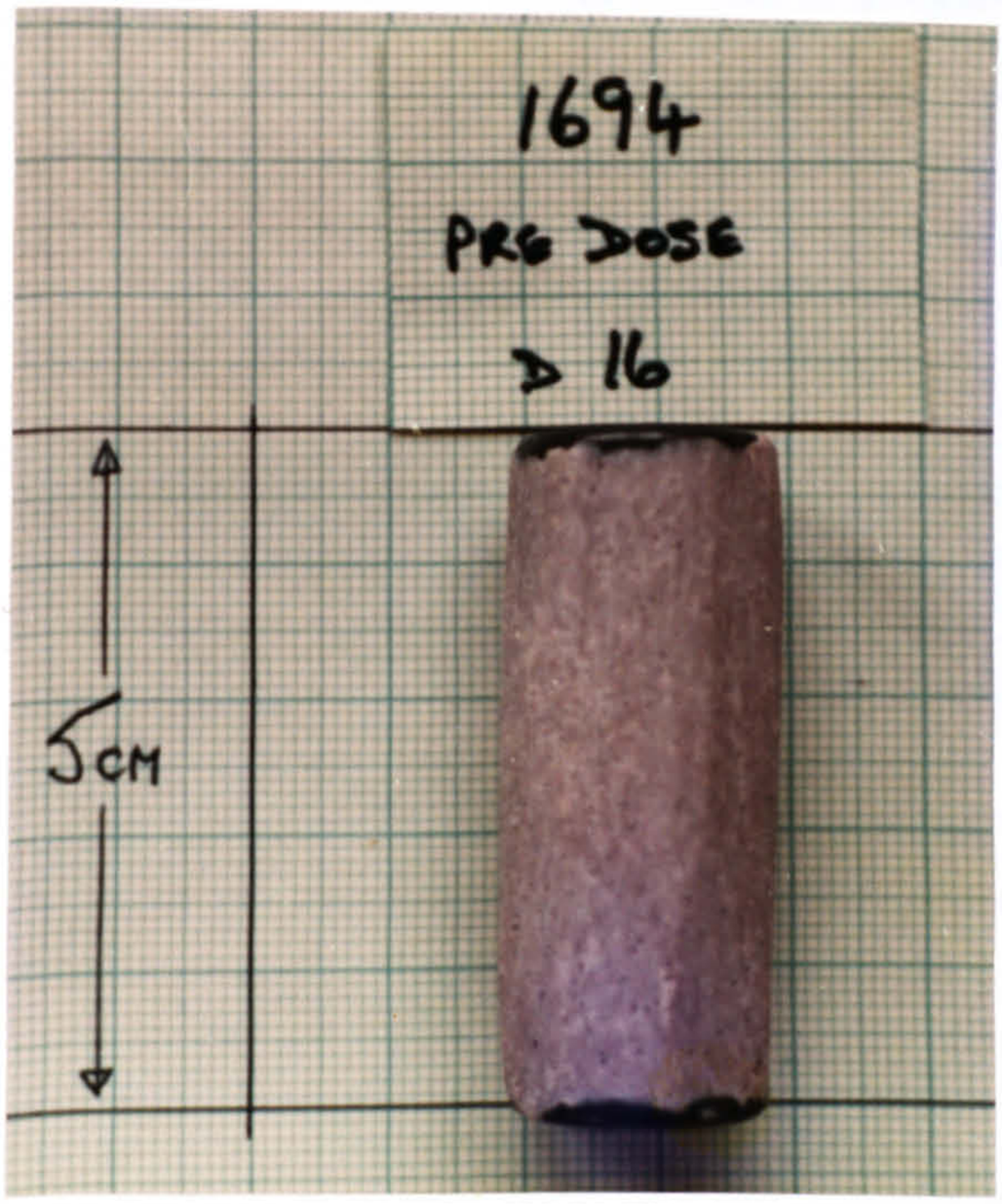
The results obtained for all the matrix formulations are summarised in Table 29.

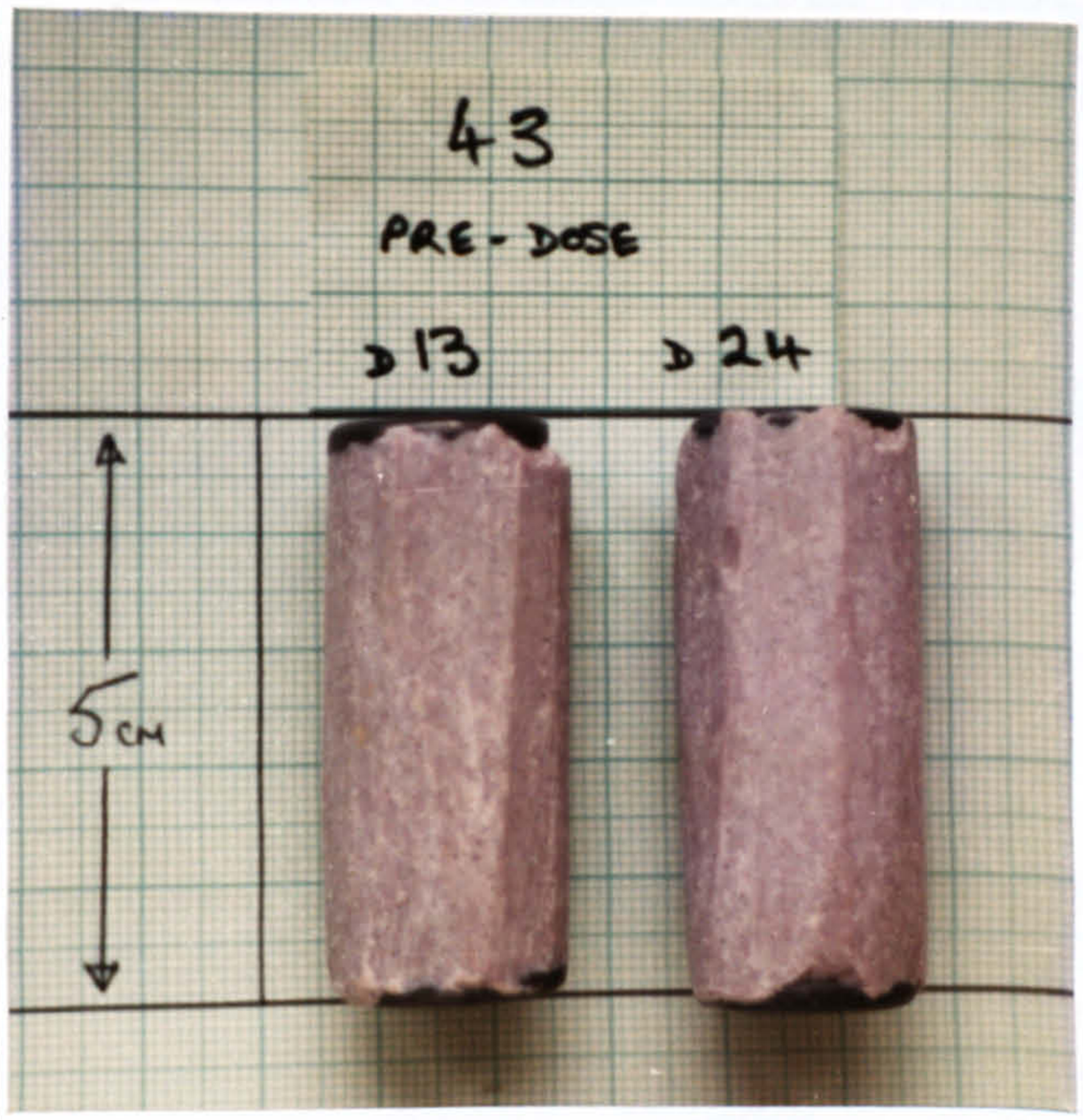
All the 'Dobbins' administered in pairs gave individual increased erosion rates compared to the single dose. The extra erosive power of the two together was noticeable in the shape of the load at recovery. Examples of the progression of erosion obtained with four of the matrices are illustrated in Plates 20 - 23. The single and paired 'Dobbins' of the same matrix have been included on the same Plate for comparison.

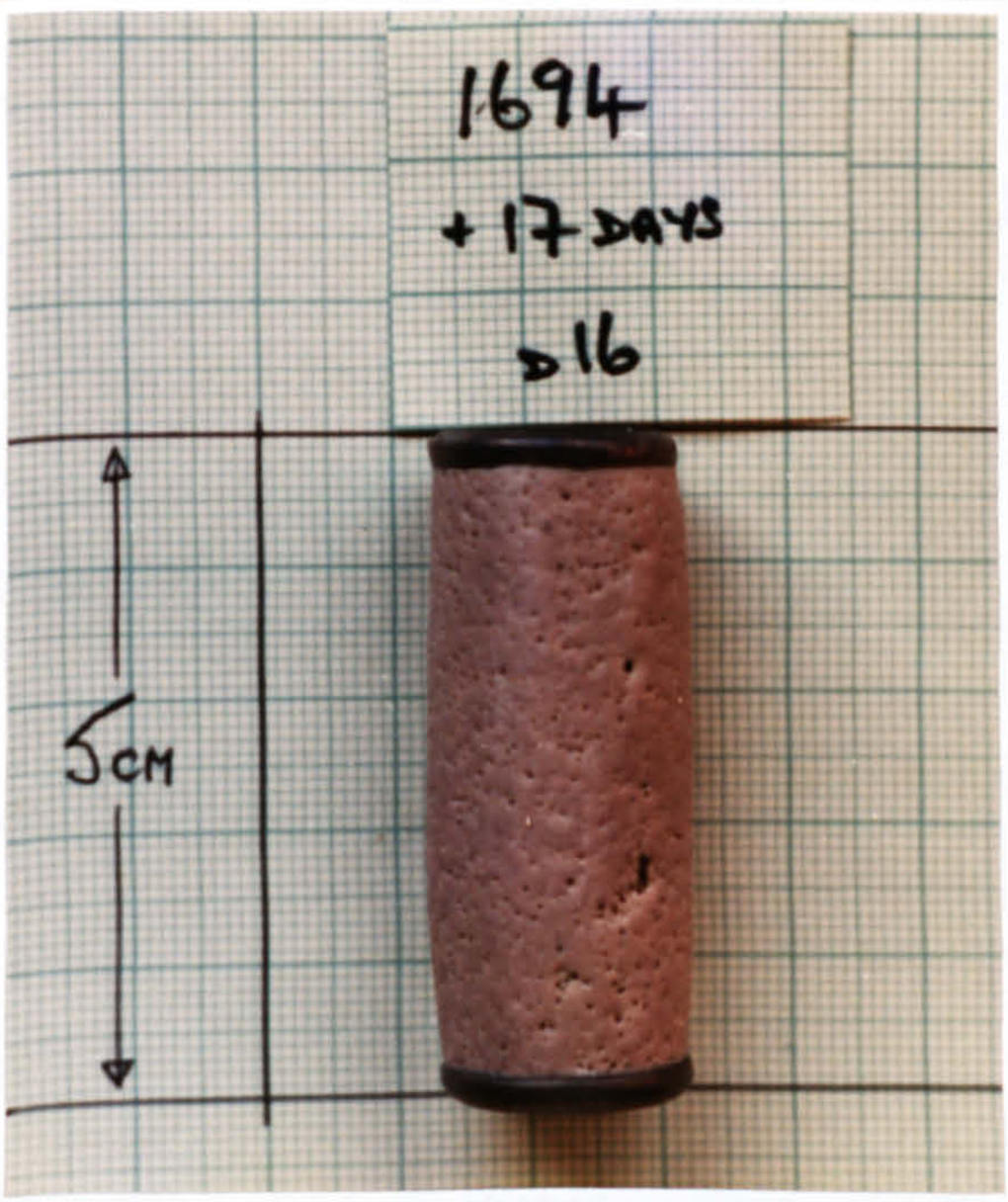
TABLE 29 : Summary of the drug release rates achieved from various matrices when dosed alone or in pairs. Experiment 8.

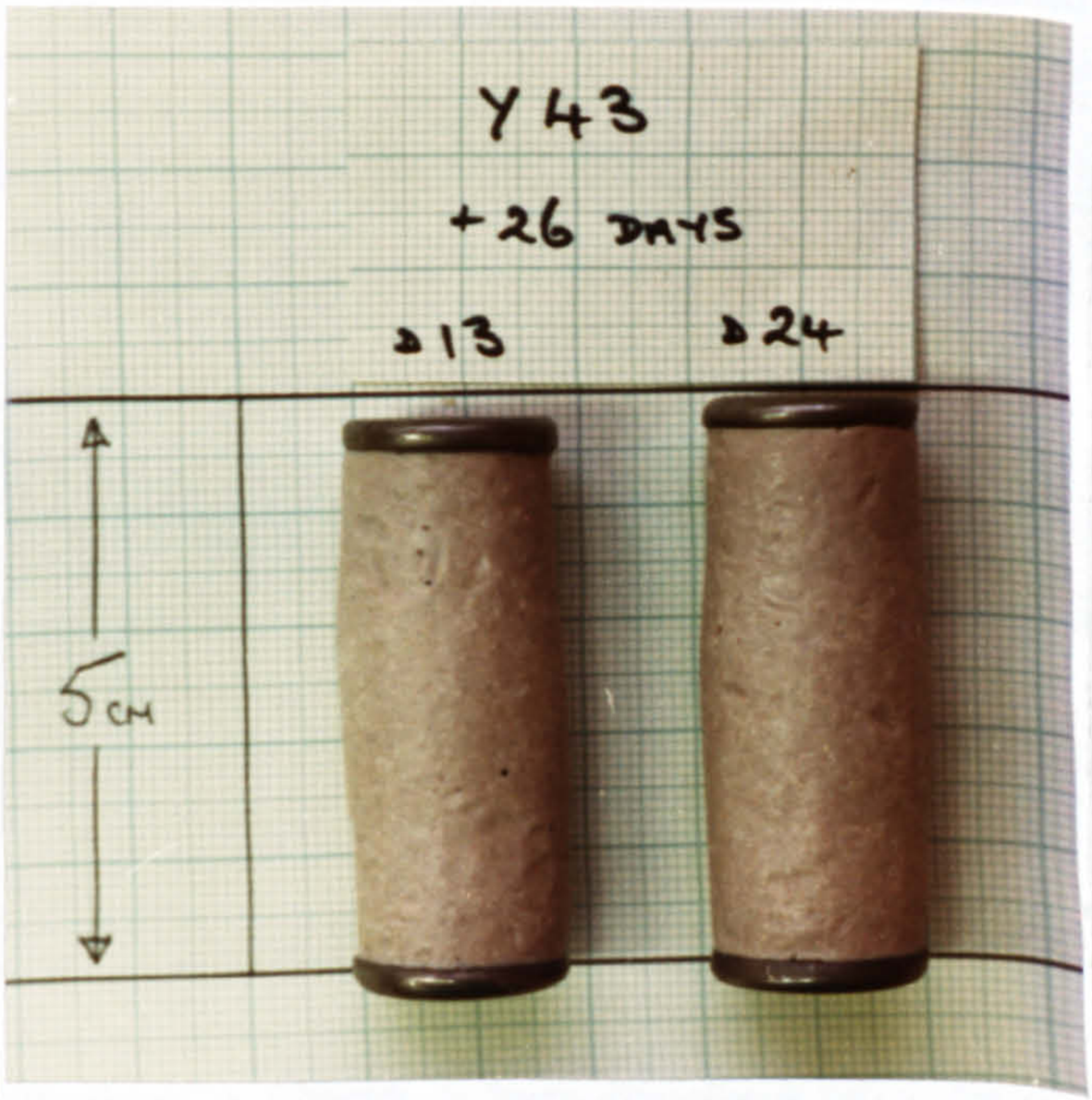
Matrix No.	Sheep No.	Pre-dose 'Dobbin' weight (gms)	Density	Day post-dosing	Daily weight loss (mg)	Mg thiophanate per day	Day post-dosing	Daily weight loss (mg)	Mg thiophanate per day	Days post-dosing	Daily weight loss (mg)	Mg thiophanate per day
1	1694	33.07	2.23	17	78.8	45.5	56	52.3	30.2	17 - 56	40.8	23.5
	43	33.7 35.08		26	115.0 119.2	66.4 68.8	64	102.7 106.6	59.2 61.5	26 - 64	94.2 97.9	54.3 56.5
2	Y22	29.84	1.83	24	67.5	33.75	59	61.2	30.6	24 - 59	56.8	28.4
	57	32.91 32.96					48	129.8 129.4	64.9 64.7			
3	1679	33.03	2.14	18	73.9	43.9	69	59.1	35.1	18 - 69	53.9	32.0
	Y48	33.62 33.87		26	133.8 132.3	79.5 78.6	64	Empty 107.2	63.7	26 - 64	90.0	53.5
4	Y25	30.68	1.8	32	98.4	49.2	71	82.8	41.4	32 - 71	70.0	35.0
	72	30.49 32.10		38	211.8 192.1	105.9 96.05	Not replaced					
5	1686	30.19	2.02	19	61.1	30.5	44	52.3	26.1	19 - 44	45.6	22.8
	1685	30.49 30.68		38	127.1 126.6	63.5 63.3	70	102.4 101.8	51.2 50.9	38 - 70	73.1 72.5	36.5 36.25
6	1644	33.53	2.4	15	76.7	37.9	68	74.8	37.0	15 - 68	74.3	36.8
	Y35	30.11 30.86	1.9	19	272.6 307.9	134.9 152.4	61	Empty				
7	178	33.31	2.43	31	34.8	16.5	76	30.9	14.7	31 - 76	28.2	13.4
	1667	33.12 33.39		31	101.6 102.6	48.4 48.8	76	93.4 93.8	44.4 44.6	31 - 76	87.8 87.8	41.8 41.8
8	20	32.91	2.05	29	37.6	25.6	60	36.8	25.1	29 - 60	36.1	24.6
	23	32.25 31.34		26	98.1 96.9	66.9 66.1	60	85.0 84.5	58.0 57.6	26 - 60	75.0 75.0	51.2 51.2

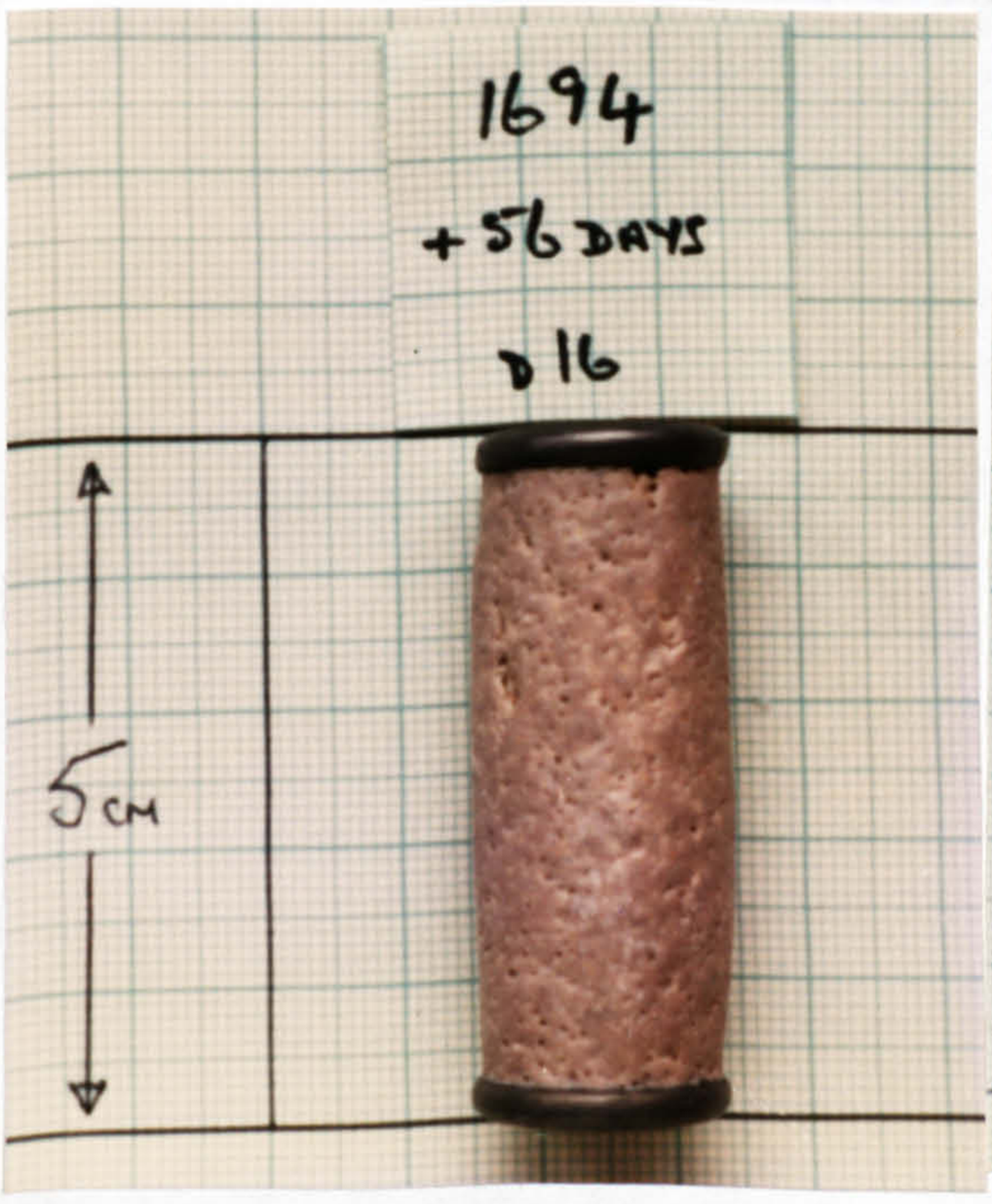
PLATE 20 : MATRIX 1 - SALT. Experiment 8











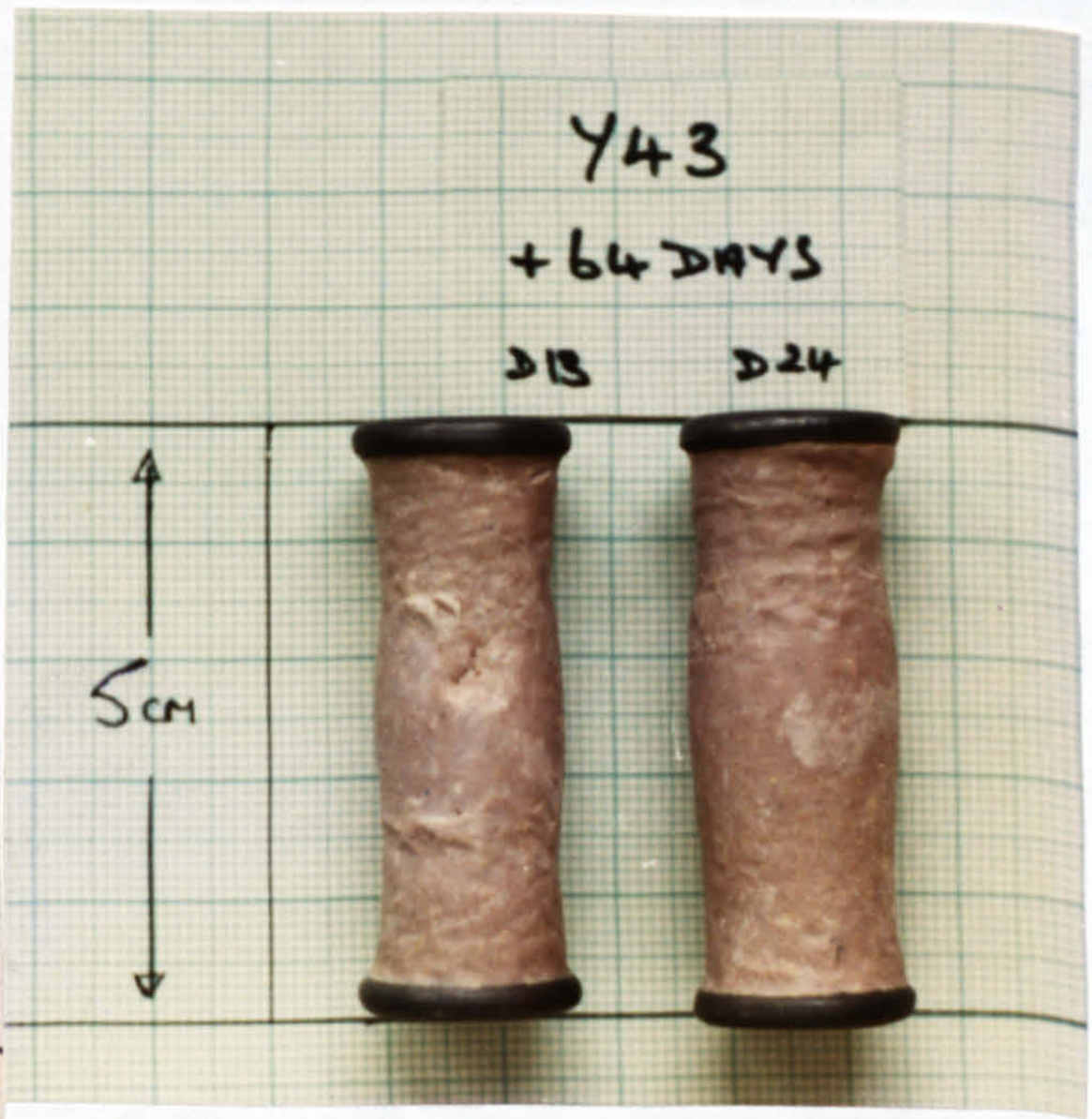
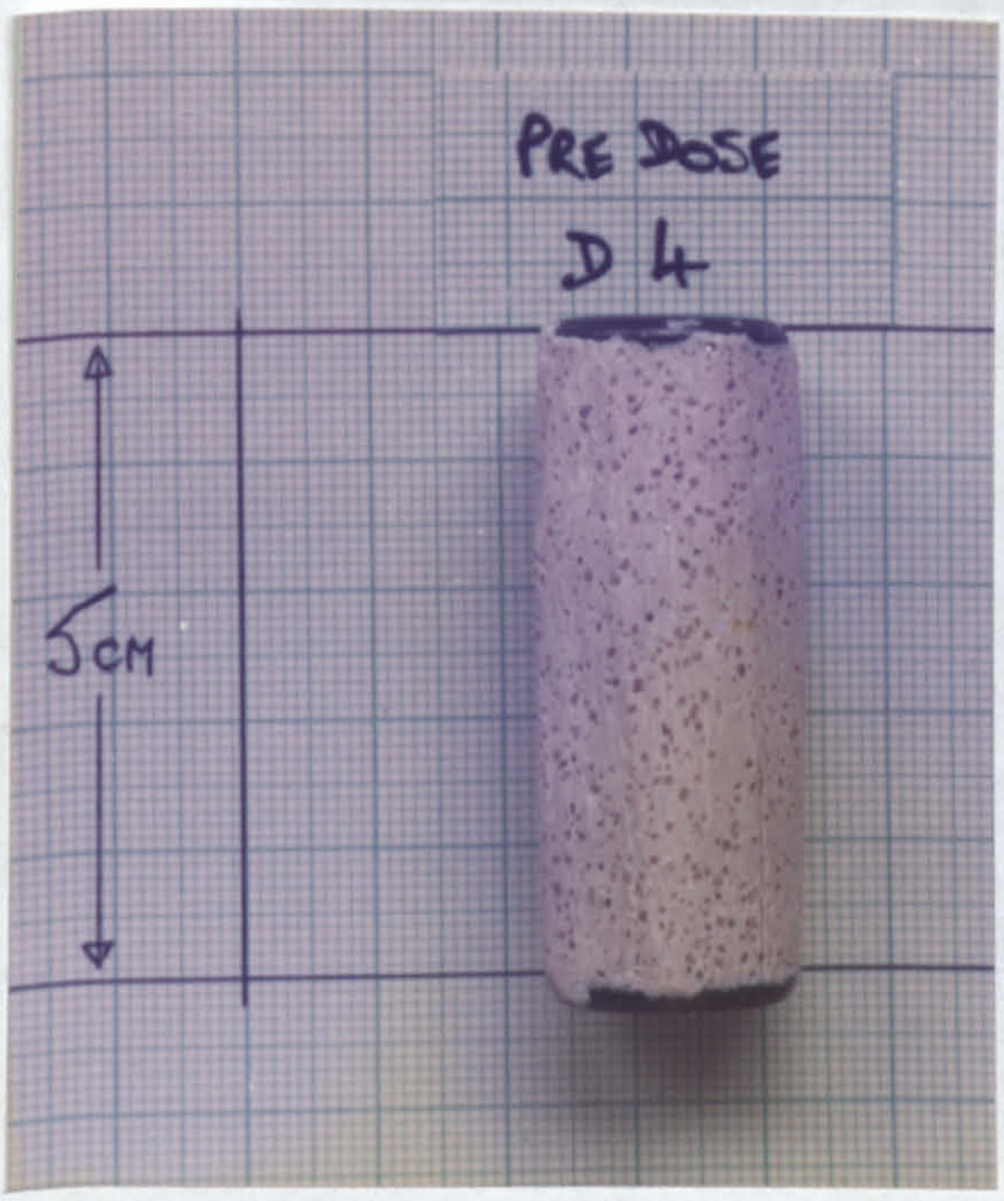
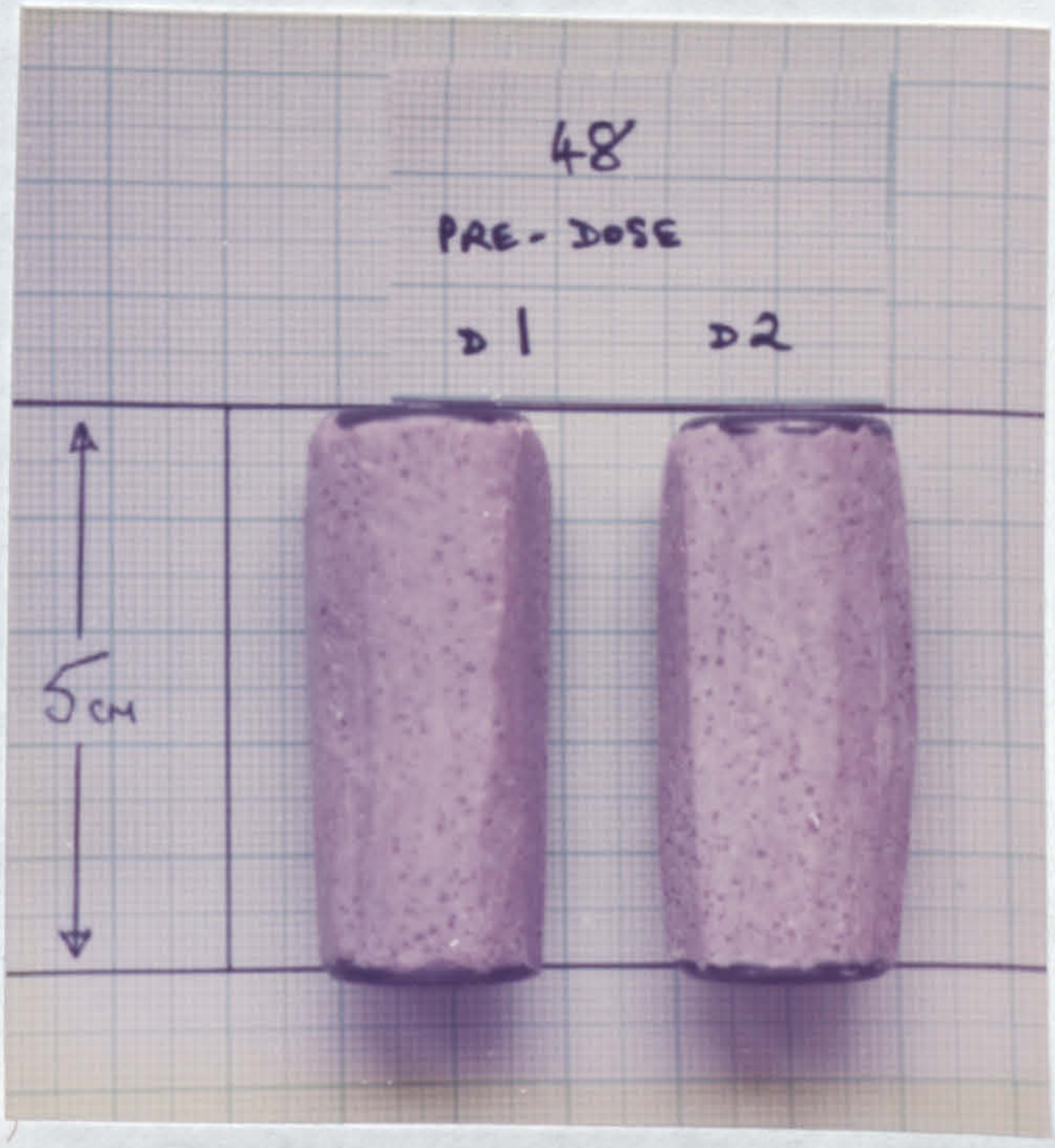
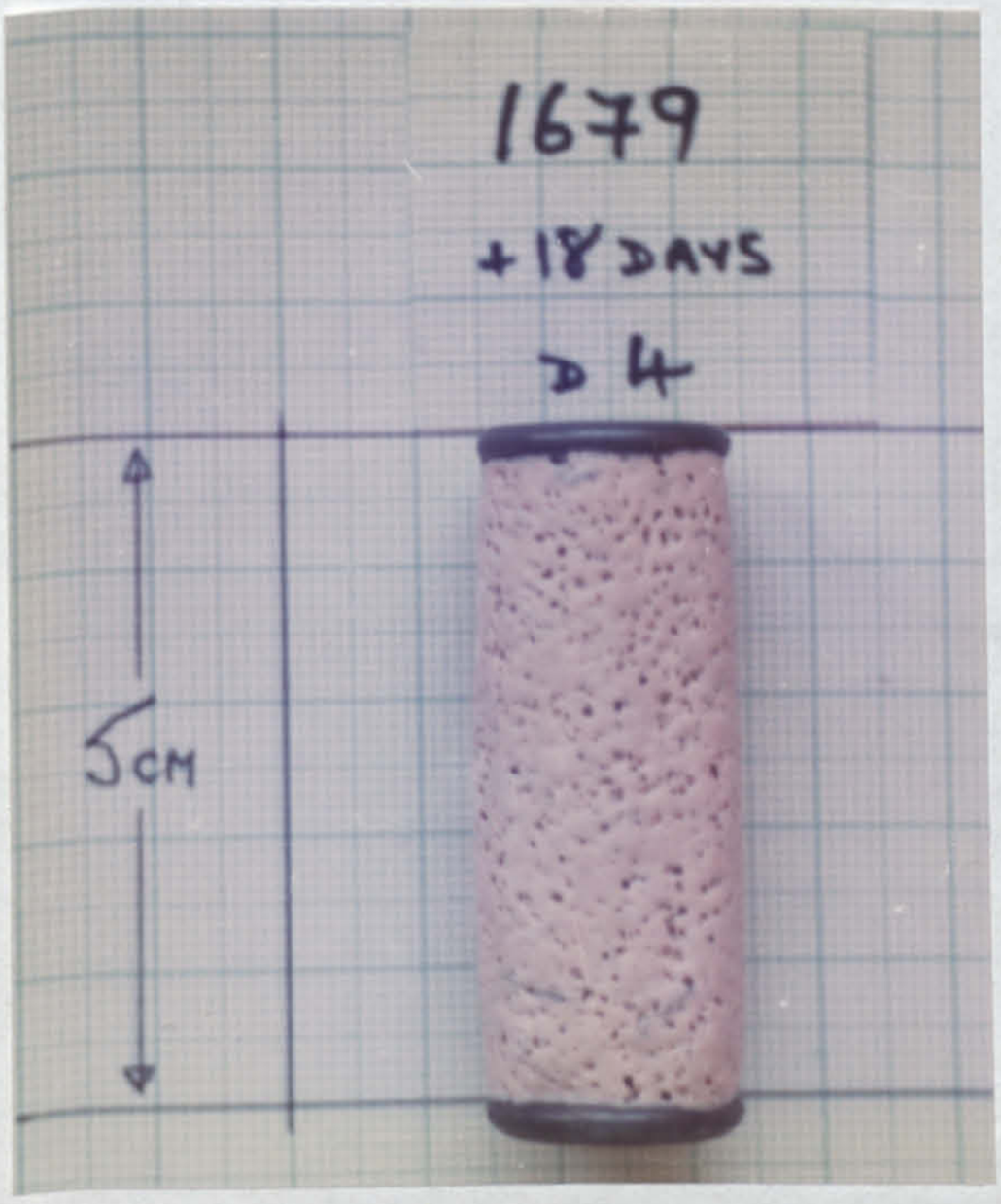
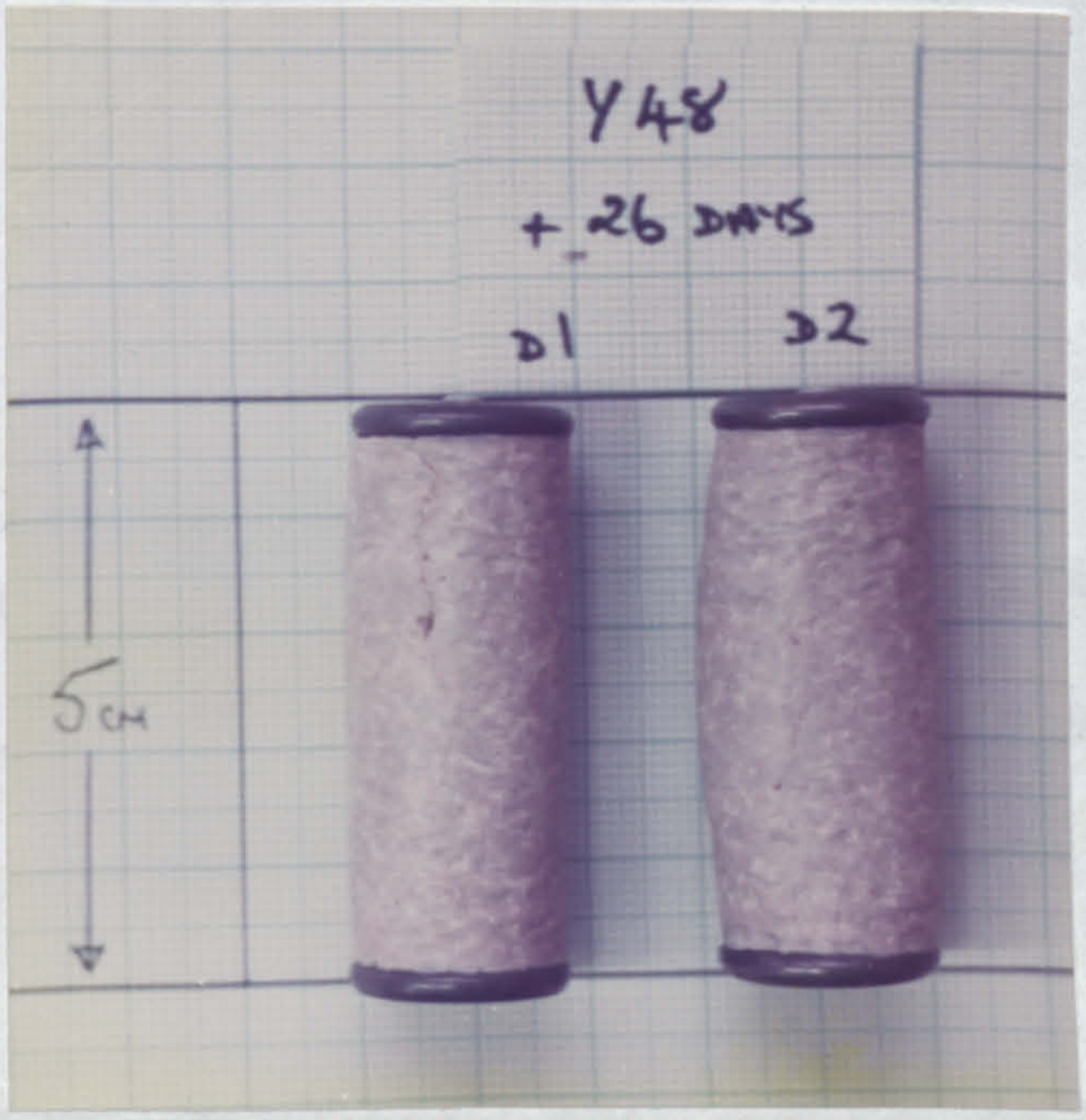


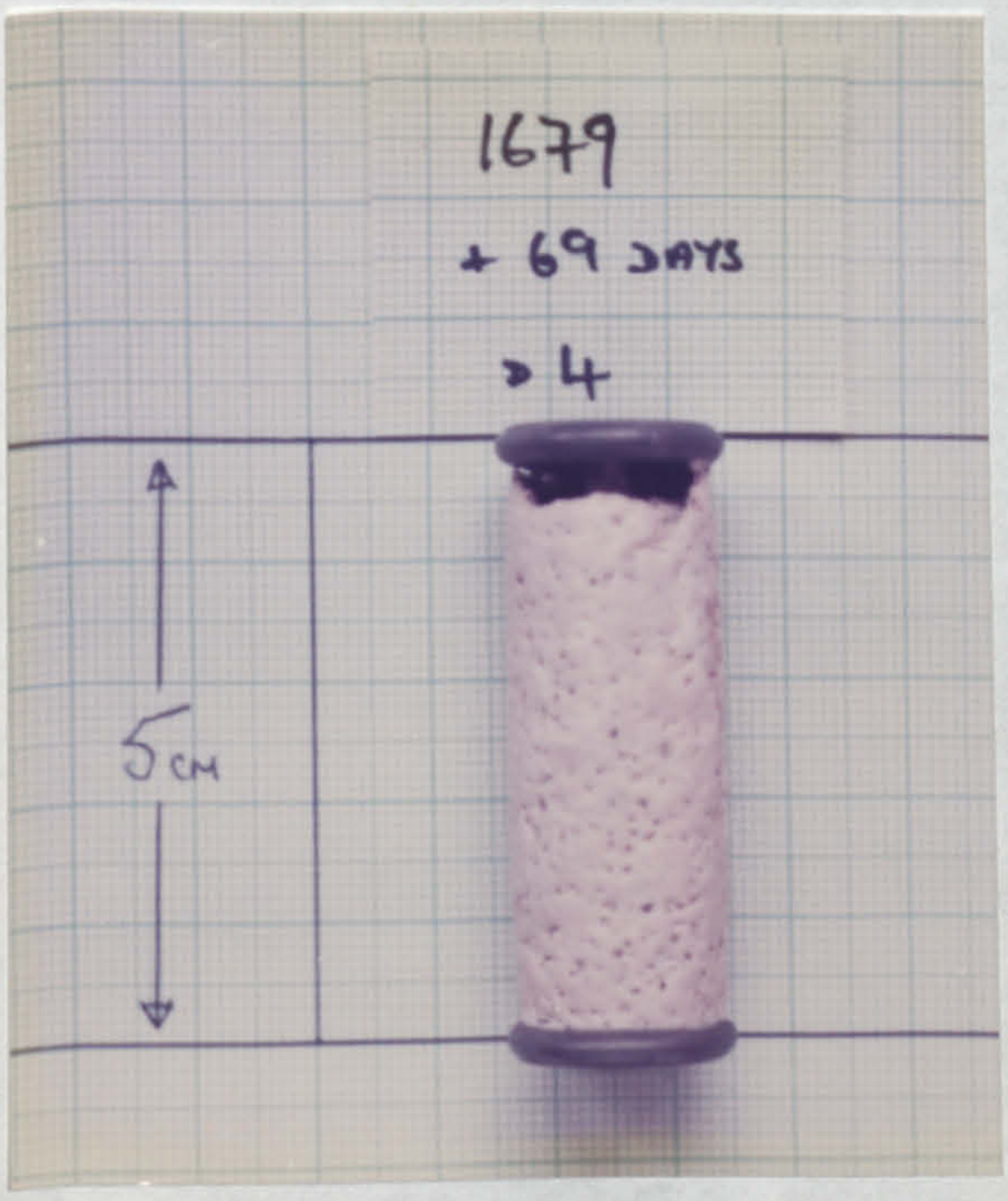
PLATE 21 : MATRIX 3 - GRANULATED SUGAR. Experiment 8











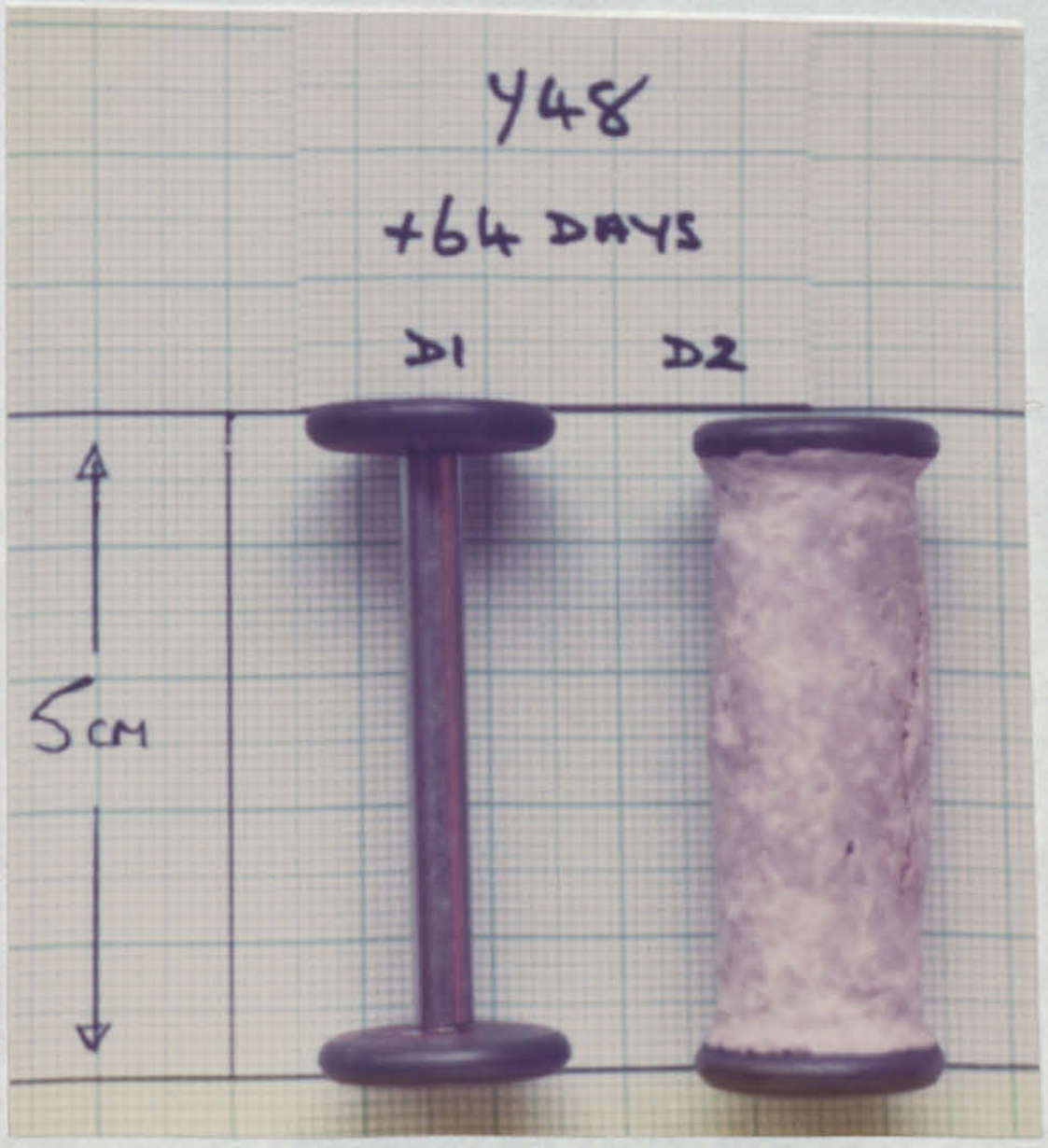
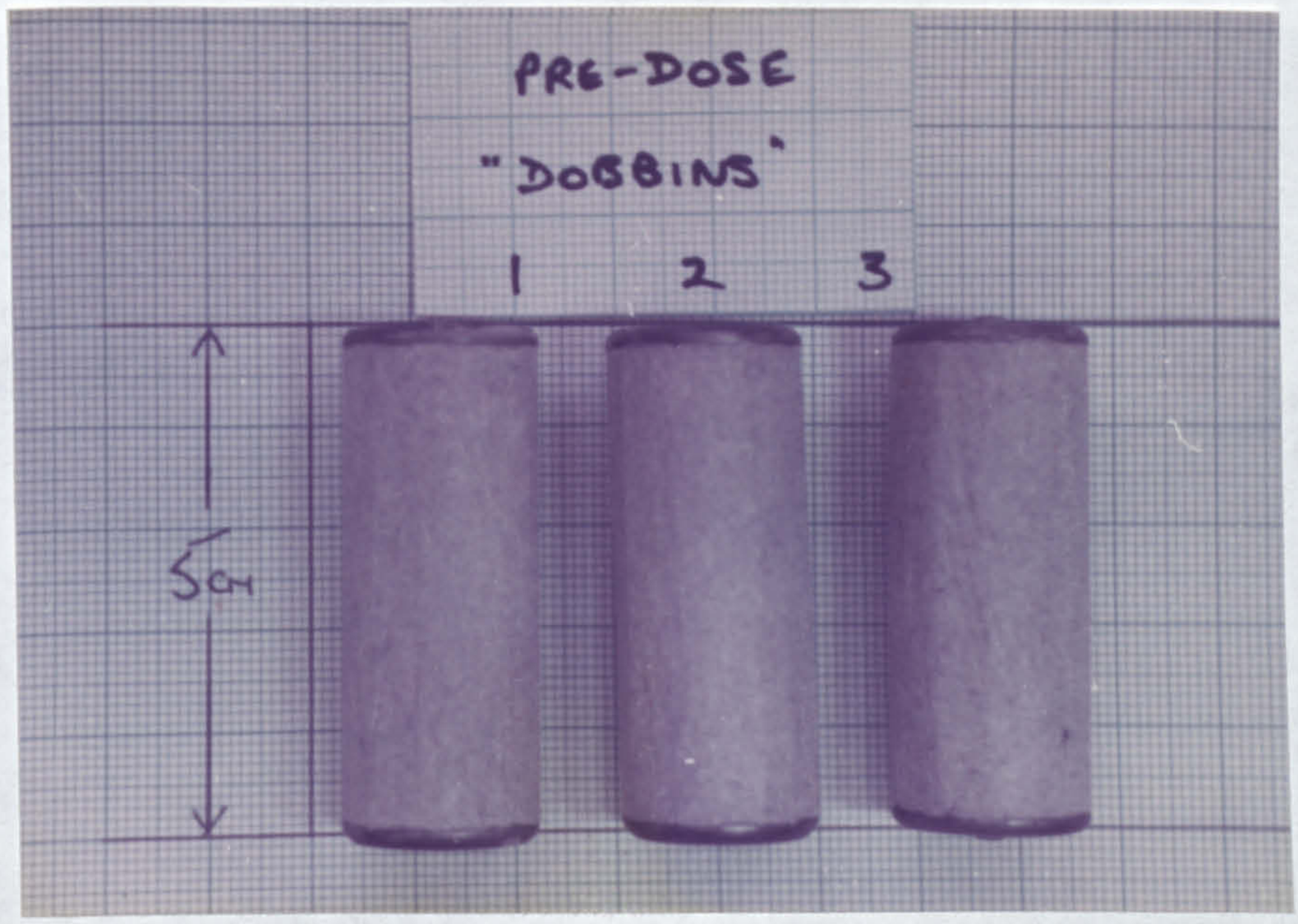
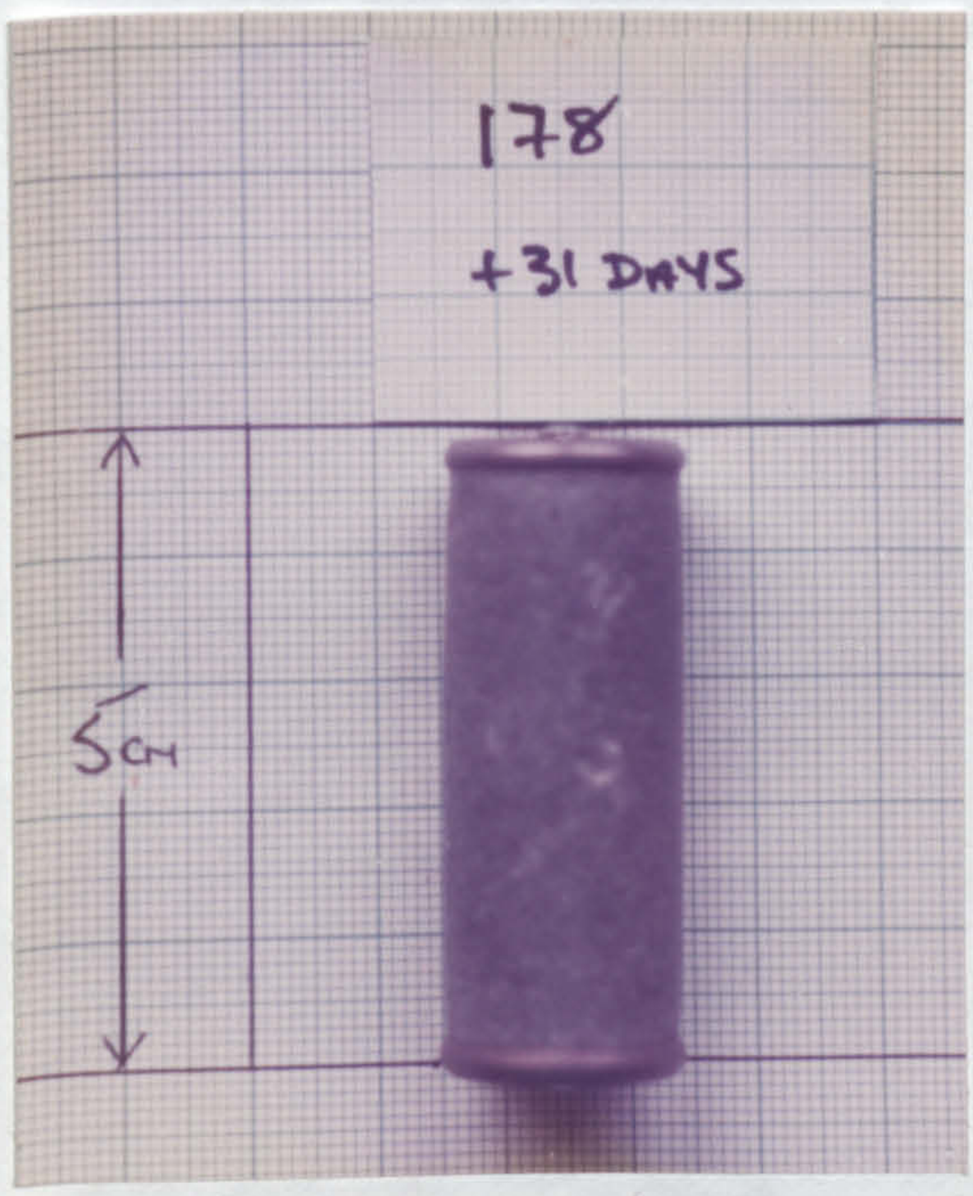
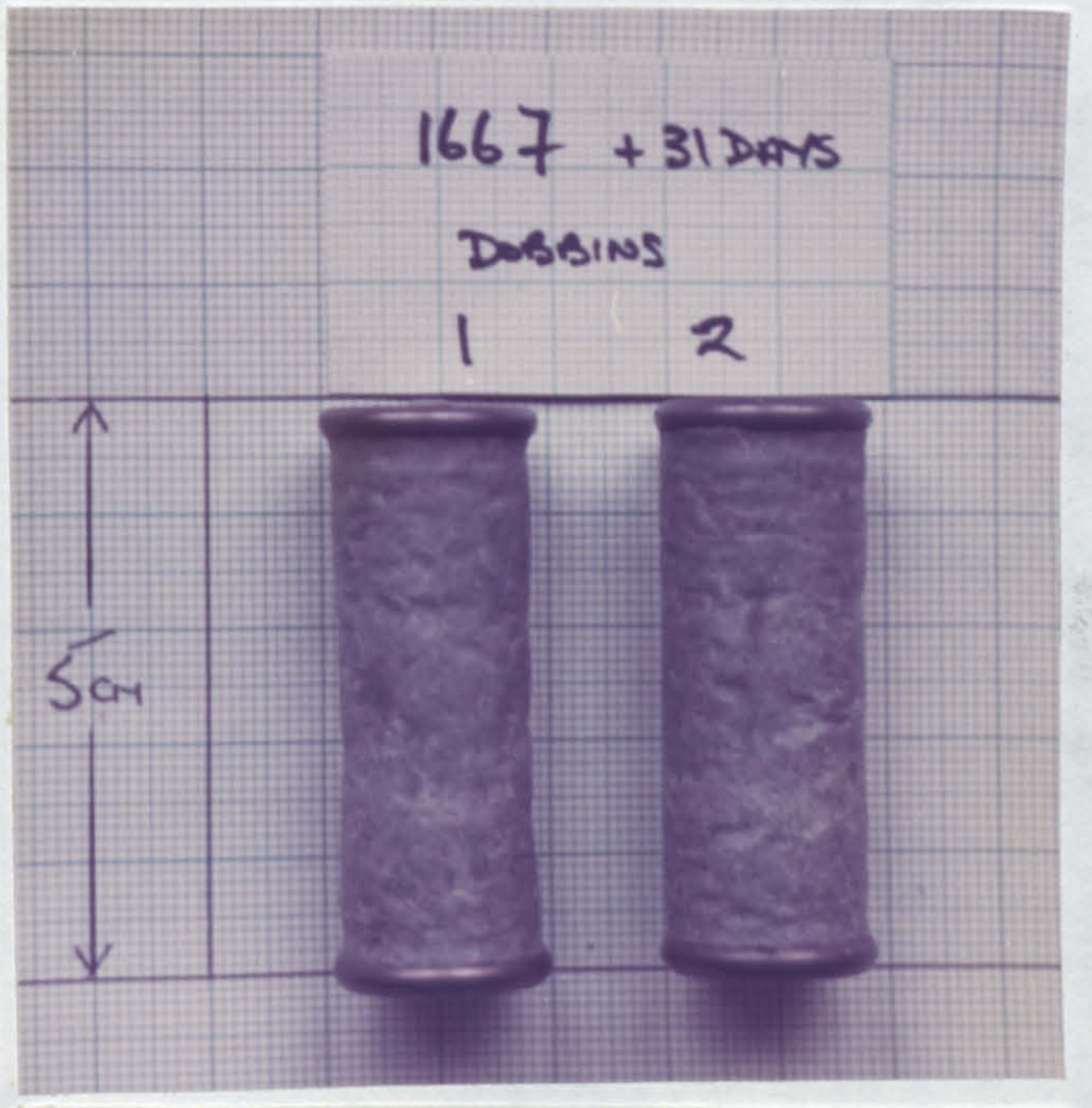
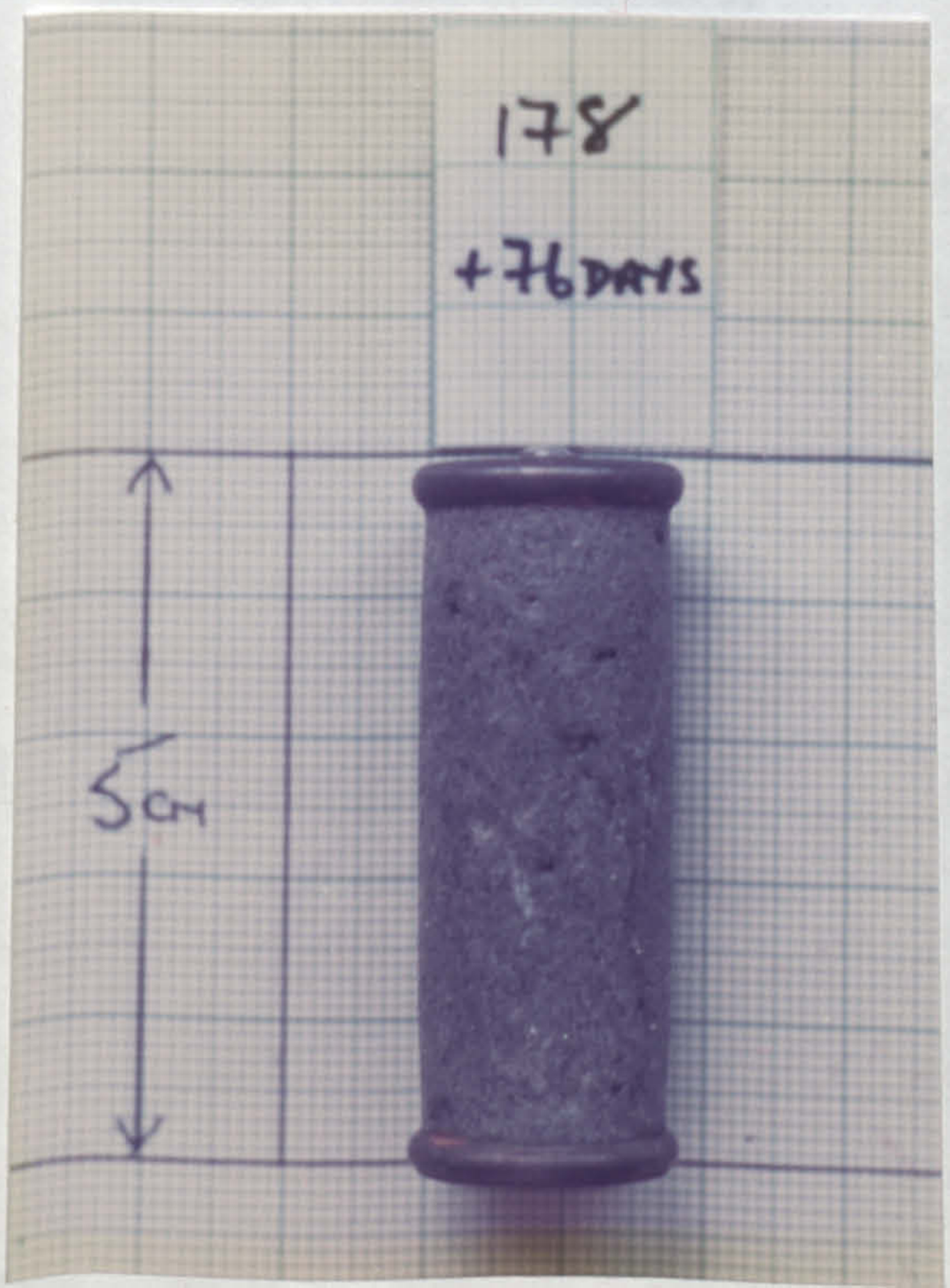


PLATE 22 : <u>MATRIX 7 - TRAGACANTH MUCILAGE WITH IRON POWDER</u>. Experiment 8









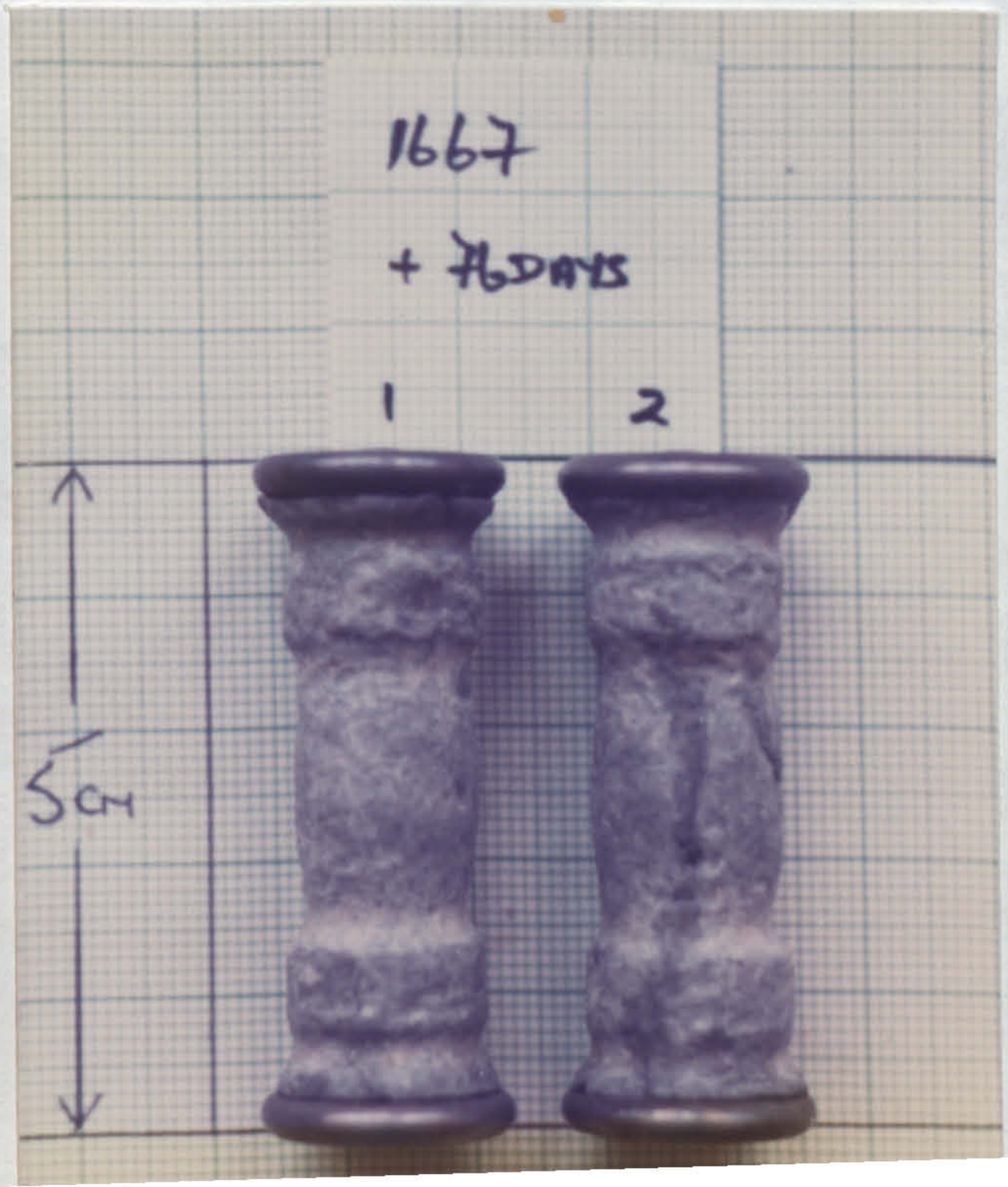
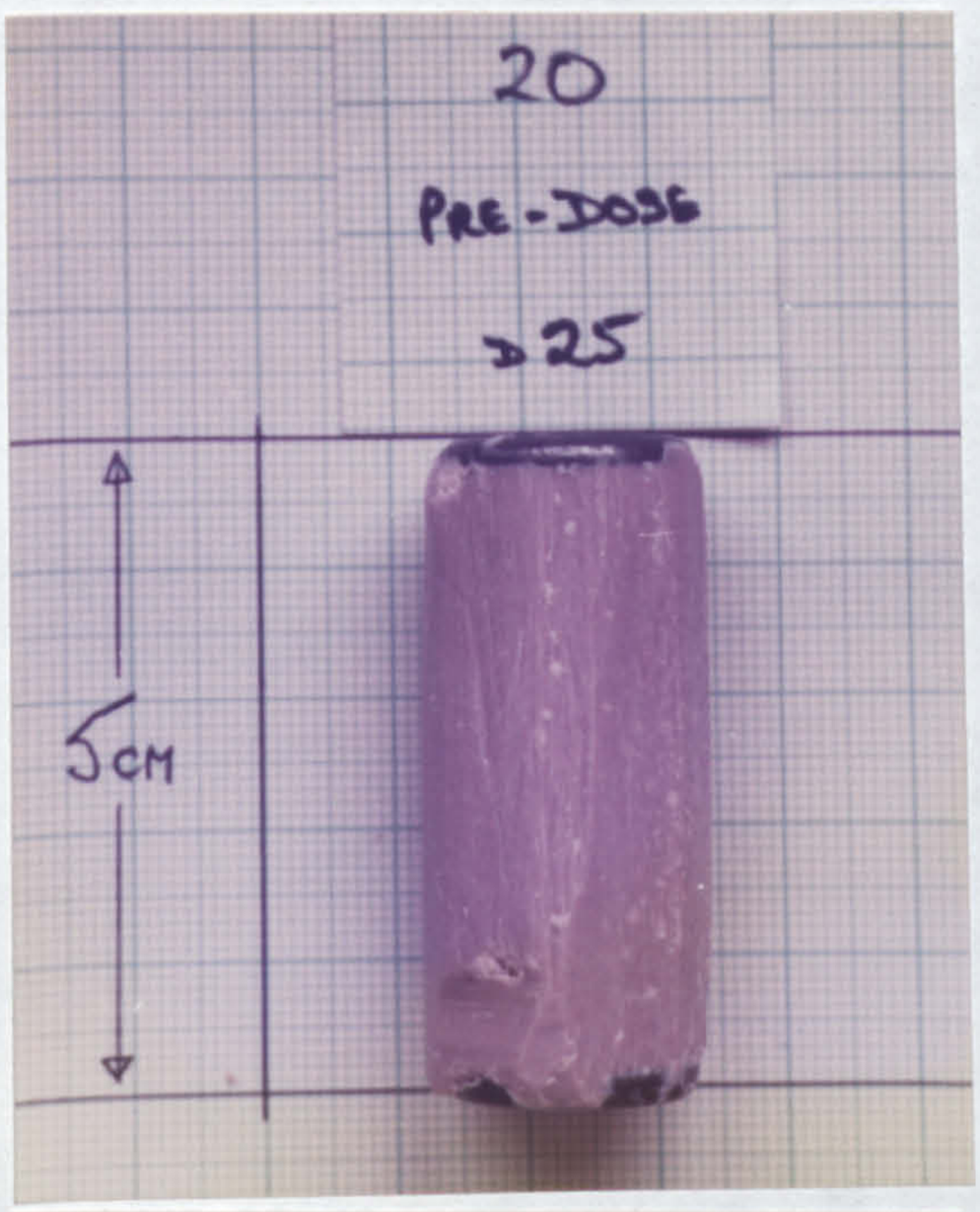
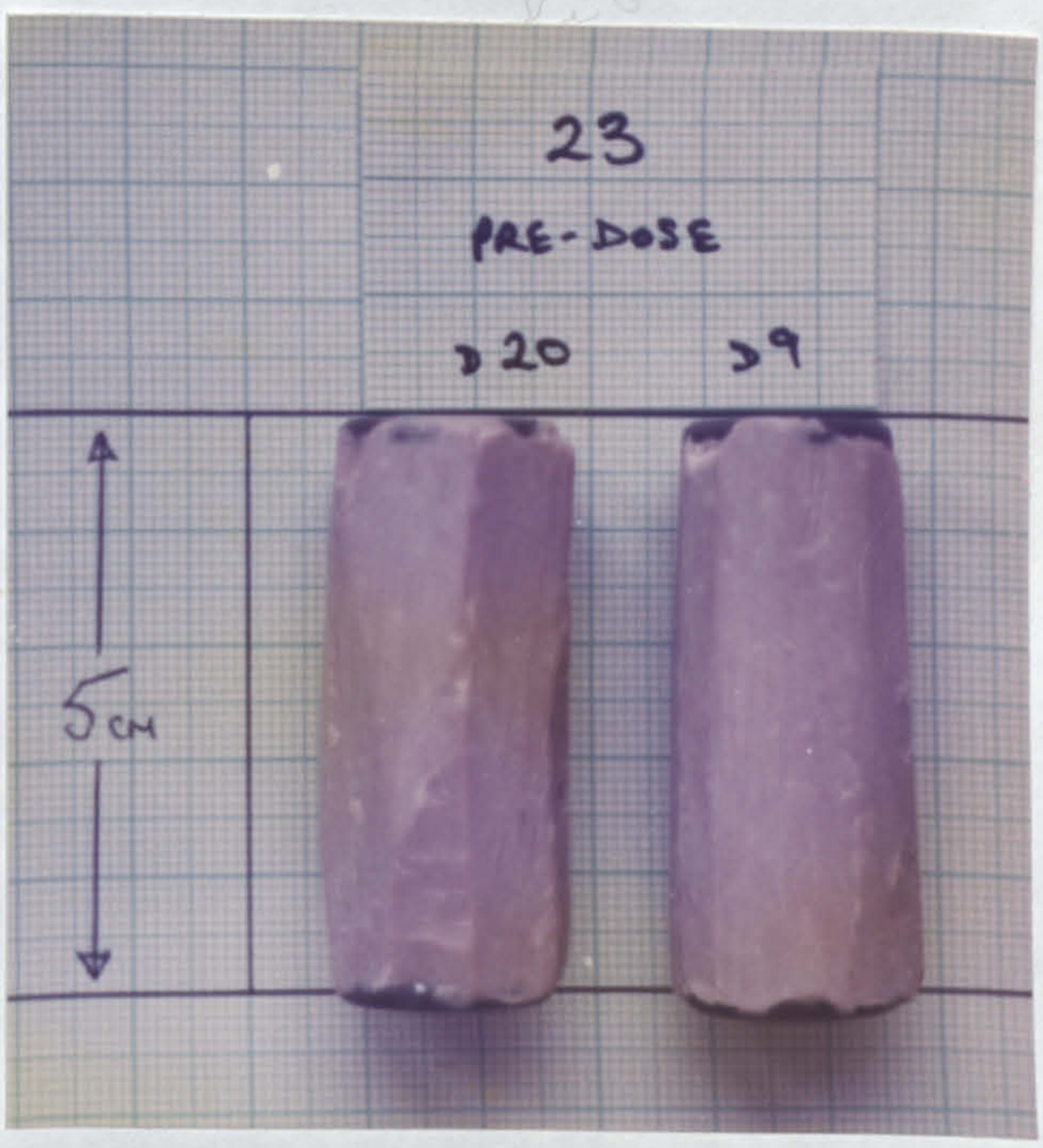
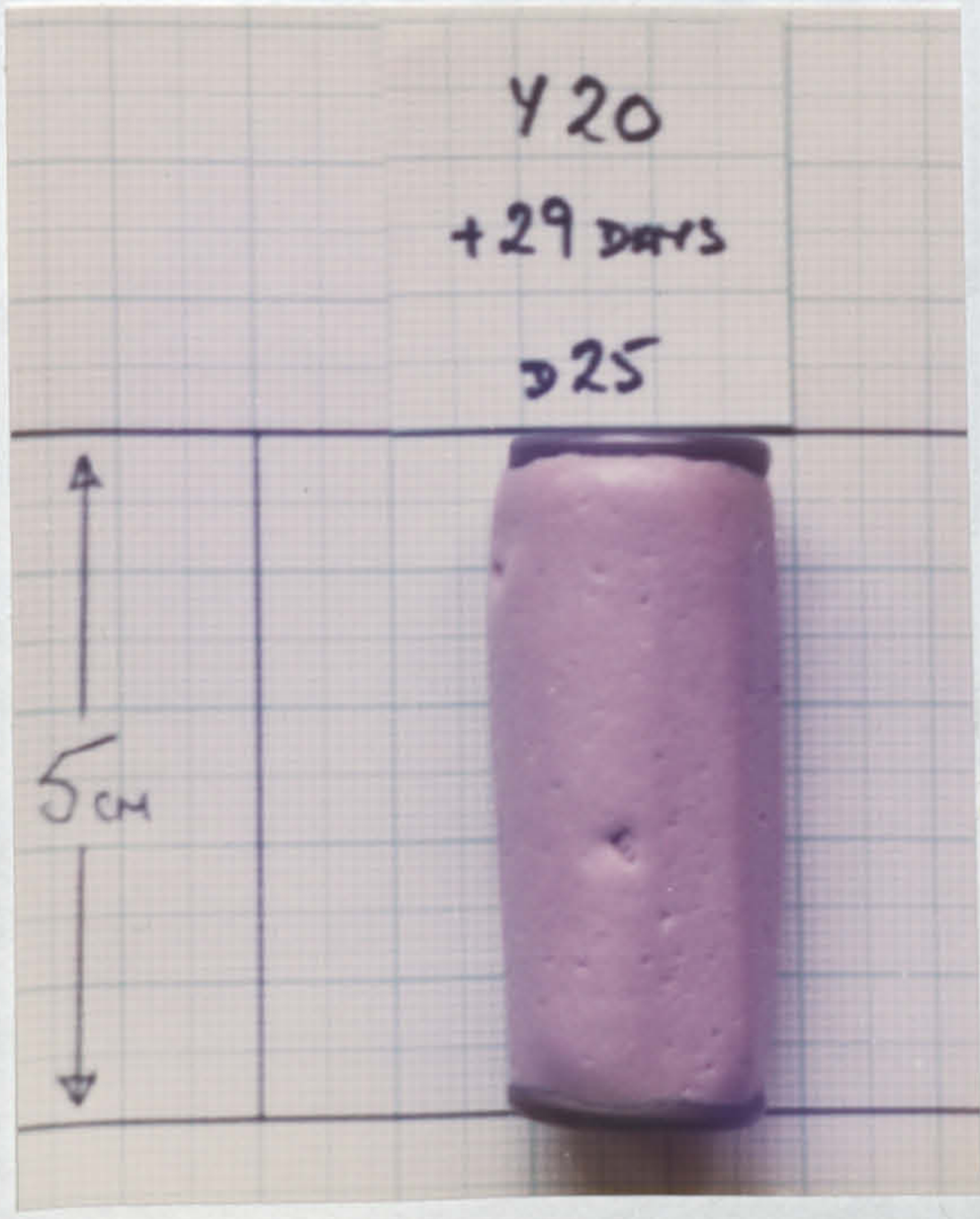
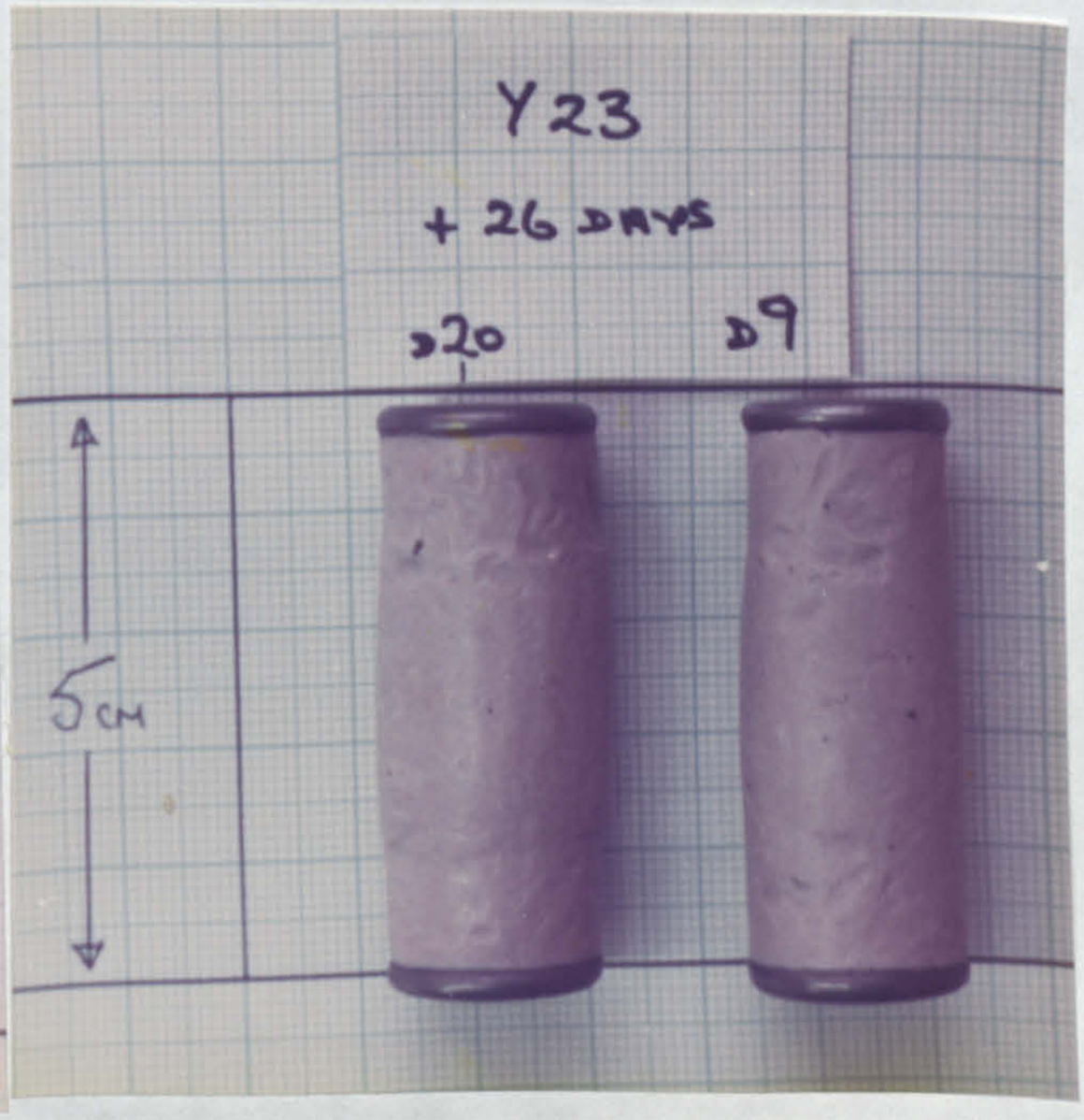


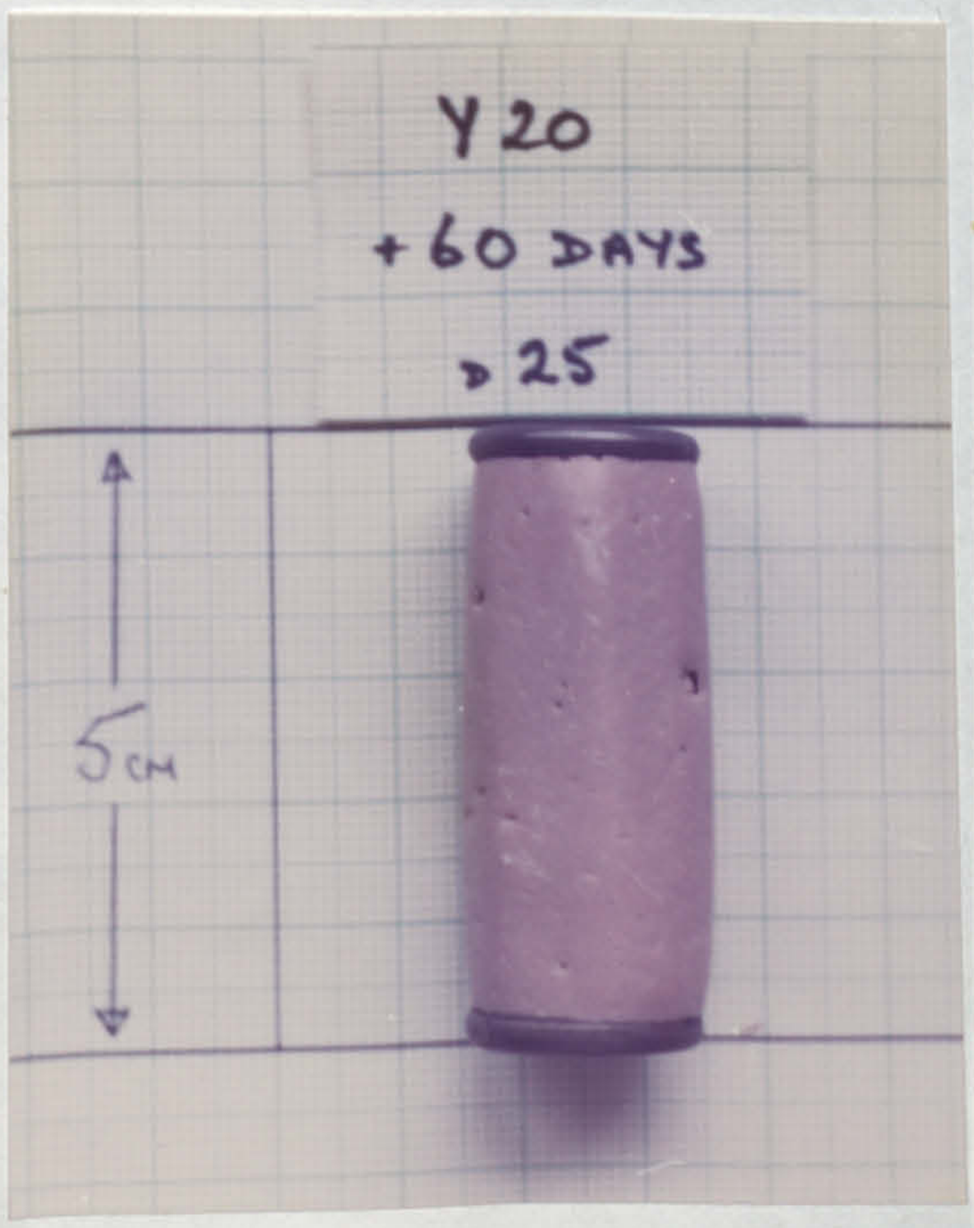
PLATE 23 : MATRIX 8 - PLAIN CONTROL. Experiment 8

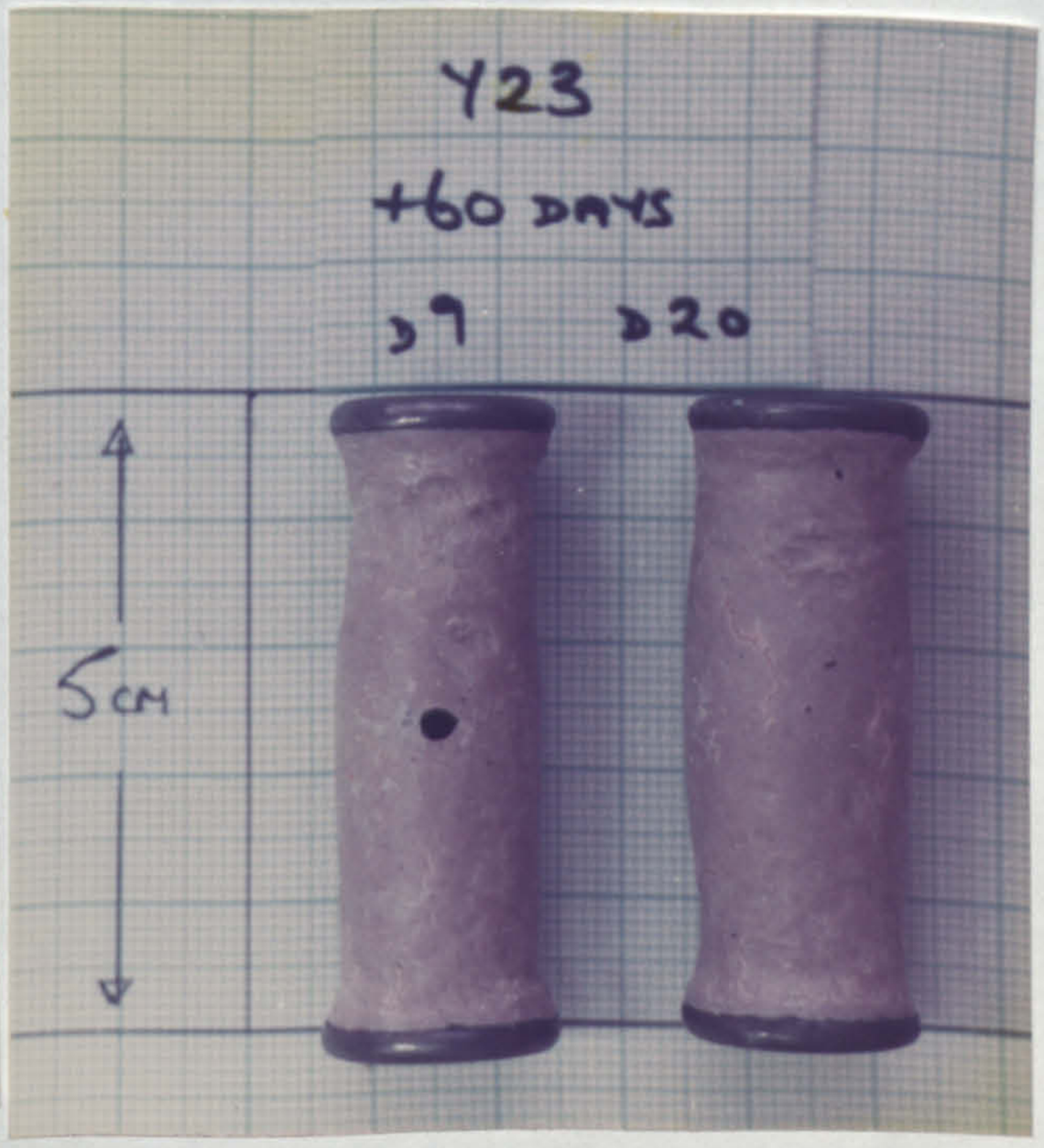












The lambs on test were in the bodyweight range of 28 to 45 kg. The actual daily dosage of thiophanate received per lamb ranged from 0.39 to 0.99 mg per kg bodyweight for a single 'Dobbin' treatment and 2.27 to 5.0 mg per kg for a pair over the total medication period.

8.3. Discussion

This study proved conclusively that with a suitable matrix and using the 'Dobbin' as the "carrier", an increased level of drug release could be achieved by administering the boluses in pairs.

The weight loss of each 'Dobbin' was fairly consistent between the pairs. As in previous studies, a higher release rate was observed during the initial retention period.

All the releasing agents incorporated into the matrix aided the erosion rate, an increased daily weight loss per 'Dobbin' being achieved - 117.1, 129.6, 133.05, 201.9, 126.8, 290.2 and 102.1 mg for matrices 1 to 7 respectively (paired 'Dobbins') compared to a loss of 97.5 mg from the paired control matrix. Because the percentage of thiophanate was lowered to accommodate the various releasing agents, the final drug release achieved per 'Dobbin' during the initial retention period was only improved by the paired 'Dobbins' loaded with matrices 3, 4 and 6 - 79.1, 100.9 and 143.7 mg thiophanate per day compared to a release of 66.5 mg from the control matrix.

The iron powder appeared to assist the erosive process as indicated by matrices 3 and 4 which both contained sugar but the latter also incorporated iron powder from which a higher daily weight loss was achieved from both the single and paired treatments.

From the results obtained with thiophanate in the infusion studies as discussed in Section A, the daily dosage rates achieved from the paired matrices of all but number 7 would have prevented pasture contamination ($\geq$ 3.0 mg thiophanate per kg bodyweight per day) and

matrix numbers 3, 4 and 8 would have been effective against a challenge nematode infection ($\geq$ 4.5 mg thiophanate per kg bodyweight per day). As expected, none of the single dosed 'Dobbins' released a sufficient level of drug.

9. ACTIVITY EXPERIMENT TO COMPARE FOUR PARAFFIN WAX MATRICES DOSED IN PAIRS

The following experiment was designed to monitor the anthelmintic activity of four of the matrices tested in the previous study in order to confirm the conclusions drawn from that trial.

9.1. Experimental data

The four matrices used were:-

1. Matrix 8 - plain control - wax : thiophanate. 31.8 : 68.2 per cent
2. Matrix 6 - 9.8 per cent sucrose with iron powder
3. Matrix 1 - 19.2 per cent salt
4. Matrix 3 - 19.8 per cent granulated sugar.

All metal 'Dobbins' were used with the exception for matrix 6 which was loaded onto nylon rod-metal flanged 'Dobbins'. The final bolus weights ranged from 30.45 to 35.08 gms and their densities were 1.9 to 2.2.

Four lambs were dosed with two 'Dobbins' (1 lamb per matrix) the day following infection with H.contortus, O.circumcincta, T.colubriformis and N.spathiger. Another lamb was infected and retained as an untreated control.

The anthelmintic activity was assessed by nematode faecal egg counts and egg viability and the breakdown of the matrix was monitored by the detection of excreted drug using the plate assay.

The erosion rates were monitored after 26 days ruminal retention and again after a further 34 or 38 days, the subsequent drug release levels being calculated.

9.2. Results

Even erosion occurred between the paired 'Dobbins' in each lamb as shown by the drug release rates summarised in Table 30. Both 'Dobbins' dosed to lamb 2 (sucrose matrix) and one from lamb 4 (granulated sugar matrix) were completely eroded by 60/64 days. The same pattern of erosion was apparent as illustrated previously in Experiment 8 (Plates 20 to 23).

The average lamb weights during the medication period were 30.2, 34.7, 38.0 and 35.2 kg for lambs 1 to 4 respectively. The daily dosage of thiophanate actually received by each lamb was, therefore, 4.5, 6.5, 3.7 and 4.7 mg per kg bodyweight during the first 26 days and 3.8 and 3.2 mg per kg for lambs 1 and 3 during the final retention period.

No faecal nematode egg counts were recorded from lambs 1, 2 and 4 throughout the medication period or for up to 4 weeks after removal of the boluses. The faecal egg count from the remaining treated lamb was recorded positive 24 days after infection but remained low (highest figure recorded - 400 e.p.g.) and the eggs passed were non-viable. The faecal egg count from the untreated control was recorded positive 17 days after infection and remained so throughout the experimental period, rising to a high of 8200 e.p.g., the eggs passed hatching normally.

The diameter measurements of the zones of activity recorded from the faecal drug output on the plate assays are plotted in Fig.16. Faecal samples collected from the untreated control lamb were recorded negative throughout. A consistent drug output was monitored in the faeces from all treated lambs during the medication period. The output from lamb 2 (sucrose matrix) became negative 50 days following treatment and remained so to the end of the medication period.

TABLE 30 : Summary of the drug release rates achieved from paired 'Dobbins'. Experiment 9.

Matrix* No	Lamb No.	'Dobbin' weight (gms)	Recovery + 26 days				Recovery + 60/64 days				+ 26 – + 60/64 days		
			Weight (gms)	Loss (gms)	Mg/day	Mg thiophanate per day	Weight (gms)	Loss (gms)	Mg/day	Mg thiophanate per day	Loss (gms)	Mg/day	Mg thiophanate per day
8	1	31.34	28.82	2.52	96.9	66.1	26.27	5.07	84.5	57.6	2.55	75.0	51.2
		32.25	29.70	2.55	98.1	66.9	27.15	5.1	85.0	58.0	2.55	75.0	51.2
6	2	31.12	25.6	5.52	212.3	104.0	Empty						
		30.45	24.6	5.85	225.0	110.25	Empty						
1	3	33.7	30.71	2.99	115.0	66.4	27.13	6.57	102.6	59.2	3.58	94.2	54.3
		35.08	31.98	3.1	119.2	68.8	28.26	6.82	106.6	61.5	3.72	97.9	56.5
3	4	33.62	30.14	3.48	133.8	79.5	Empty						
		33.87	30.43	3.44	132.3	78.6	27.01	6.86	107.2	63.7	3.42	90.0	53.5

* 8 = wax and thiophanate only (31.8 : 68.2 per cent)

6 = with sucrose and iron powder (21.6 : 49.0 : 9.8 : 19.6 per cent)

1 = with salt (23.1 : 57.7 : 19.2 per cent)

3 = with granulated sugar (20.8 : 59.4 : 19.8 per cent)

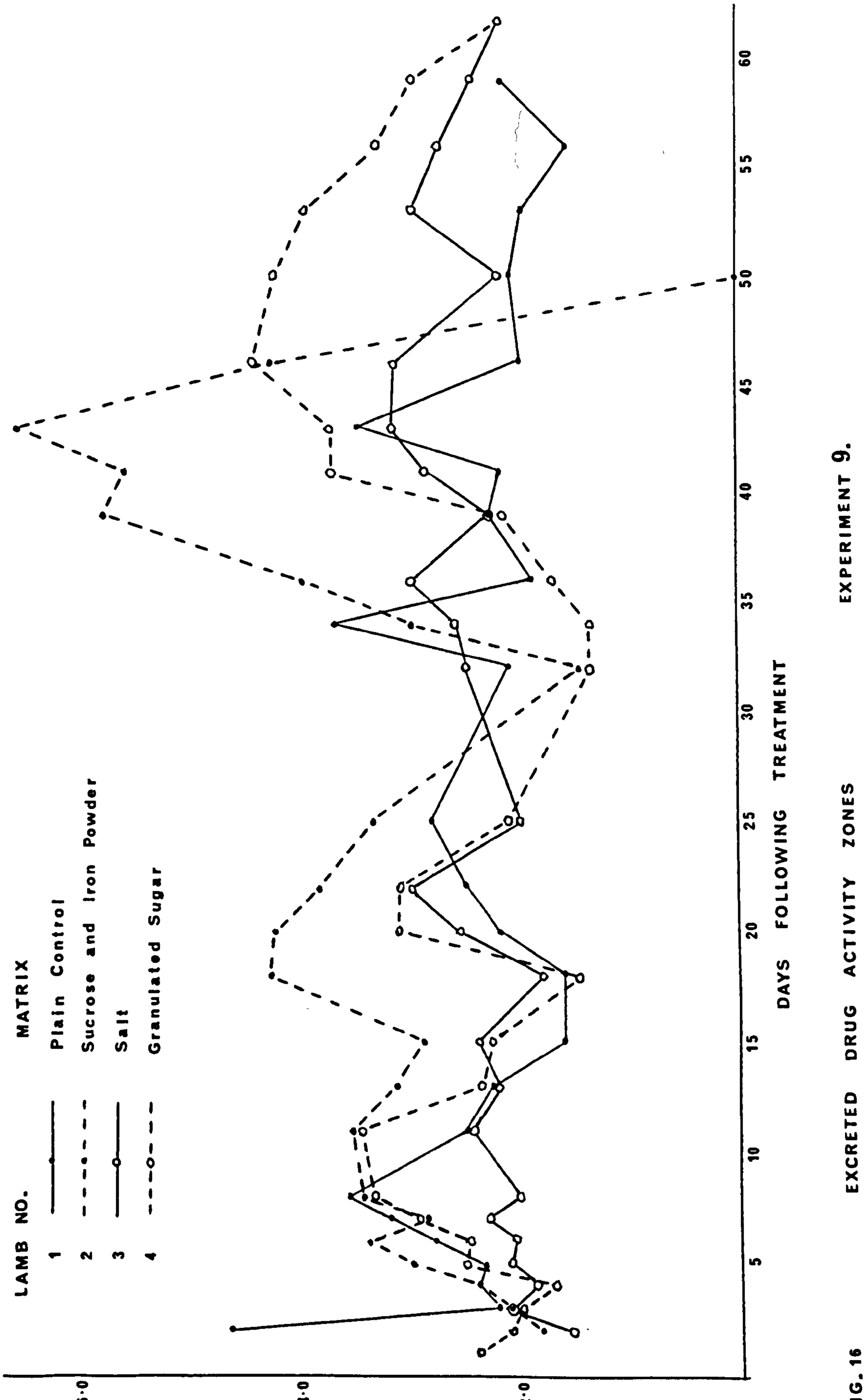

MATRIX
Plain Control
Sucrose and Iron Powder
Salt
Granulated Sugar
LAMB NO.
1
2
3
4
6·0
4·0
2·0
MEAN ZONE DIAMETER (CMS)
5
10
15
20
25
30
35
40
45
50
55
60
DAYS FOLLOWING TREATMENT
EXCRETED DRUG ACTIVITY ZONES
EXPERIMENT 9.

FIG. 16

9.3. Discussion

As previously observed, a higher drug release rate was apparent during the first 26 days of medication. The empty 'Dobbins' recovered from lambs 2 and 4 confirmed the previous recovery results obtained with these matrices (sucrose with iron powder and granulated sugar) in Experiment 8.

The erosion of the 'Dobbins' appeared fairly even from the diameter measurements of the zones of drug activity measured on the plate assay. These readings also confirmed the empty 'Dobbin' recovery results from lambs 2 and 4 by showing an elevated output during the second retention period and in the case of lamb 2, a drop to zero. The zone sizes measured from the faecal samples obtained from lamb 3 gave the steadiest readings but the level of drug released from this salt matrix was not effective anthelmintically.

The conclusions drawn from the previous results (Experiment 8) that the level of drug released from the granulated sugar and plain control matrices would be effective against a nematode challenge was confirmed (lambs 1 and 4). Theoretically, the drug levels from the sucrose with iron powder matrix in Experiment 8 would have prevented pasture contamination but in practice, in the experiment reported here, they were vermicidal. The smaller lamb received a higher daily dosage of thiophanate - 6.5 mg per kg compared to 4.0 mg per kg previously. Even though the matrix had completely eroded by 60 days, the nematode infection would have been mature at the time of the first recovery (26 days), the anthelmintic effect was therefore achieved during this period.

It was also concluded from Experiment 8 that the drug level released from the salt matrix would theoretically have prevented pasture contamination and this was confirmed by the output of non-viable eggs from lamb 3 throughout the period of medication.

Under the conditions of a primary challenge infection as used in this trial, it was concluded that a slow release bolus containing thiophanate incorporated into a wax, a wax/granulated sugar or a wax/sucrose with iron powder matrix was effective in preventing the establishment of a nematode infection when dosed in pairs, and a wax/salt matrix prevented pasture contamination.

All the results obtained so far confirm the observation that this method of medication is an effective means of anthelmintic treatment for ruminants.

10. EXPERIMENTS TO INCREASE THE DRUG RELEASE RATE FROM A SINGLE 'DOBBIN'

The previous studies have shown that by administering the 'Dobbin' in pairs, good anthelmintic activity could be achieved against a primary nematode infection. The use of two boluses however, is not economically viable or always practical in the field. Work was therefore undertaken to try to achieve the required release rate of a minimum of 120 mg thiophanate per day from a single 'Dobbin' by the inclusion into the basic paraffin wax-thiophanate matrix of various groups of releasing aids.

Iron powder was again incorporated into some of the matrices to provide additional density and abrasiveness. All metal 'Dobbins' were used to carry the matrices without iron powder, while nylon rod-metal flanged 'Dobbins' were used for those with. The thiophanate concentrations were kept at the highest feasible level, the amount of wax varied with the consistency of the molten mix.

Each lamb was dosed with one 'Dobbin' of one formulation only. Erosion and subsequent drug release rates were monitored by bolus recovery by rumenotomy at various intervals following dosing.

10.1. Inclusion of digestible materials

Cellulose and starch (insoluble polymeric nutrients) are two substances fermented in the rumen by bacteria. Baker, Nasr, Morrice & Bruce (1950) showed that on introduction into the rumen fluid they are rapidly colonized by certain bacterial species, digesting them.

By incorporating such substances within the matrix, the erosion process would be aided by digestion, theoretically increasing the release of the active component.

Cellulose (sodium carboxymethyl cellulose) and starch (potato starch powder) were incorporated into the wax-thiophanate matrix at various levels between 1 and 18 per cent for cellulose and 5 to 29.5 per cent for starch.

All the 'Dobbins' were retained for both matrix types, the densities ranging from 1.9 to 2.3.

At an inclusion rate above 8.0 per cent, cellulose caused complete disintegration of the matrix within 17 days following dosing. At levels below 8.0 per cent, from the recovery results summarized in Table 31, erratic degradation and cracking of the matrix occurred with a tendency to break away from the "carrier" (Plate 24). The addition of iron powder produced a more stable matrix but the weight loss reached a critical level above which rapid disintegration again occurred.

A high enough percentage of starch could not be incorporated into the matrix to achieve the required drug release (Table 32). Pitting and cracking occurred at the higher inclusion levels (Plate 25). As observed with cellulose, the addition of iron powder increased the drug release rate.

TABLE 31 : Summary of the drug release rates achieved from the inclusion into the matrix of various levels of cellulose. Experiment 10.1.

	Percentage cellulose														
	7.3		4.0	4.0*	3.3	3.2	3.0	3.0*	2.5	2.1	2.0*	1.8*	1.5*		1.0*
Sheep No.	165	599	Y40	40	Y42	Y49	Y15	28	Y50	Y30	Y38	Y31	17	Y3	1673	7
Pre-dose 'Dobbin' weight (gms)	29.64	29.12	32.12	32.83	32.28	34.63	31.94	28.3	34.26	34.42	32.70	34.09	31.59	32.2	32.01	31.17
Day following dosing	10	10	29	24			25	24		35	33		22		19	34
Daily weight loss (mg)	75.0	78.0	260.0	Empty			40.8	Empty		105.0	76.9		32.3		52.1	30.6
Mg thiophanate per day	36.6	38.1	171.6				27.2			70.8	40.0		16.1		26.0	15.3
Day following dosing	34	34			46	49	68		46	60	71	55	62	57	44	62
Daily weight loss (mg)	52.3	37.6			Empty	Empty	86.9		Empty	82.5	Empty	37.4	42.9	33.16	48.6	33.2
Mg thiophanate per day	25.5	18.4					57.9			55.5		17.9	21.4	16.6	24.3	16.6

* Plus iron powder

PLATE 24 : DIGESTIBLE MATERIALS. Experiment 10.1.
3.0 per cent cellulose

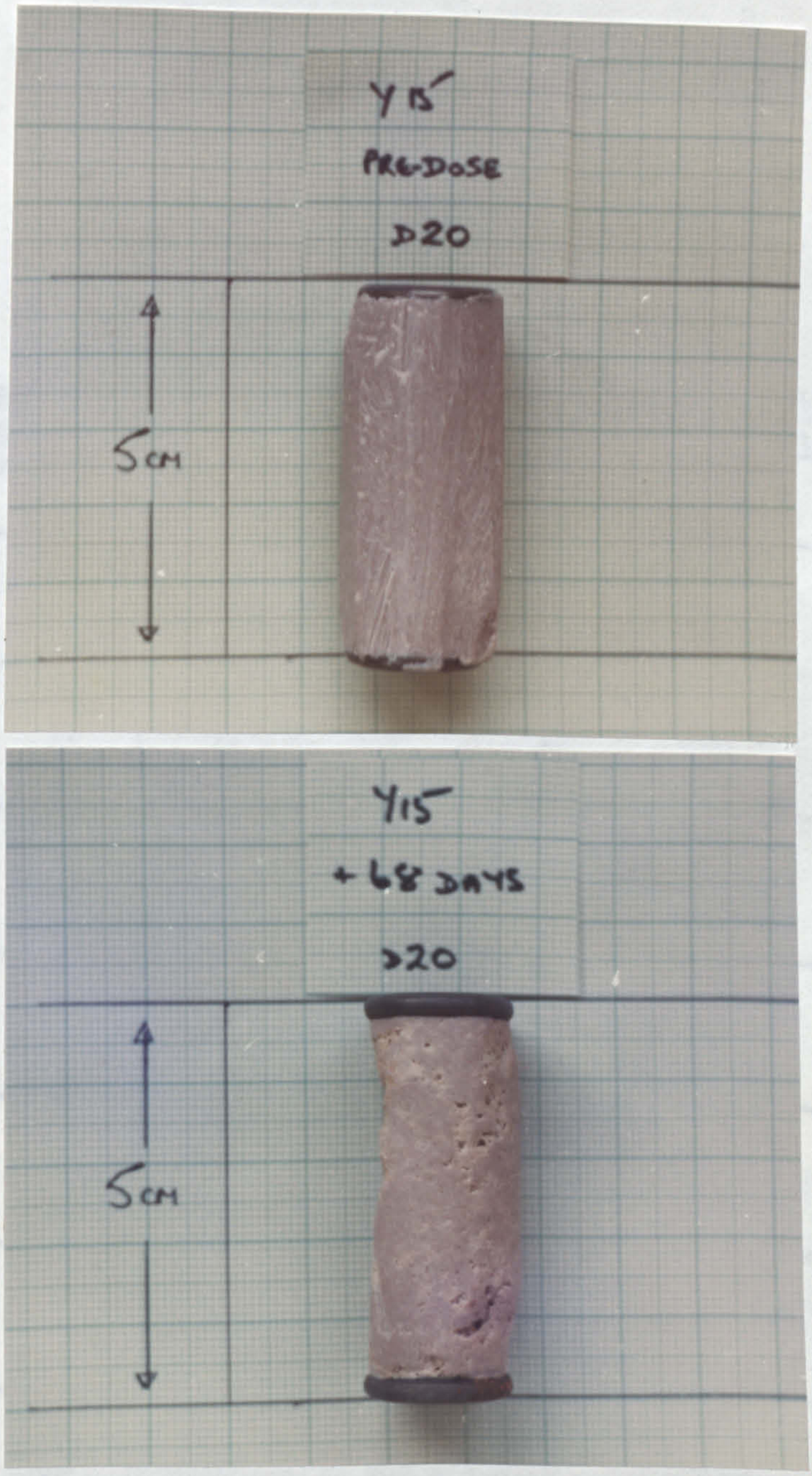
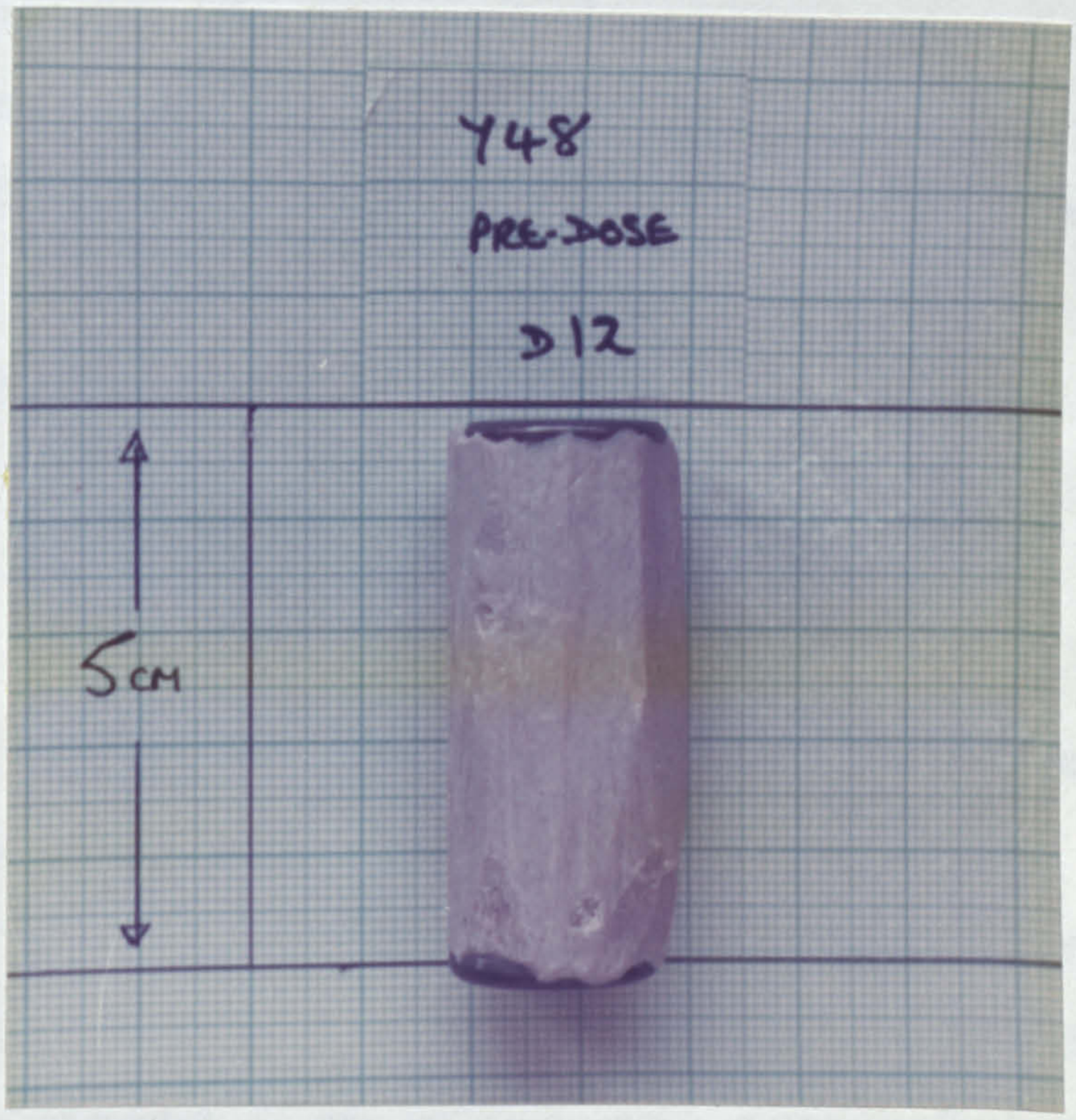


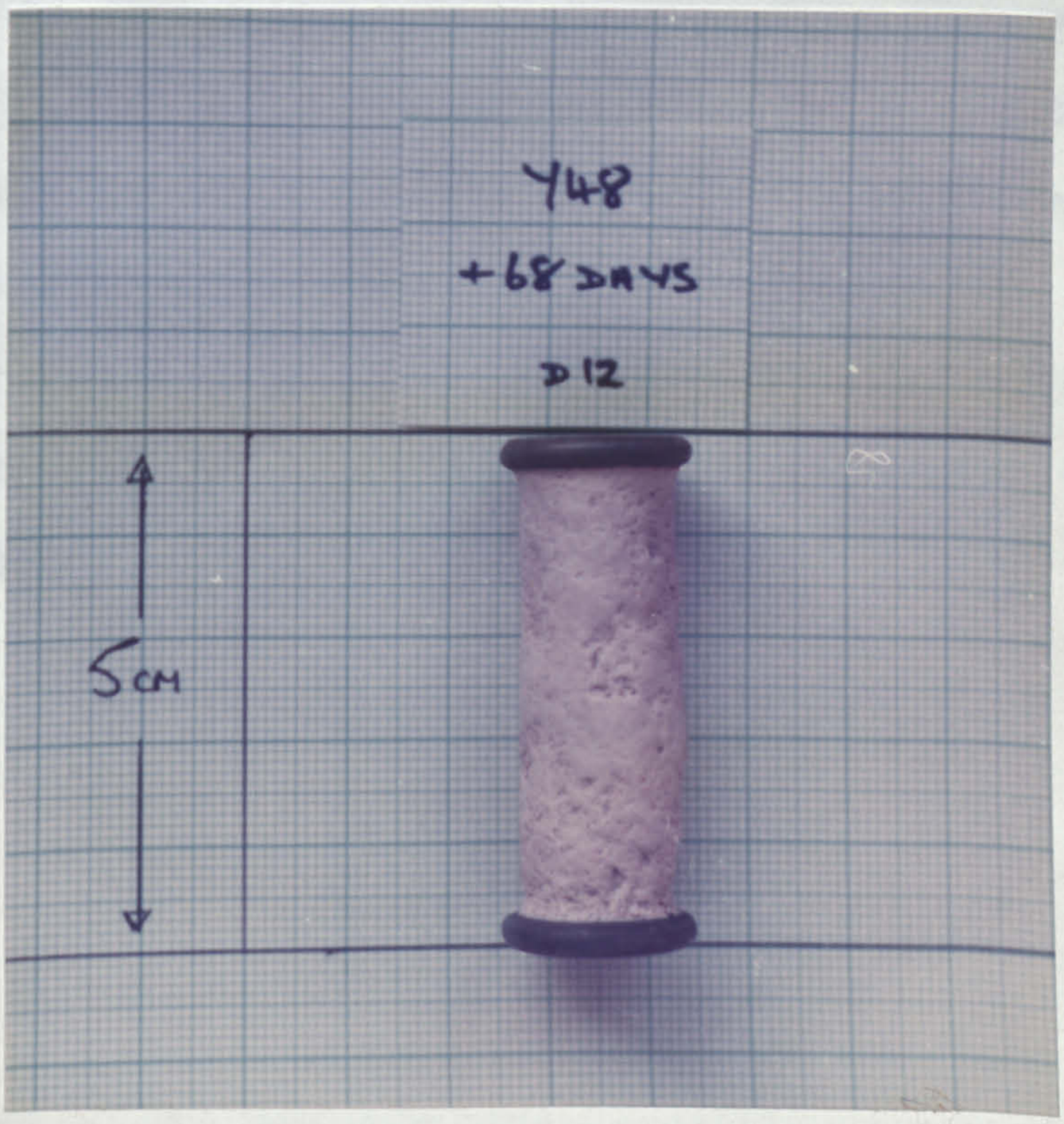
Table 32 : Summary of the drug release rates achieved from the inclusion into the matrix of various levels of starch. Experiment 10.1.

	Percentage starch					
	5.4	11.1*	12.5	20.0*	21.8	29.4
Sheep No.	17	Y7	Y50	Y16	Y55	Y48
Pre-dose 'Dobbin' weight (gms)	31.56	29.76	31.71	32.84	31.54	32.63
Day following dosing	23	23	35	39	23	35
Daily weight loss (mg)	42.6	73.9	44.3	119.2	66.08	109.4
Mg thiophanate per day	28.8	41.1	27.7	59.6	35.9	53.6
Day following dosing	60	60	67		60	68
Daily weight loss (mg)	30.1	64.7	38.5		58.5	95.4
Mg thiophanate per day	20.4	35.9	24.1		31.8	46.8

* Plus iron powder

PLATE 25 : DIGESTIBLE MATERIALS. Experiment 10.1.
29.4 per cent starch





10.2. Inclusion of a wetting agent

Three wetting agents were selected - Tween 80, Melfoam* and Tragacanth mucilage. The latter had already been used successfully in the infusion studies (Section A) and in a previous bolus formulation (Experiment 8) with no adverse side effects occurring in any treated animal.

These agents were incorporated into the matrix at various percentage levels between 0.05 and 0.5, 0.1 and 1.4 and 4.8 and 28.9 for Tween 80, Melfoam and Tragacanth mucilage respectively.

All the 'Dobbins' were retained for all the matrix types, their densities ranging from 1.7 to 2.5.

Only a small increase in the amount of Tween 80 (from 0.2 to 0.23 per cent) or Melfoam (0.5 to 0.7 per cent) was required before disintegration occurred as the release rates summarised in Tables 33 and 34 indicate. Very little erosion occurred below this level with Tween 80. 0.5 per cent Melfoam released 122.7 mg thiophanate per day over 43 days but the matrix appeared very pliable when recovered (Plate 26). As observed with the digestible materials, the inclusion of iron powder increased the disintegration rate - complete with 0.2 per cent Tween 80 and 0.5 per cent Melfoam. As previously, very little erosion occurred below this level with Tween 80 (Plate 27).

*Melfoam household detergent - Melzone Manufacturing Co.Ltd.

TABLE 33 : Summary of the drug release rates achieved from the inclusion into the matrix of various levels of Tween 80. Experiment 10.2.

	Percentage Tween 80																	
	0.5*	0.4	0.3		0.23	0.2	0.2*		0.19	0.18*		0.16*	0.15*	0.12	0.1*		0.05*	
Sheep No.	1681	Y22	62	Y40	Y54	Y49	1675	Y46	Y19	Y44	Y17	1689	1678	Y34	25	13Y	1675	1670
Pre-dose 'Dobbin' weight (gms)	31.76	32.22	33.01	33.31	32.14	33.3	31.29	32.11	32.13	32.72	32.10	32.56	32.32	34.38	31.22	30.52	32.08	31.57
Day following dosing	19	29		33	19	35	20	16	25		36	25	18	25	24	47	46	15
Daily weight loss (mg)	Empty	Empty		Empty	Empty	42.0	Empty	Empty	52.0		36.9	71.2	49.4	41.2	78.3	55.9	46.3	62.0
Mg thiophanate per day						29.9			37.1		18.5	35.6	24.7	29.4	39.2	27.9	23.0	31.0
Day following dosing			40							53		60	69		62	70	84	60
Daily weight loss (mg)			Empty							Empty		65.2	44.2		55.3	52.1	38.7	48.7
Mg thiophanate per day												32.6	22.1		27.7	26.1	19.3	24.3

* Plus iron powder

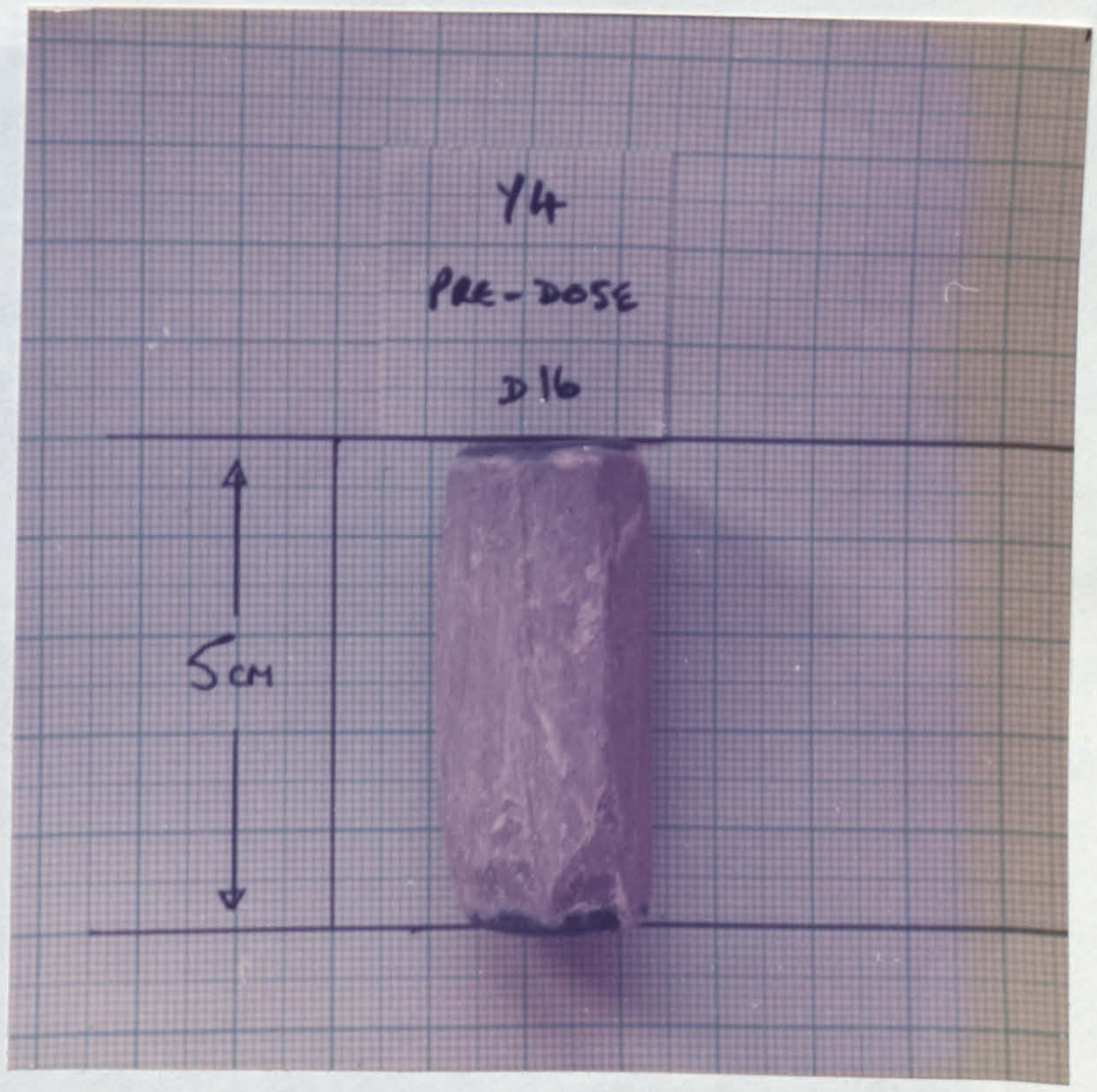
Table 34 : Summary of the drug release rates achieved from the inclusion into the matrix of various levels of Melfoam. Experiment 10.2.

	Percentage Melfoam							
	1.4	0.7	0.5	0.5*	0.4*	0.3*	0.1*	
Sheep No.	Y13	Y20	Y4	27	Y49	Y39	34	109
Pre-dose 'Dobbin' weight (gms)	31.19	32.03	32.65	30.37	34.43	34.85	35.57	36.06
Day following dosing		35		19	40	25	16	30
Daily weight loss (mg)		Empty		Empty		74.0	51.8	50.3
Mg thiophanate per day						37.0	25.8	25.1
Day following dosing	42		43		40	68	44	76
Daily weight loss (mg)	Empty		172.6		166.7	70.1	49.0	45.3
Mg thiophanate per day			122.7		89.4	35.1	24.5	22.6

* Plus iron powder

PLATE 26 : <u>WETTING AGENTS.</u> Experiment 10.2.

<u>0.5 per cent Melfoam</u>



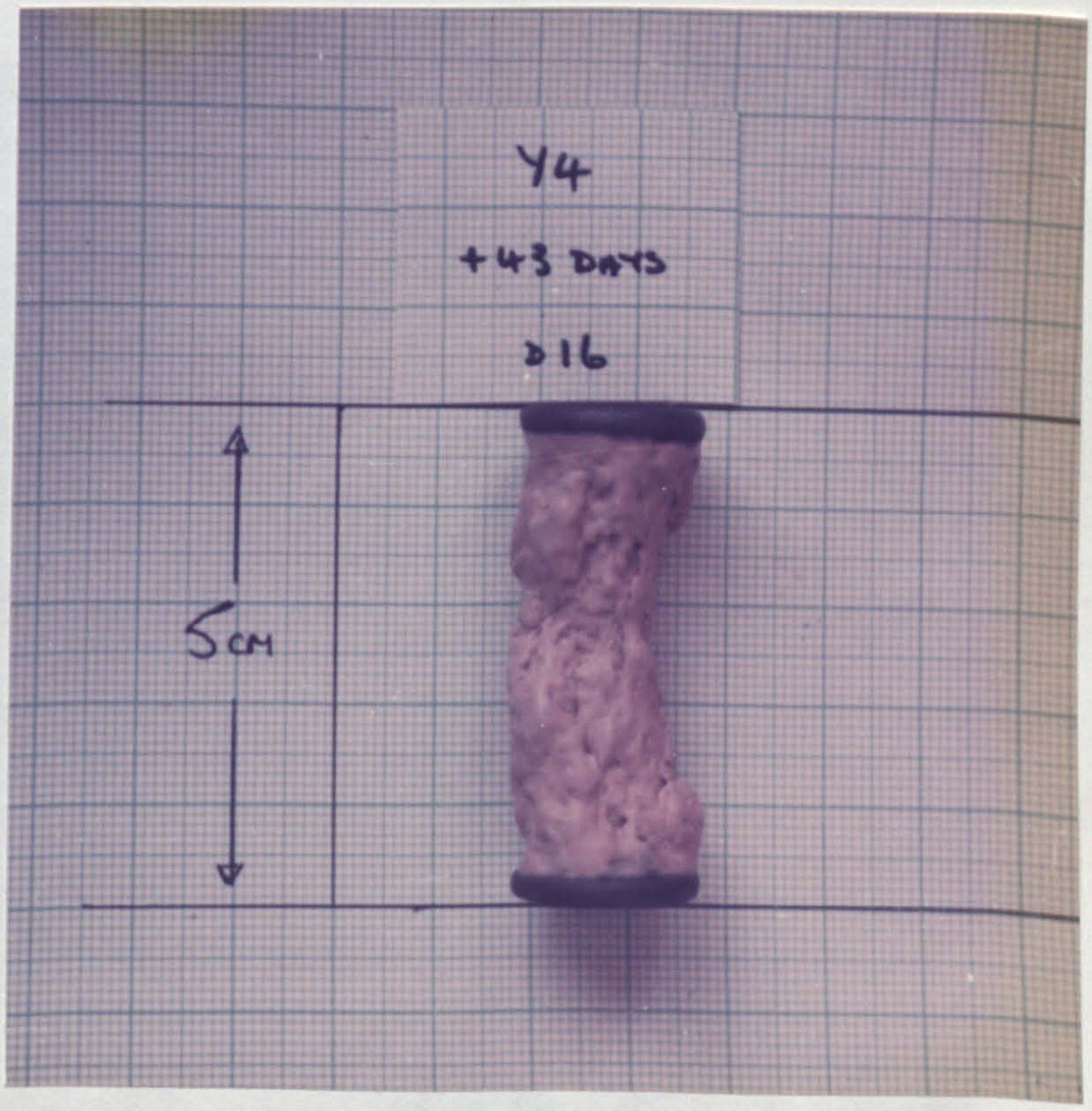
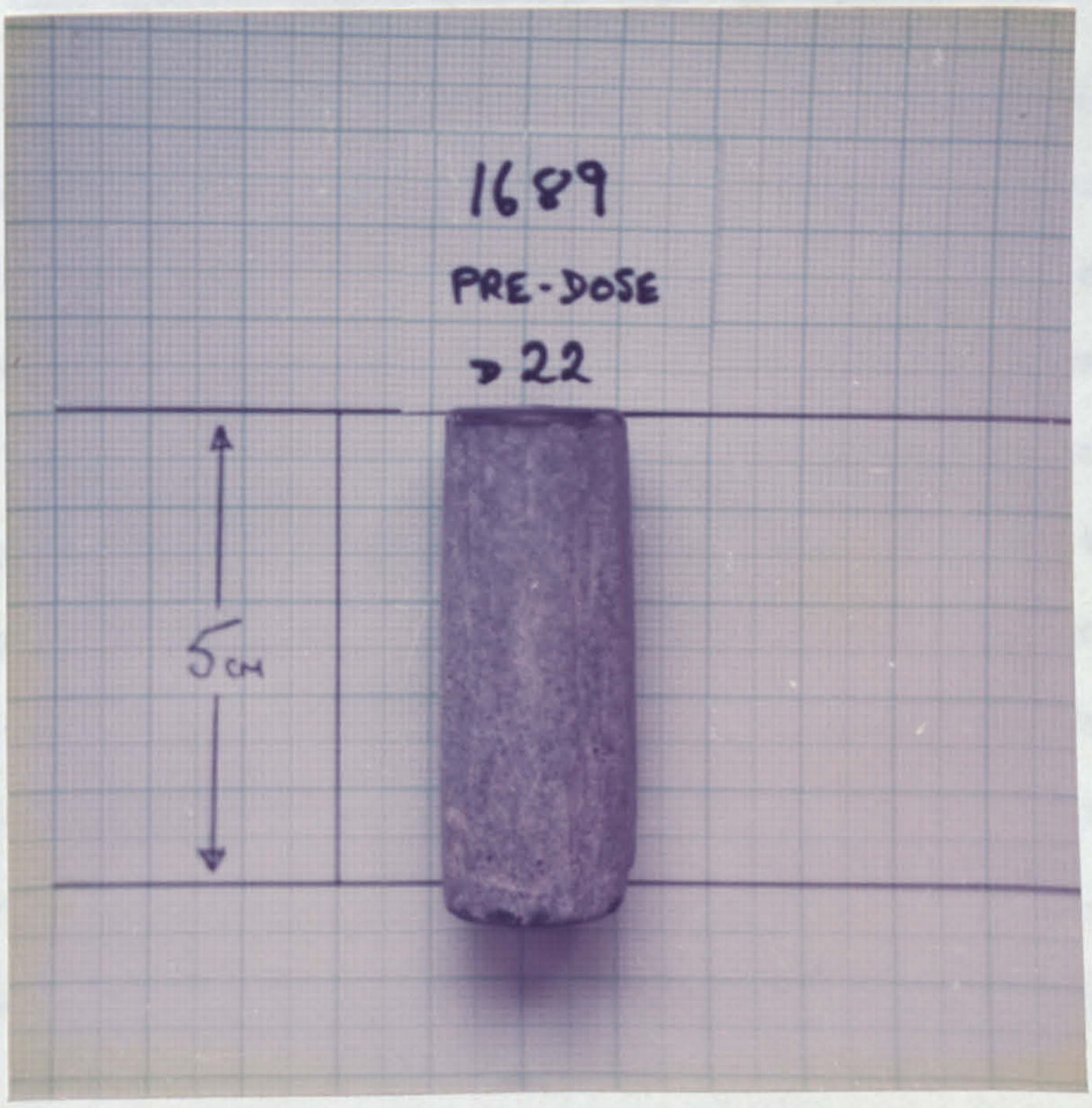
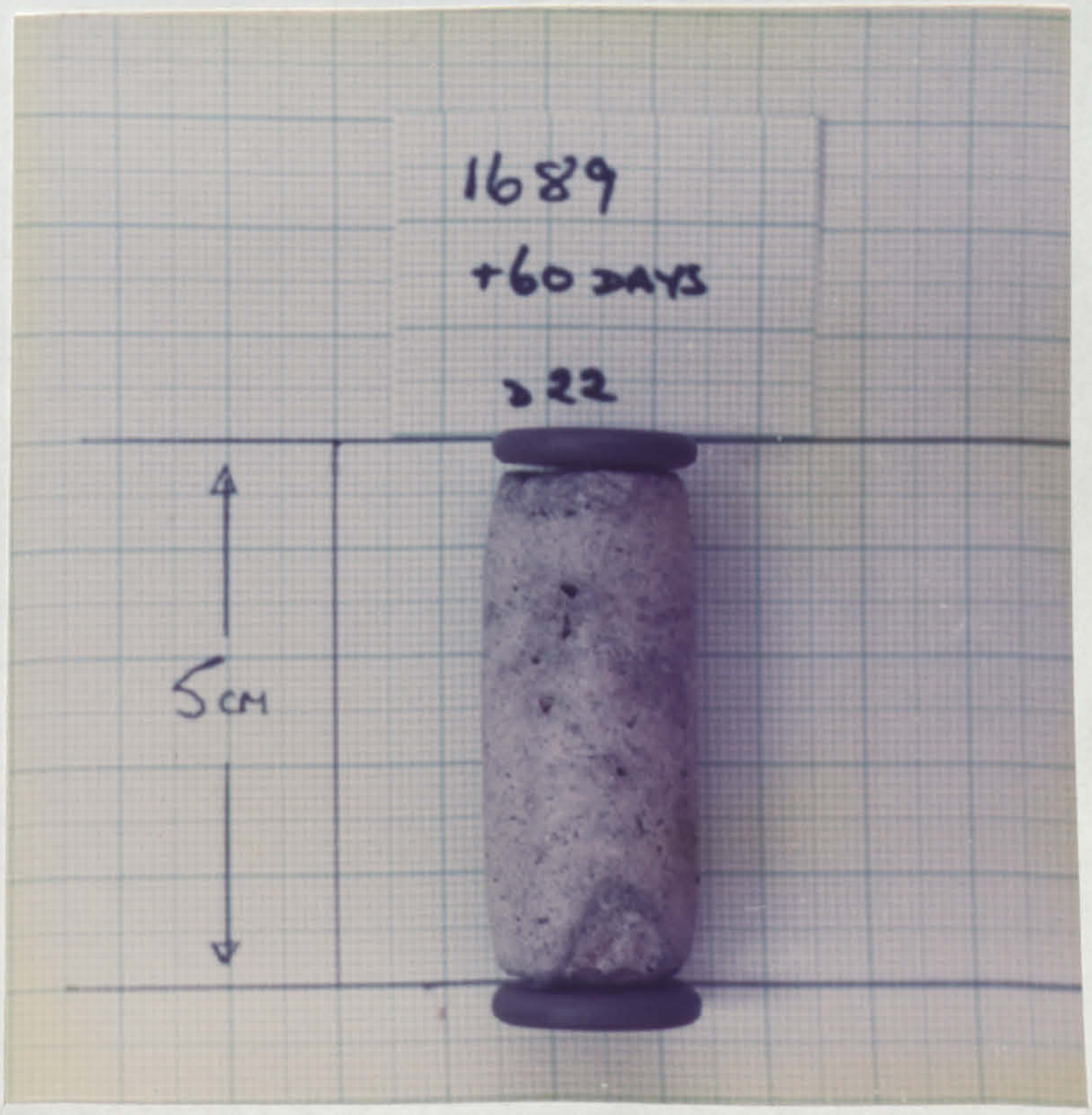


PLATE 27 : WETTING AGENTS. Experiment 10.2.
0.16 per cent Tween 80 with iron powder





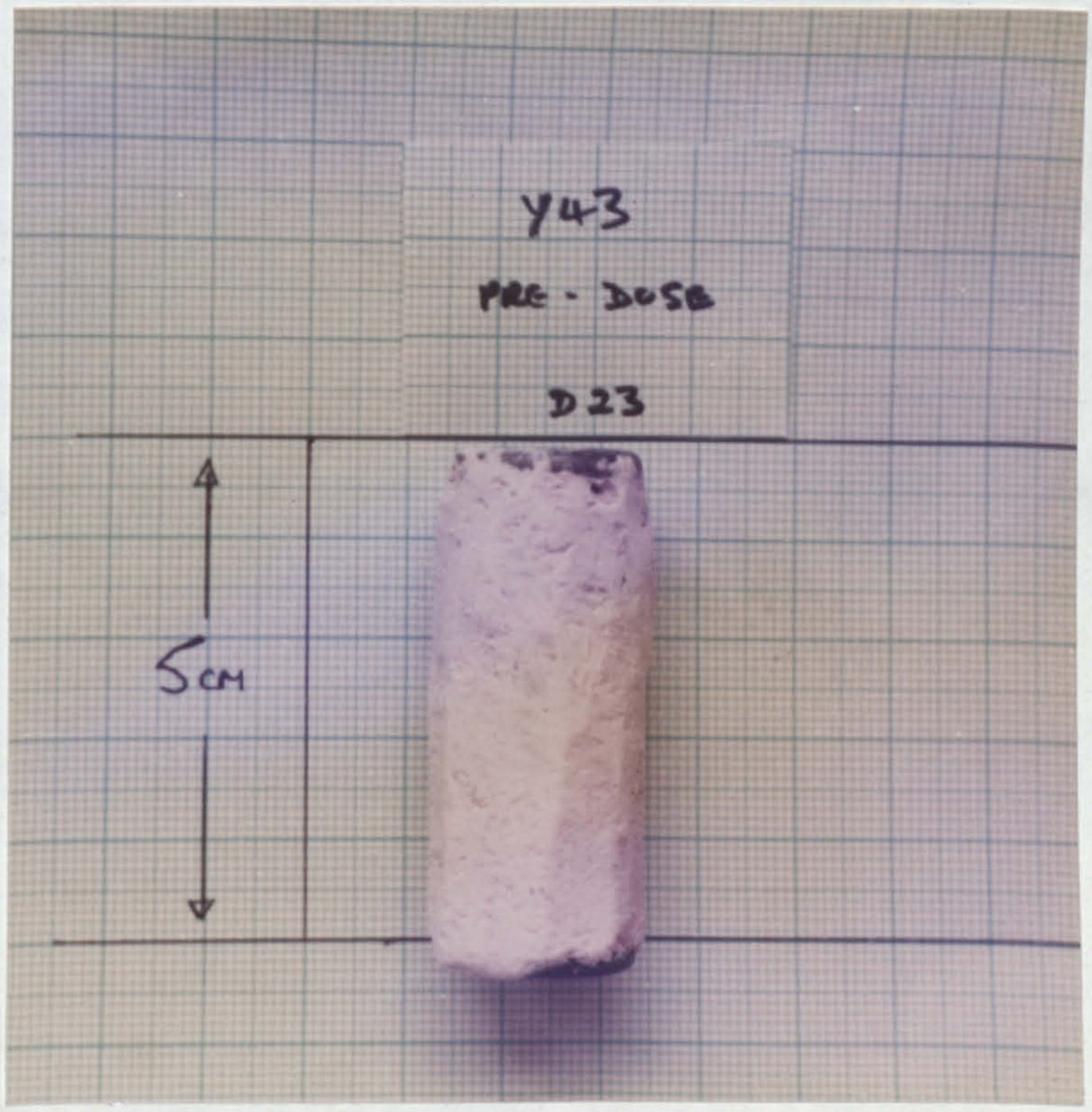
By using a mucilage, higher levels of Tragacanth could be incorporated without the mix becoming too dry, but a critical level was reached above which the amount of wax was too low to harden the formulation. The release rates obtained with Tragacanth are summarised in Table 35. At the highest inclusion level of 28.9 per cent, a release of 164.9 mg thiophanate per day over 35 days, averaging out to 124.6 mg over 59 days was achieved. At a level one per cent less, a daily release of 157.7 mg was achieved over 49 days (Plate 28). An increase in the wax level of 3 to 5 per cent appeared to increase the daily weight loss if the Tragacanth level was kept above 26 per cent. The addition of iron powder lowered the level of thiophanate that could be incorporated, so consequently a lower drug release rate was recorded. Comparing the 'Dobbins' recovered from sheep Y39 and Y14 (24 and 25 per cent Tragacanth), the daily weight loss was comparable but the final drug release dropped from 106 to 89 mg due to the inclusion of iron powder (lamb Y14).

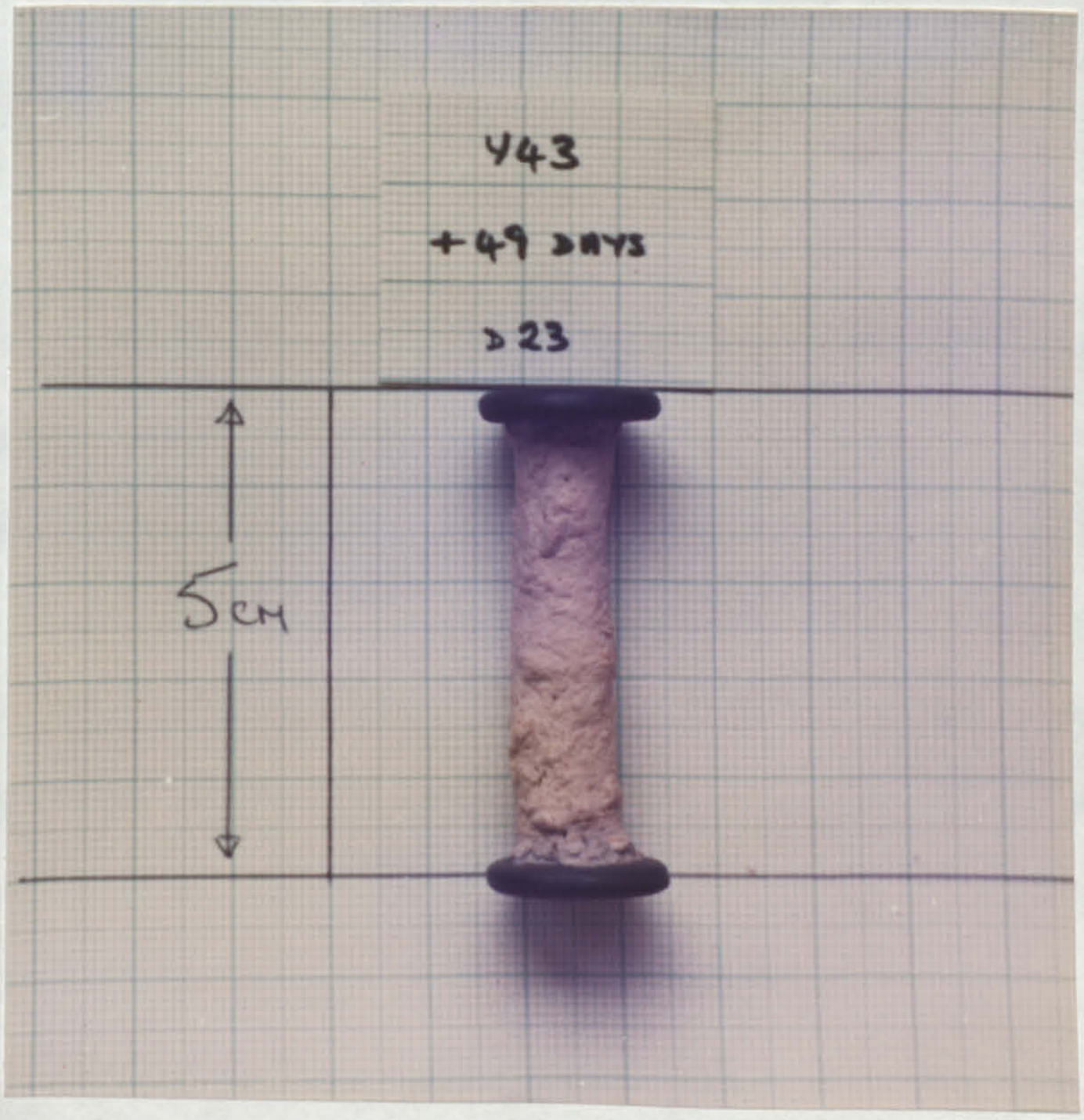
TABLE 35 : Summary of the drug release rates achieved from the inclusion into the matrix of various levels of Tragacanth mucilage. Experiment 10.2.

	Percentage Tragacanth mucilage												
	4.8*	10.0*	11.1	16.7*	18.1*	19.3	22.0*	24.1	25.0*	26.8		27.9	28.9
Sheep No.	178	1700	Y38	1686	Y28	17	Y18	Y39	Y14	64	Y31	Y43	1676
Pre-dose 'Dobbin' weight (gms)	33.31	29.91	31.59	29.81	31.96	31.16	35.19	35.31	29.64	29.98	32.64	34.21	33.15
Day following dosing	31	20	19	35	32	31				35	31		35
Daily weight loss (mg)	34.8	41.5	58.4	22.3	107.5	87.7				280.0	273.2		268.3
Mg thiophanate per day	16.5	20.7	38.9	11.6	58.6	53.9				164.9	160.9		164.9
Day following dosing	76	59	61	70	64	62	58	52	42		72	49	59
Daily weight loss (mg)	30.9	40.2	41.8	25.4	95.9	70.5	101.2	173.8	178.0		Empty	266.3	202.5
Mg thiophanate per day	14.7	20.1	27.9	13.2	52.3	43.3	54.65	106.2	89.0			157.7	124.6

* Plus iron powder

PLATE 28 : WETTING AGENTS. Experiment 10.2.
27.9 per cent Tragacanth mucilage





10.3. Inclusion of a soluble releasing agent

Sugars, as well as being highly soluble are also fermented by the rumen bacteria. The addition of sugars of various types and particle sizes within the matrix should therefore aid the drug release three-fold by erosion, digestion and solubility.

Three household solid sugars were selected - granulated, icing and demerara (for variation of particle size with one sugar type, demerara was also incorporated ground to a powder). Since a high release rate was achieved in the previous study with a mucilage, golden syrup was also included. Sucrose and glucose as basic sugars were tried and also salt.

The following ranges of percentage inclusion levels were used:-

Granulated sugar - 10 to 30

Icing sugar - 22 to 31

Glucose - 1 to 31

Sucrose - 0.1 to 29

Demerara sugar - 19 and 30 only

Syrup - 11 to 20

Salt - 1 to 30

All the 'Dobbins' were retained for all matrix types, their densities ranging from 1.8 to 2.4.

As observed previously with a starch matrix a high level of granulated sugar, glucose, demerara sugar or salt could not be incorporated to give a realistic drug release level. The rates obtained from all the soluble releasing agents are summarised in Tables 36 to 38. Examples of the various matrices at recovery are illustrated in Plates 29 to 31.

TABLE 36 : Summary of the drug release rates achieved from the inclusion into the matrix of various levels of either granulated sugar or icing sugar. Experiment 10.3.

	Percentage granulated sugar										Percentage icing sugar				
	10.0		15.0*	19.2	19.8		20.0*	20.0	25.0*	30.0	21.7	24.6	28.6	29.7	30.8
Sheep No.	1692	1691	Y30	64	1689	1679	Y25	Y28	Y37	25	24	Y33	Y43	Y24	Y41
Pre-dose 'Dobbin' weight (gms)	30.64	31.38	32.04	34.84	32.47	33.03	30.68	36.25	32.18	33.13	34.68	33.79	32.74	34.58	34.47
Day following dosing	47	24	29			18	32	19		43	35	35	35		
Daily weight loss (mg)	40.6	46.25	88.9			73.9	98.4	106.8		92.3	178.3	141.0	194.0		
Mg thiophanate per day	24.4	27.7	44.5			43.9	49.2	64.1		48.1	96.8	69.4	92.3		
Day following dosing	70	62	60	40	51	69	71	61	40	68	59	59	68	63	48
Daily weight loss (mg)	38.7	37.1	74.2	72.0	67.8	59.1	82.8	73.9	106.5	81.9	Empty	167.9	198.9	Empty	Empty
Mg thiophanate per day	23.2	22.2	37.1	41.5	40.3	35.1	41.4	44.14	53.2	40.9		82.6	94.7		

* Plus iron powder

TABLE 37 : Summary of the drug release rates achieved from the inclusion into the matrix of various levels of either sucrose or glucose. Experiment 10.3.

	Percentage sucrose										Percentage glucose							
	0.1*		1.0*		9.9*	27.3	28.6		28.8		1.0*		10.0*	19.2	20.0*	25.0*	26.7	31.2
Sheep No.	808	094	281	791	1644	Y50	Y2	Y14	82	8	16	1686	5	1695	1692	Y35	Y46	28
Pre-dose 'Dobbin' weight (gms)	35.75	36.72	35.62	36.85	33.53	31.95	35.87	35.33	33.65	33.41	30.17	30.19	31.3	32.37	31.15	30.95	33.18	32.05
Day following dosing		15	15		15	29		34	35	31	34	19	20	17	42	32	31	20
Daily weight loss (mg)		49.3	58.7		76.7	151.7		283.5	262.6	272.9	62.0	61.0	73.5	51.2	80.7	110.6	78.1	92.5
Mg thiophanate per day		24.6	29.5		37.9	68.9		134.9	126.0	131.3	31.0	30.5	36.7	29.5	40.3	55.3	39.0	43.4
Day following dosing	61	68	68	61	68	60	42	72	57	55	62	44	59	56	77	64	76	56
Daily weight loss (mg)	43.6	43.5	45.7	54.4	74.8	143.0	225.0	Empty	Empty	240.4	54.2	52.3	52.7	41.2	86.1	101.4	71.9	103.6
Mg thiophanate per day	21.8	21.7	22.9	27.2	37.0	64.9	107.1			115.6	27.1	26.1	26.3	23.8	43.1	50.7	35.9	48.6

* Plus iron powder

TABLE 38 : Summary of the drug release rates achieved from the inclusion into the matrix of various levels of either demerara sugar, syrup or salt. Experiment 10.3.

	Percentage demerara sugar			Percentage syrup						Percentage salt					
	19.8		30.0	11.1	16.7	17.2*	20.0*	20.0		1.0*		10.0*	19.2	20.0*	30.0
Sheep No.	Y13	Y29‡	Y33‡	Y18	Y37	Y34	Y15	Y51**	Y45	1696	6	8	1694	Y22	21
Pre-dose 'Dobbin' weight (gms)	35.83	33.88	35.11	33.97	35.36	35.34	35.61	34.89	35.61	30.28	31.23	30.45	33.07	29.84	34.06
Day following dosing	35	35	38	25	35					34	19	22	17	24	33
Daily weight loss (mg)	83.7	92.0	148.7	172.4	157.7					35.3	37.9	69.1	78.8	67.5	86.9
Mg thiophanate per day	49.7	54.6	74.3	115.0	98.6					17.6	18.9	34.5	45.5	33.75	43.5
Day following dosing	70	70	79			40	41	40	55	62	44	62	56	59	64
Daily weight loss (mg)	67.1	78.1	113.8			Empty	277.3	Empty	168.4	30.3	35.4	55.3	52.3	61.2	70.5
Mg thiophanate per day	39.9	46.4	56.9				138.6		101.0	15.2	17.1	27.7	30.2	30.6	35.2

* Plus iron powder

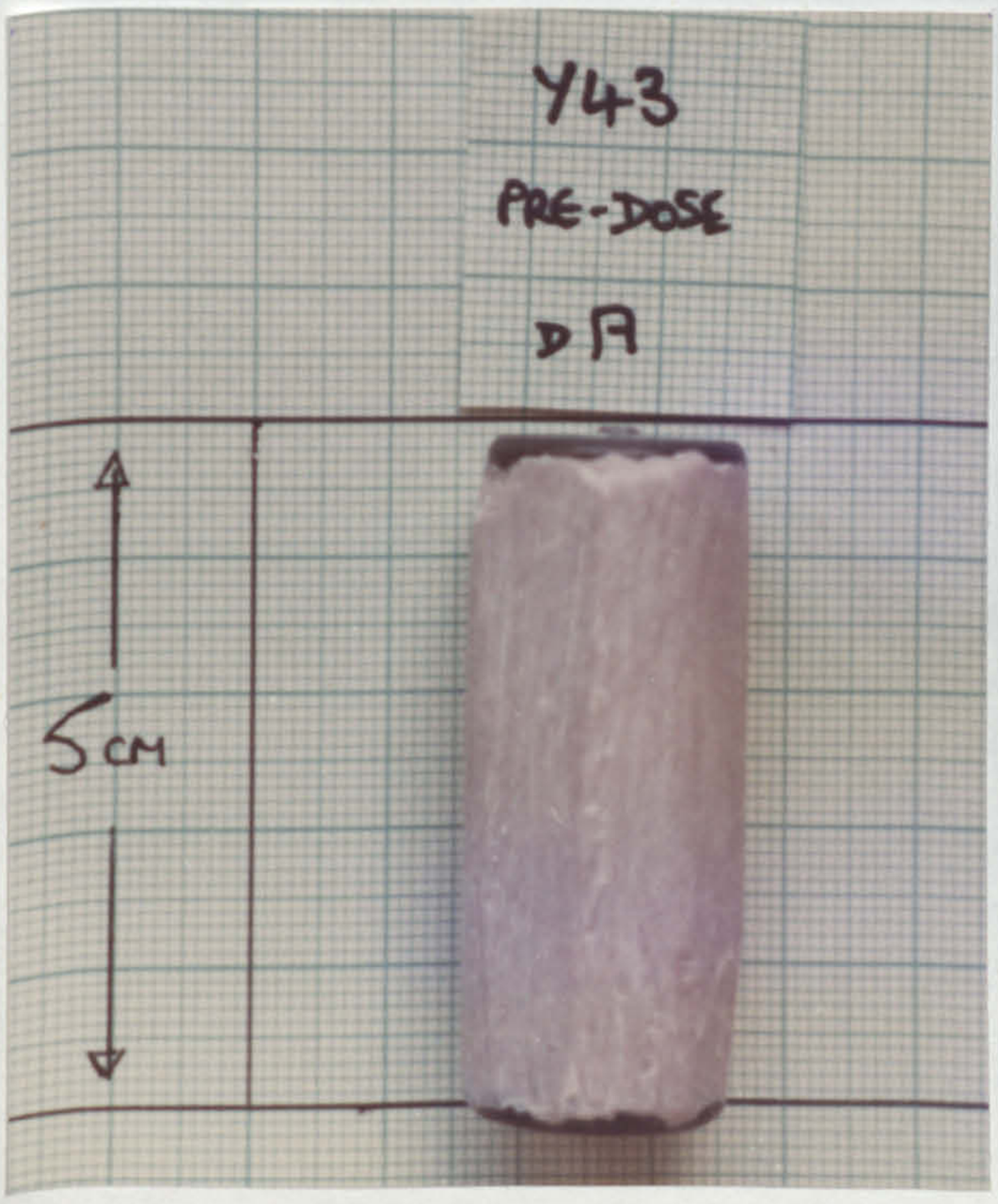
** Lower percentage of wax

‡ Powdered sugar

PLATE 29 : SOLUBLE RELEASING AGENTS. Experiment 10.3.

20 per cent granulated sugar with iron powder

28.6 per cent icing sugar



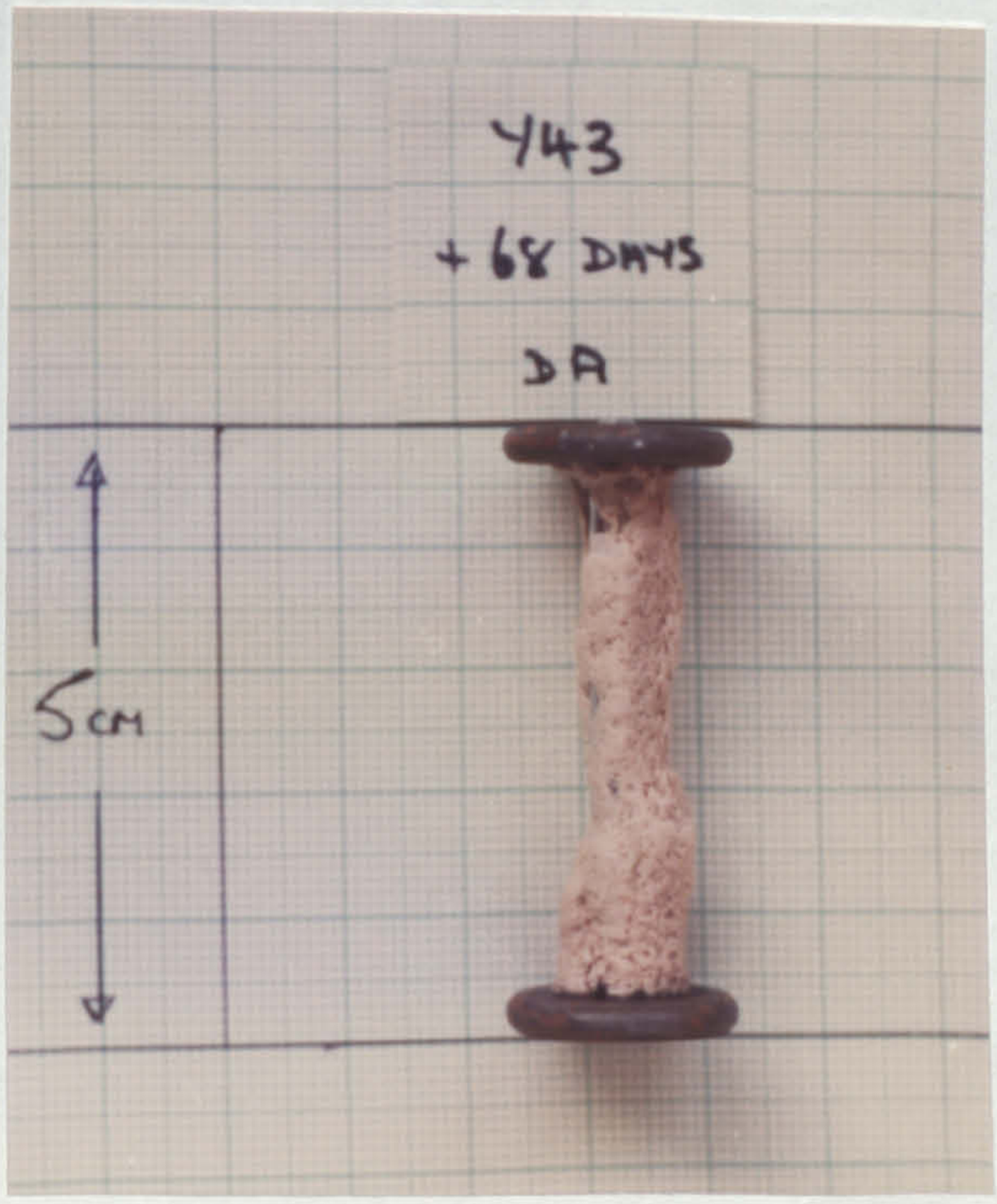
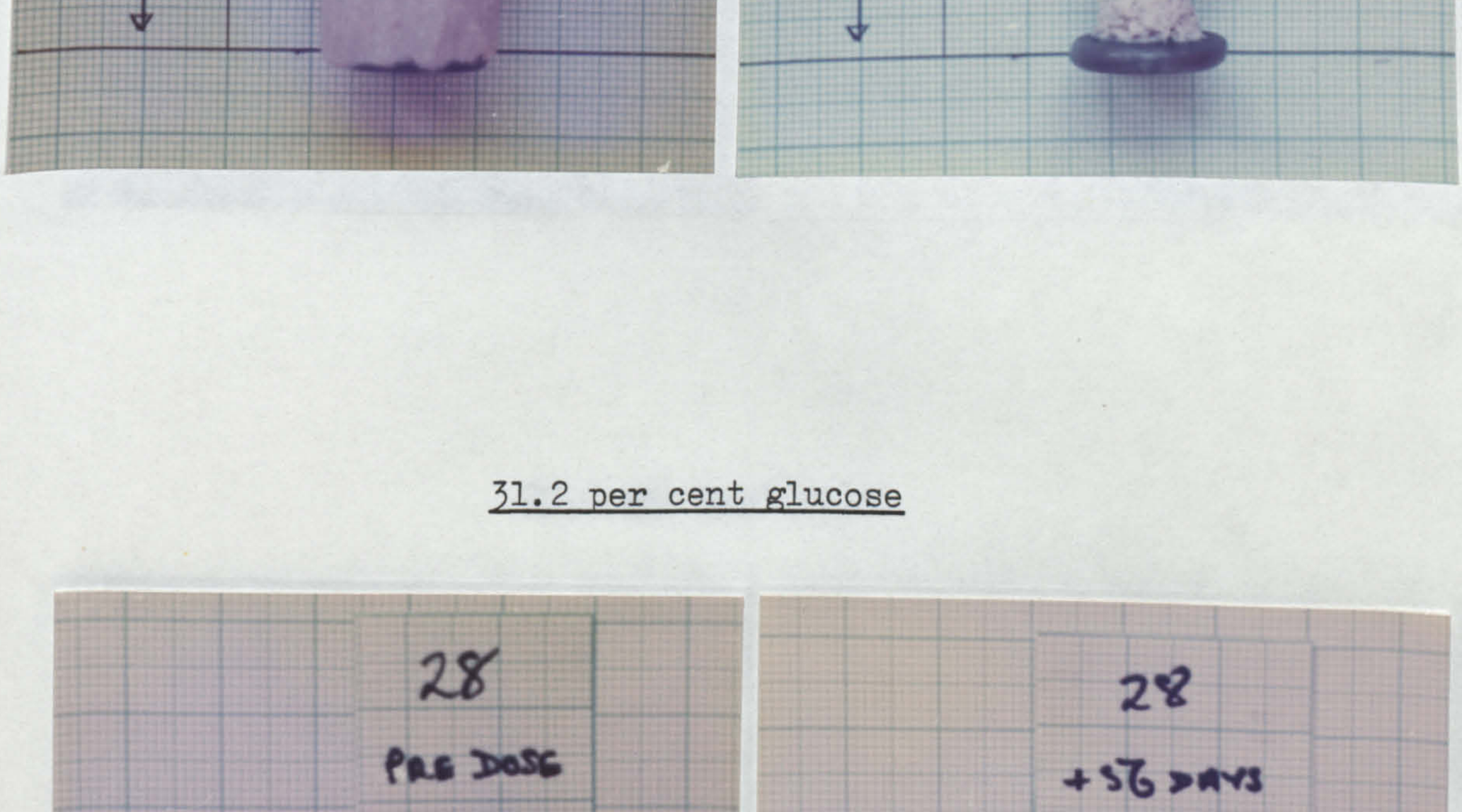


PLATE 30 : SOLUBLE RELEASING AGENTS. Experiment 10.3.

28.8 per cent sucrose



31.2 per cent glucose

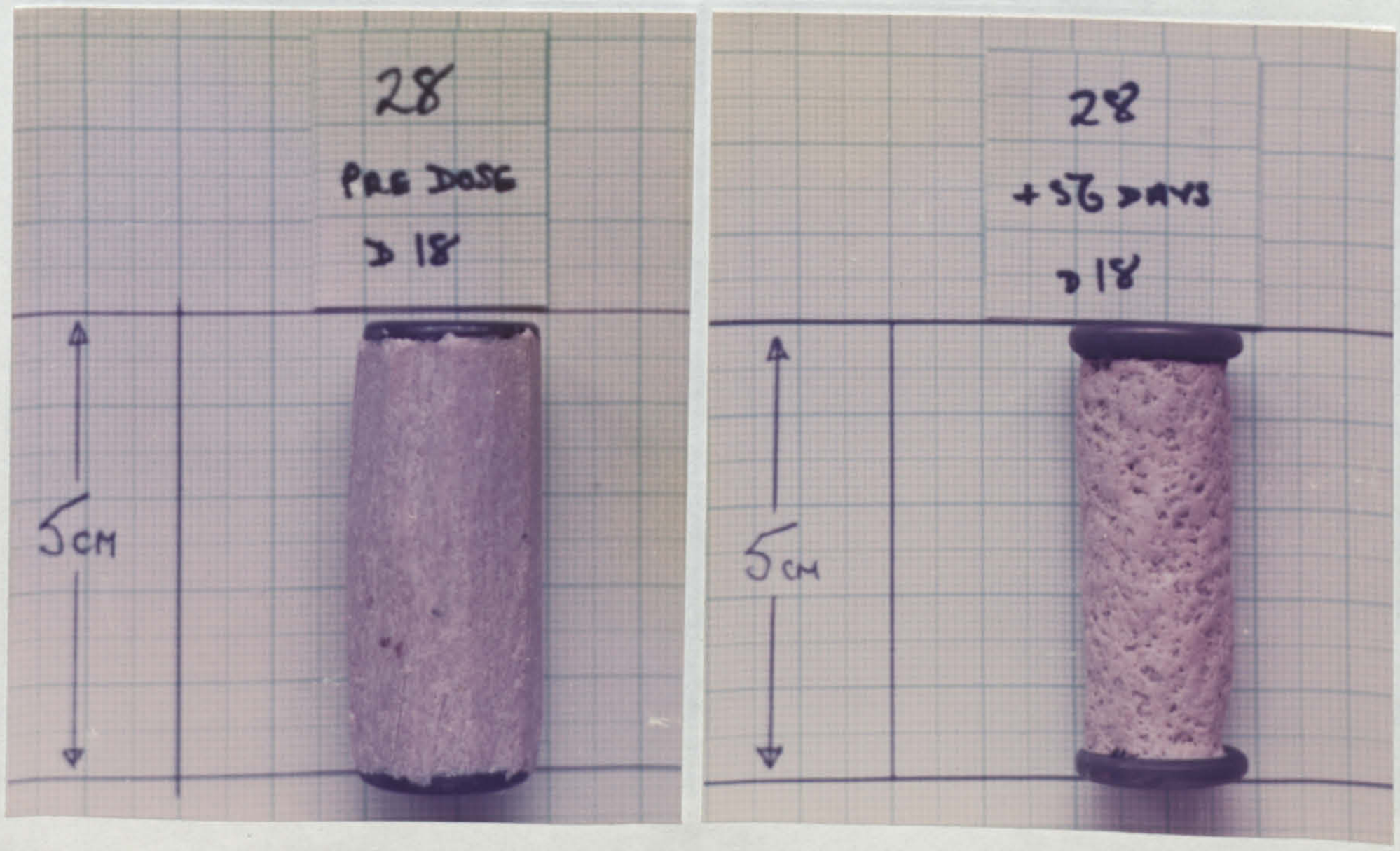
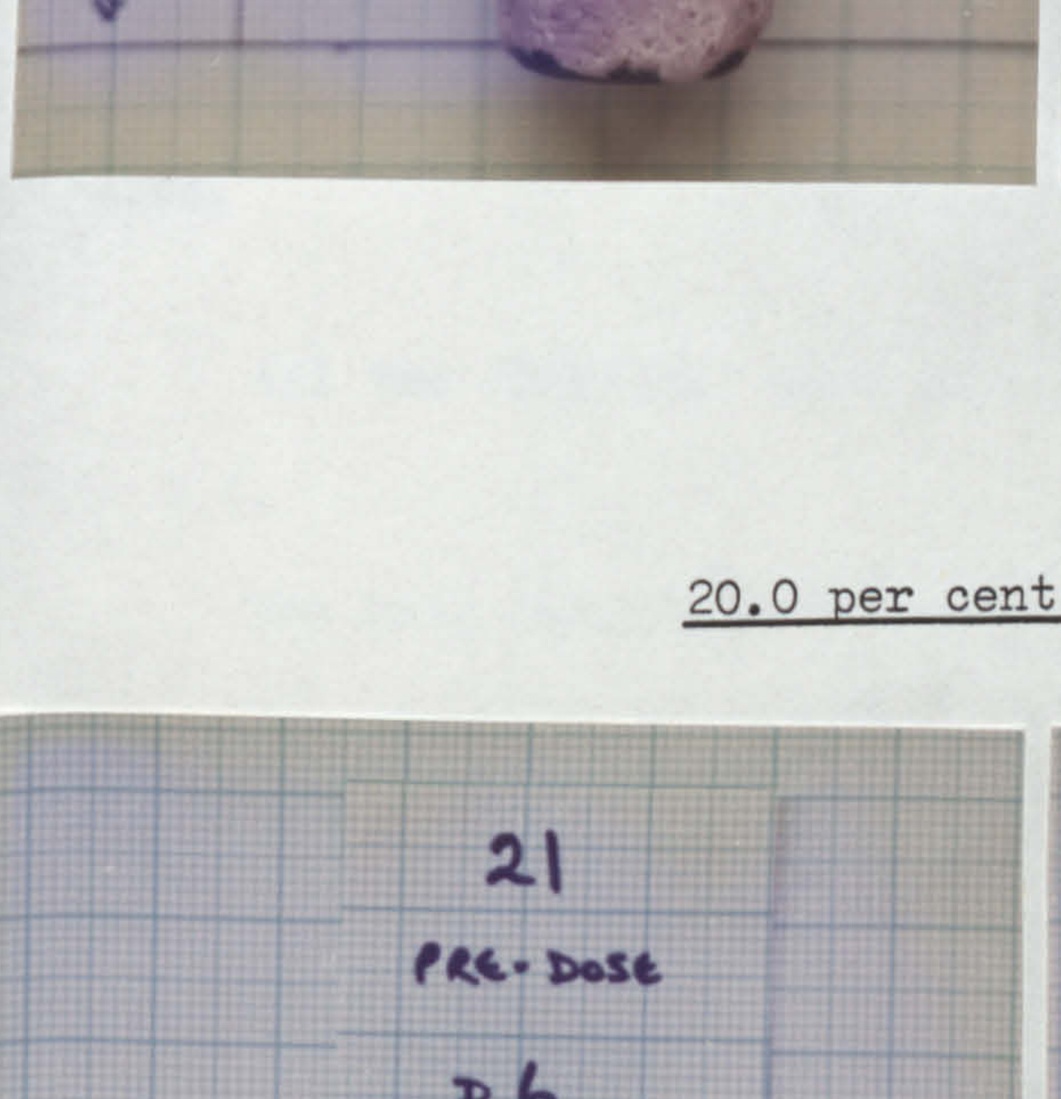
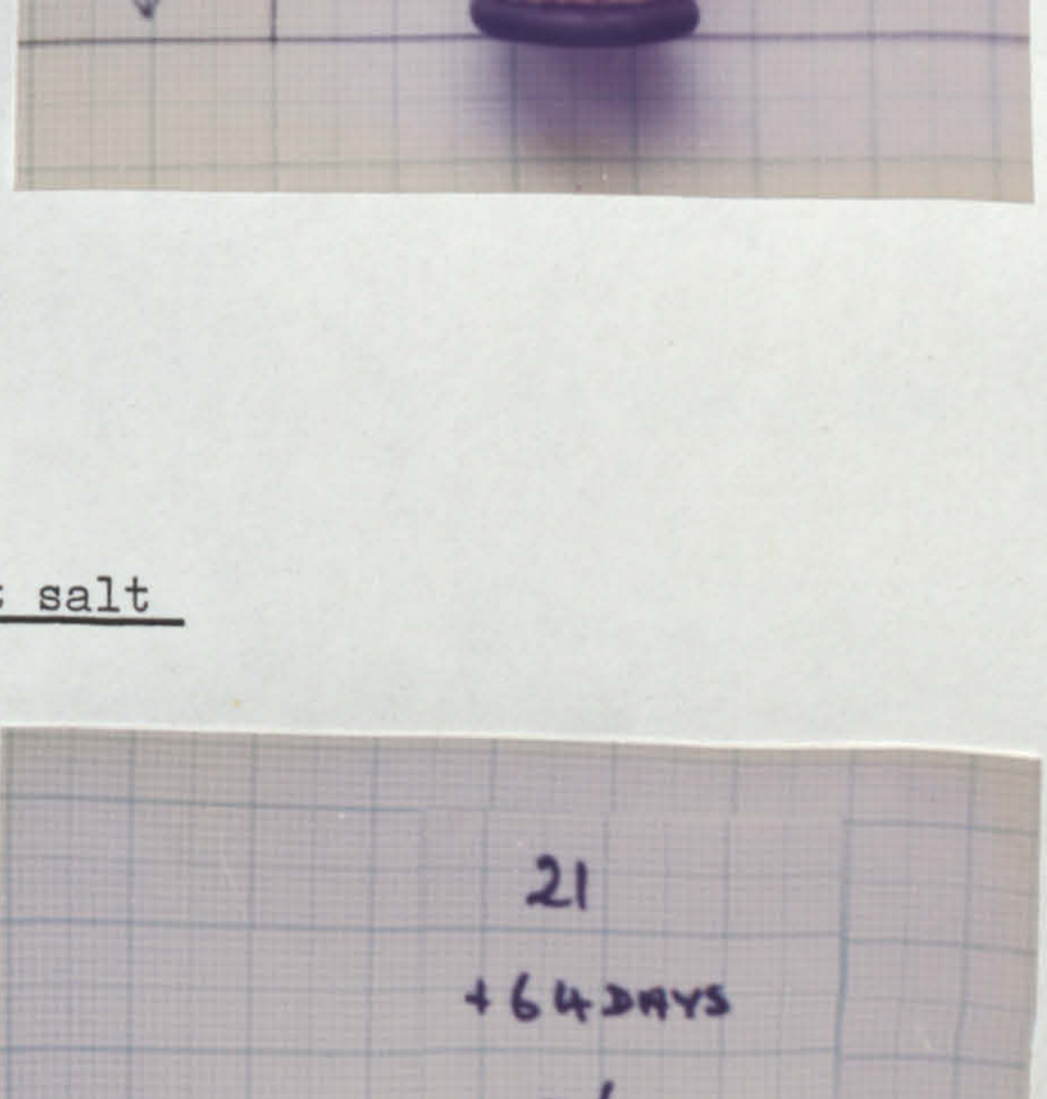


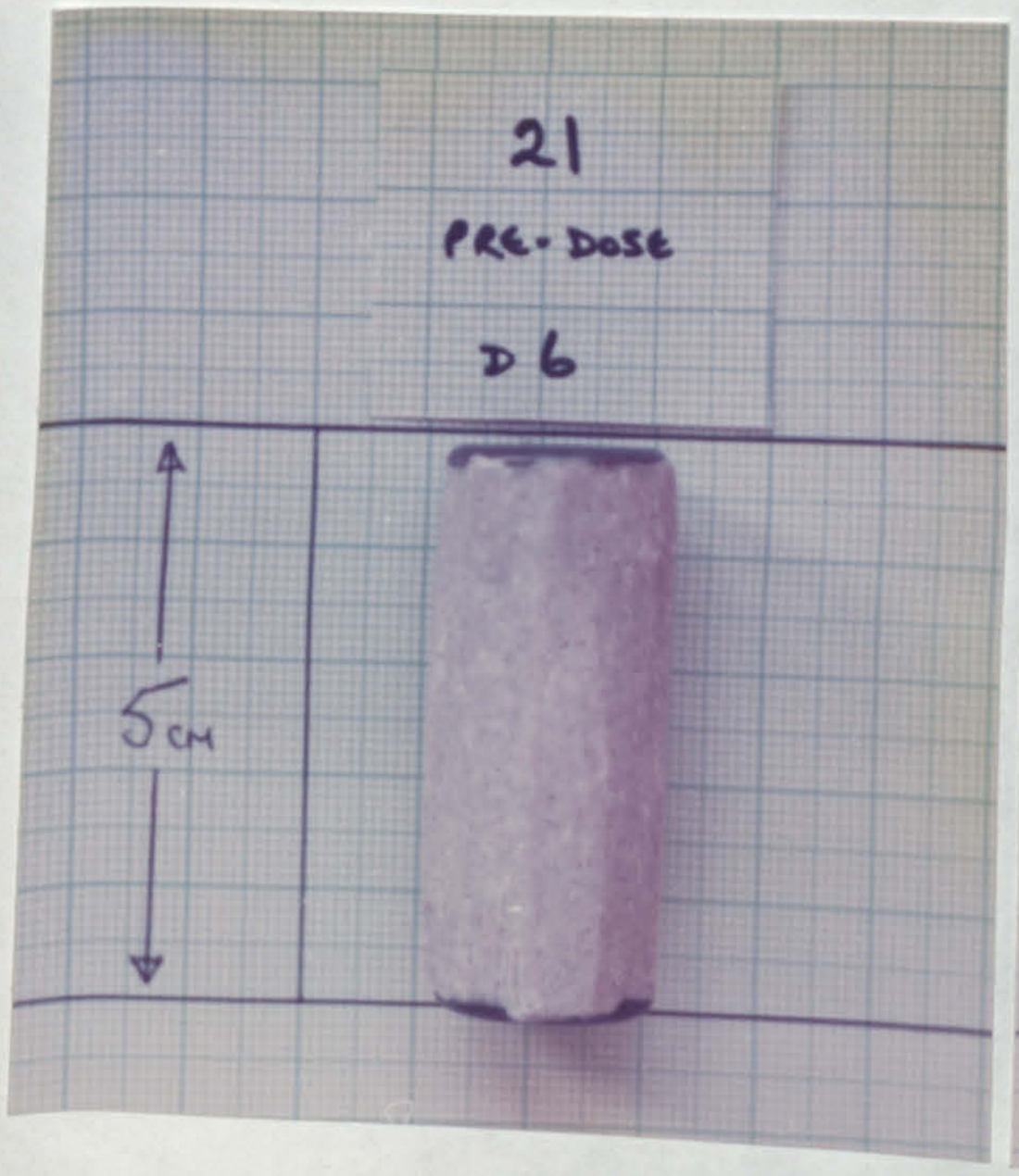
PLATE 31: SOLUBLE RELEASING AGENTS. Experiment 10.3.

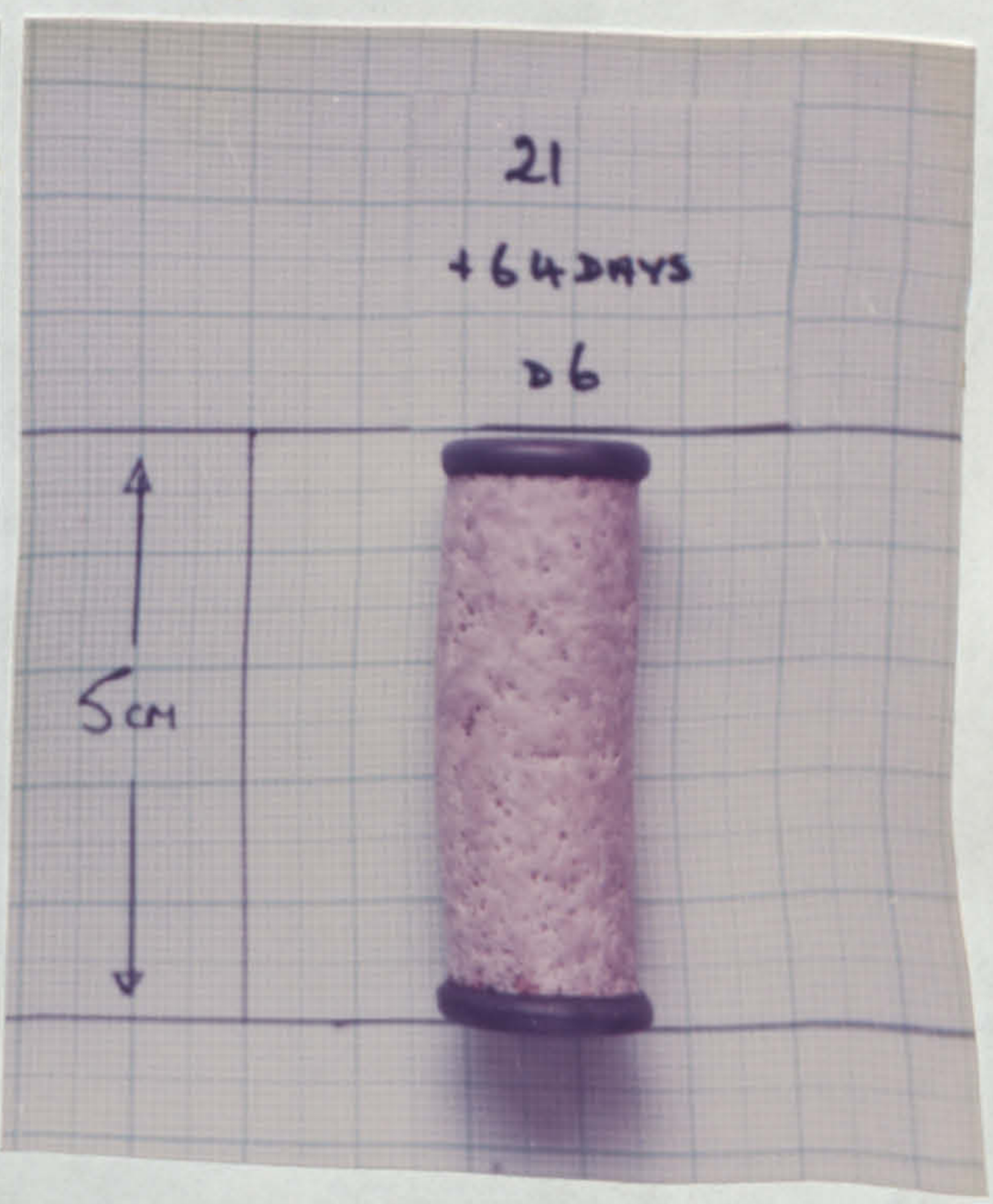
20.0 per cent syrup





20.0 per cent salt





A critical level was reached with icing sugar, above which rapid disintegration occurred (Table 36).

Powdered demerara sugar showed a higher drug release rate than the crystals at the same inclusion level of 19.8 per cent (Table 38).

The minimum required drug level was achieved with the highest inclusion level of 28.8 per cent sucrose during the first 35 days but following this the breakdown was variable within the group (lambs 82 and 8, Table 37).

The effect with golden syrup was variable but disintegration was increased by lowering the wax level (Table 38). As with Tragacanth mucilage, more experimentation varying the percentages of wax and syrup could possibly produce successful results.

10.4. Combinations

A few matrices were experimented with using combinations from the above mentioned groups of releasing agents.

The percentage levels tried were:-

Granulated sugar + cellulose	- 28.0	+ 2.0
	- 28.3	+ 1.0
	- 29.0	+ 1.0
Sucrose + melfoam	- 19.4	+ 0.2
	- 19.3	+ 0.1
	- 22.2	+ 0.06
Cellulose + sand	- 1.5	+ 28.5
	- 2.0	+ 28.0

Sand was included for comparison with iron powder for extra abrasiveness.

All the 'Dobbins' were retained, their densities ranging from 1.8 to 2.3.

The drug release rates obtained are summarised in Table 39.

The addition of cellulose to a sugar matrix increased the drug release rate and the matrix appeared more stable (Plate 32) than with cellulose alone (Plate 24). A matrix incorporating 28 per cent sugar with 2.0 per cent cellulose had disintegrated by 35 days. In comparison, a drug release of only 45 mg per day was achieved over 68 days from a 2.0 per cent cellulose matrix.

The addition of melfoam at all the inclusion levels tested caused rapid disintegration of a 19 to 22 per cent sucrose matrix (Plate 33). In comparison, a plain 27 per cent sucrose matrix released only 66.9 mg thiophanate per day over 60 days and 0.1 per cent melfoam, 23.8 mg over 76 days.

TABLE 39 : Summary of the drug release rates achieved from the inclusion into the matrix of various combinations of releasing agents.
Experiment 10.4.

	Percentage Sugar + cellulose			Percentage Sucrose + melfoam			Percentage Cellulose + sand	
	28.0 + 2.0	28.3 + 1.0	29.0 + 1.0	19.4 + 0.2	19.3 + 0.1	22.2 + 0.06	1.5 + 28.5	2.0 + 28.0
Sheep No.	Y42	Y52	Y19	Y18	Y19	88	Y4	Y69
Pre-dose 'Dobbin' weight (gms)	33.56	34.35	35.29	33.15	33.76	33.47	31.36	40.12
Day following dosing	35	42		25	39		25	
Daily weight loss (mg)	Empty	160.2		Empty	Empty		67.2	
Mg thiophanate per day		80.9					33.6	
Day following dosing		70	55			45	68*	45
Daily weight loss (mg)		Empty	216.9			Empty	202.9	384.4
Mg thiophanate per day			108.4				101.5	192.2

* Half broken away

PLATE 32 : SUGAR PLUS CELLULOSE MATRIX. Experiment 10.4.

29.0 + 1.0 per cent

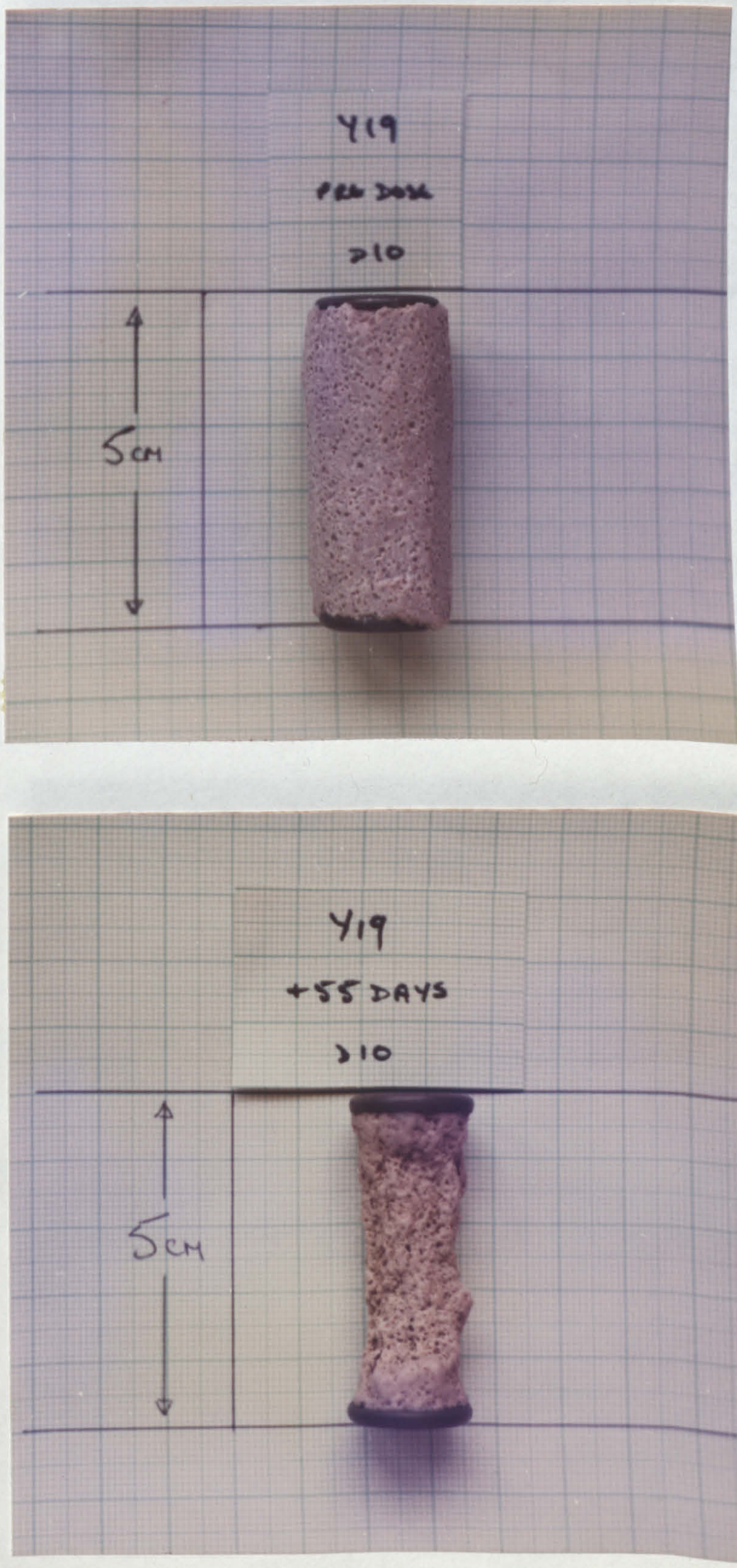
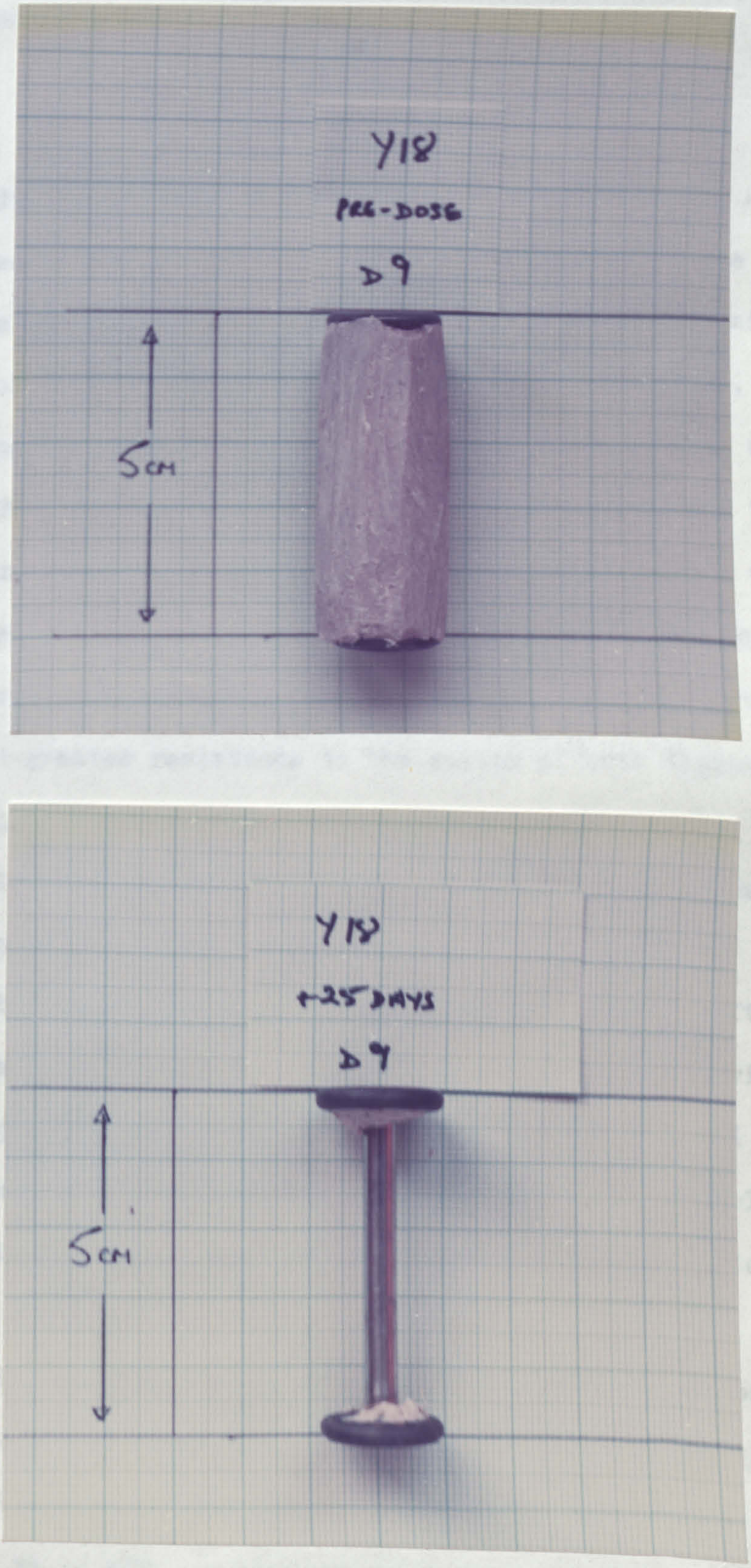


PLATE 33 : SUCROSE PLUS MELFOAM MATRIX. Experiment 10.4.

19.4 + 0.2 per cent



The inclusion of sand increased the drug release rate from a cellulose matrix (Plate 34) when compared to iron powder at the same level, 192.2 mg thiophanate per day with sand over 45 days compared to 40.0 mg with iron powder over 33 days.

10.5. Discussion

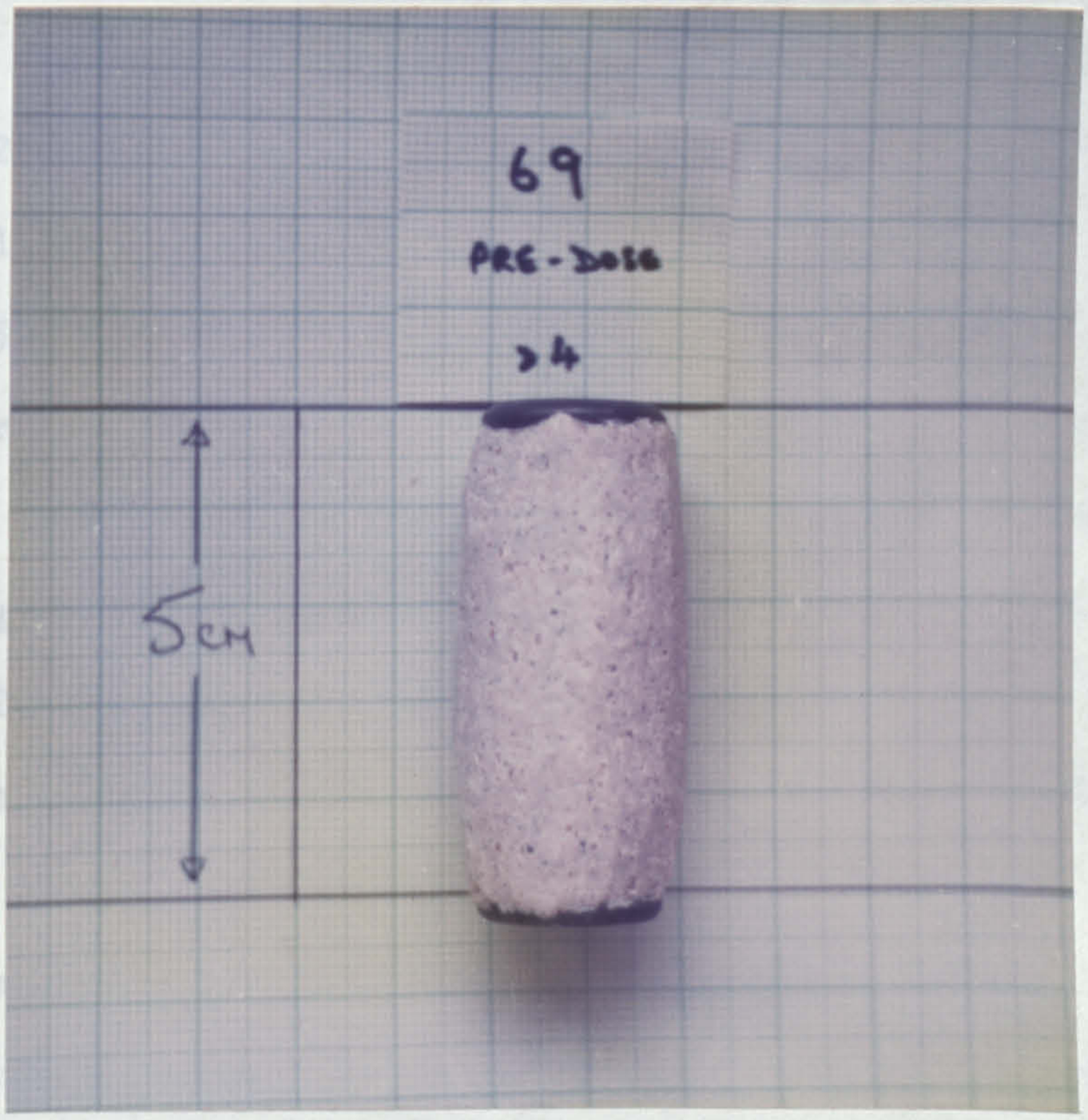
The addition of digestible materials to the matrix did not aid the drug release, the breakdown was too eratic with cellulose and it was impossible to select a level suitable for releasing the daily required amount of drug. Iron powder increased the erosion rate, for example, comparing the cellulose formulations dosed to lambs Y40 and 40, and Y15 and 28. Starch exhibited no overall improvement and to maintain a minimum level of thiophanate (50 per cent) the effect of higher percentages of iron powder with starch could not be monitored (Table 32). Baker, Nasr, Morrice & Bruce (1950) demonstrated that potato starch had greater resistance to the action of both digestive secretions and micro-organisms than, for example, maize starch. It was therefore possible that the inclusion into the matrix of an alternative starch may have produced better results.

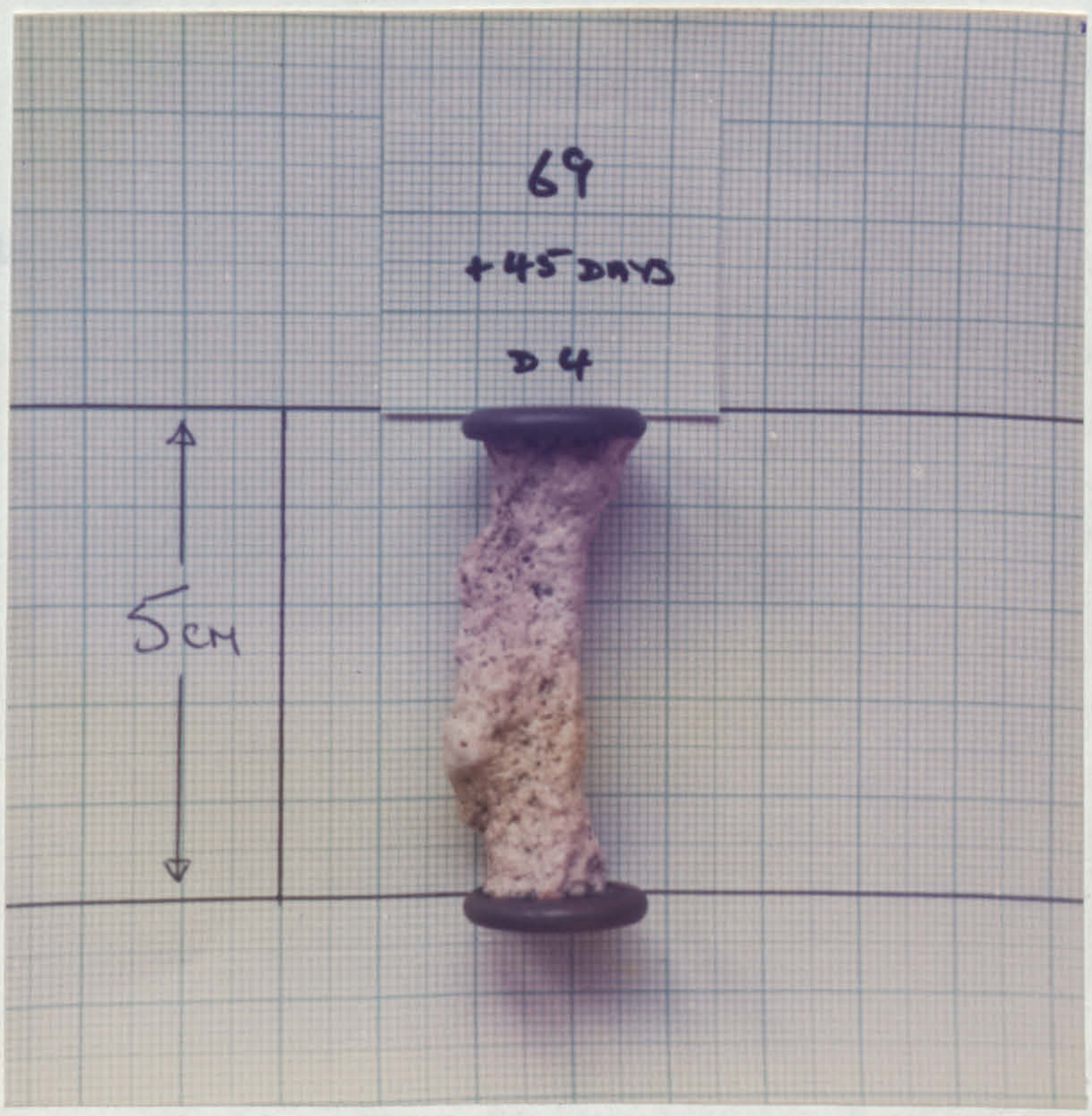
The matrices incorporating the wetting agents were softer in texture and appeared more stable with no obvious cracking occurring as seen with the digestible materials. A too finer balance existed between steady drug release and disintegration with both Tween 80 and Melfoam detergent. A suitable matrix for use in further trials was achieved using Tragacanth mucilage (Plate 28).

Solid ingredients, for example sugar and glucose, appeared more suitable for paired dosing as a high enough percentage inclusion level was not obtainable to give sufficient release from a single 'Dobbin' (Tables 35 to 38). A finer particle size appeared to give a faster drug release. As observed with Tragacanth, the level of wax in

PLATE 34 : CELLULOSE PLUS SAND MATRIX Experiment 10.4.

2.0 + 28.0 per cent



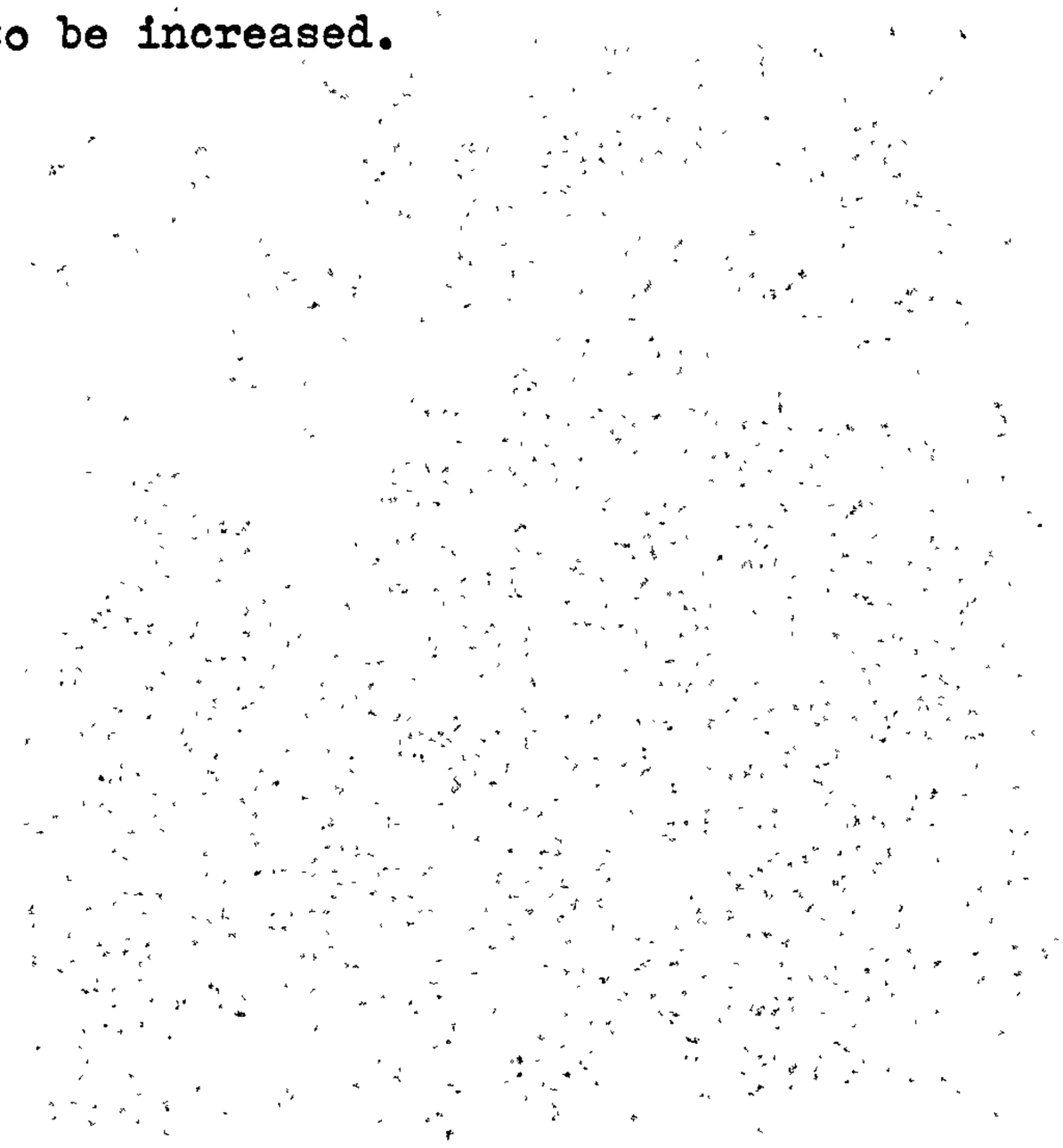


the golden syrup matrix appeared critical. With more variations tested, a suitable matrix could possibly be formed.

Lowering the percentage wax to increase the level of releasing agent made a less stable matrix, for example icing sugar matrices dosed to lambs Y33 and 24 where the percentage icing sugar incorporated was 24.6 and 21.7 per cent while the wax was included at levels of 26.2 and 20.8 per cent respectively. The latter had disintegrated by 59 days, the thiophanate level being constant in both.

The extra abrasiveness of iron powder improved the drug release rate, for example, a one per cent glucose matrix with iron powder gave as high a drug release level as a 19.2 per cent plain glucose matrix. The amount of thiophanate, however, was lowered by as much as 20 per cent in some cases to allow for the inclusion of iron powder.

Three releasing agents emerged as the most suitable candidates for further trials, namely Tragacanth mucilage, sucrose and golden syrup. More experimentation with the combinations could provide an ideal matrix, for example, by inclusion of a negligible amount of a wetting agent, the level of releasing agent could be lowered allowing the thiophanate level to be increased.



11. CORRELATION BETWEEN THE FAECAL DRUG ASSAY, DRUG RELEASE RATE AND DAILY DOSE RATE RECEIVED

The following experiment was undertaken to highlight any correlation that may exist between the drug release rate from within a matrix, the zones of activity measured on the plate assay from excreted drug and the daily dosage of drug actually received by the animal. Two matrices were selected - one suitable for a single treatment, the other for a paired dosing.

11.1. Experimental data

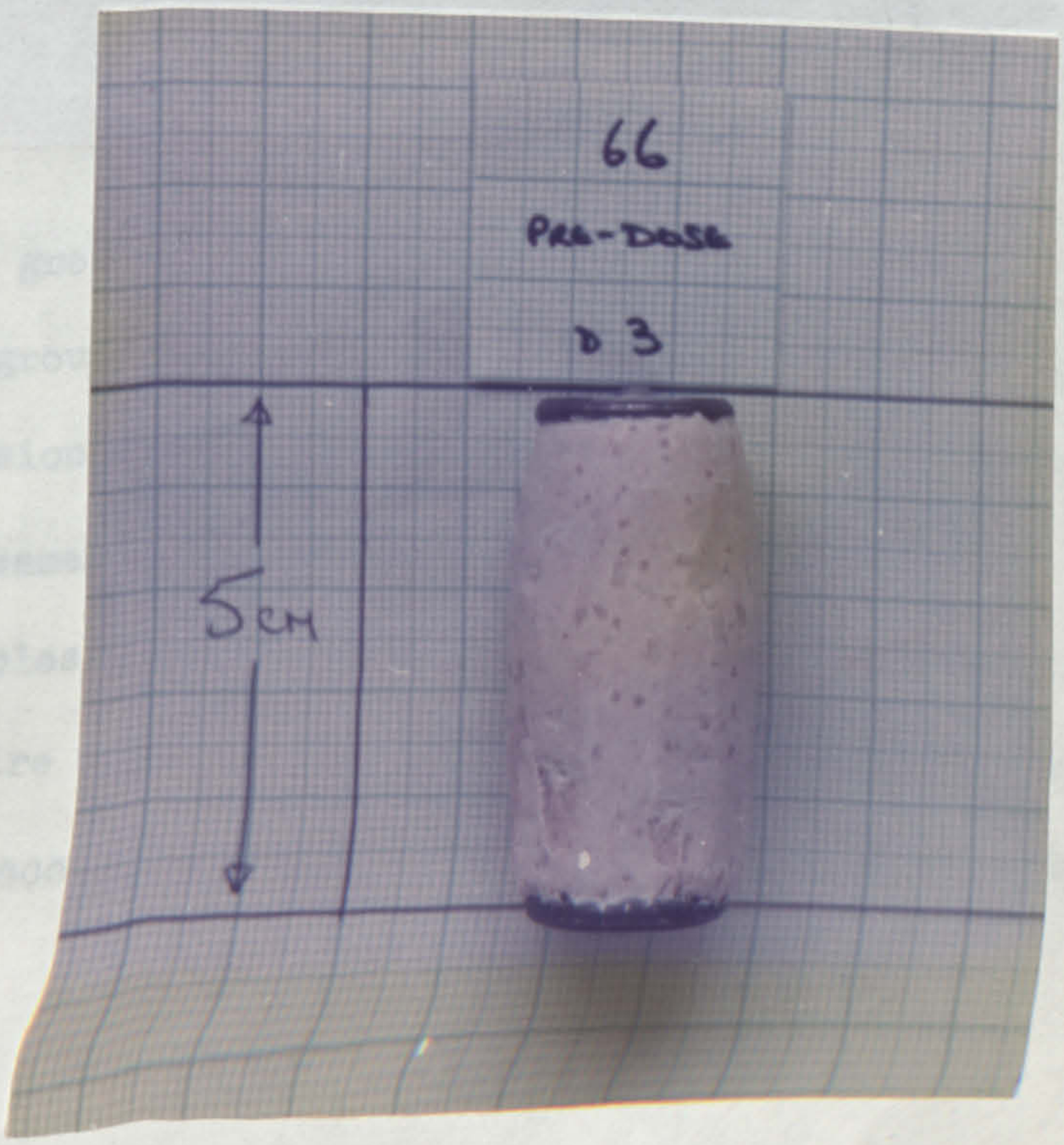
Group 1. Single 'Dobbin'

All metal 'Dobbins' were loaded with a matrix incorporating wax, thiophanate and icing sugar at inclusion levels of 24, 47.5 and 28.5 per cent respectively (Plate 35). Their loaded weights ranged from 34.4 to 37.3 gms with an average density of 2.01.

A single 'Dobbin' was administered to each of 9 lambs.

PLATE 35 : PRE-DOSE EXAMPLE OF A SINGLE DOSED 'DOBBIN'

Experiment 11.

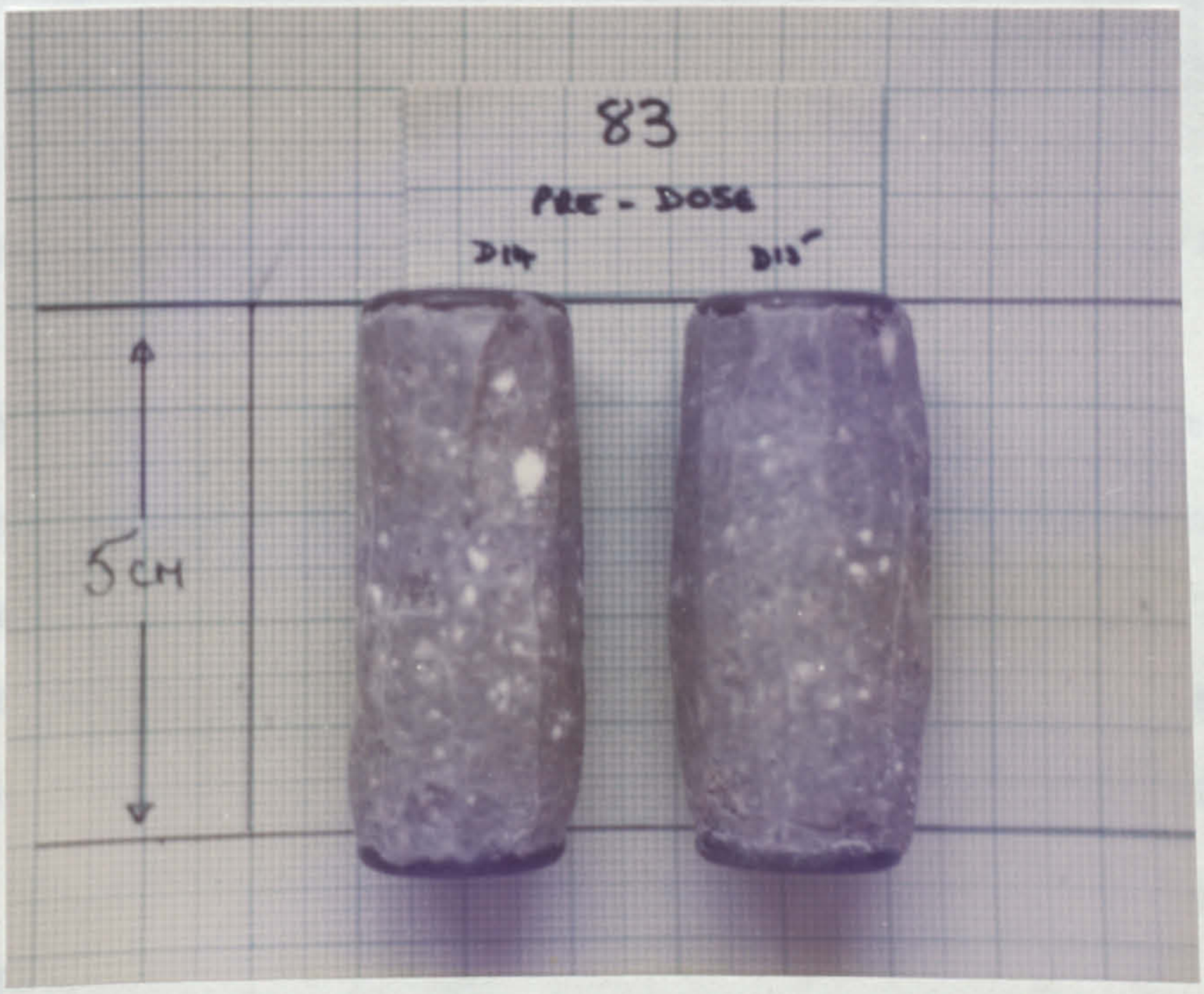


Group 2. Paired 'Dobbins'

Nylon rod-metal flanged 'Dobbins' were loaded with a matrix incorporating wax, thiophanate, sucrose and iron powder at inclusion levels of 23, 52, 8 and 17 per cent respectively (Plate 36). Their loaded weights ranged from 30.5 to 33.7 gms with an average density of 1.9.

Two 'Dobbins' were administered to each of 9 lambs.

PLATE 36 : PRE-DOSE EXAMPLE OF THE PAIR DOSED 'DOBBINS'. Experiment 11.



For both groups, 'Dobbins' were recovered at weekly intervals, from one lamb per group per week, over a period of 9 weeks and the progression of erosion with subsequent drug release rates calculated.

For assessment of excreted drug levels by the plate assay method, faecal samples were collected daily from one lamb in each group throughout the entire medication period and daily during the two weeks prior to 'Dobbin' recovery from the remaining 8 lambs per group.

11.2. Results

The drug release rates obtained from Group 1 (single dosed 'Dobbins') are summarised in Table 40. The average daily weight loss dropped slightly during the middle 20 days of the medication period ('Dobbins' recovered on days 29, 36 and 43 following dosing). With respect to the variation in rumination between stock, the daily weight loss remained fairly steady throughout the experiment. The lambs bodyweights were in the range of 49.5 to 66.5 kgs. The final daily dosage of thiophanate received per lamb ranged between 1.47 to 2.03 mg per kg bodyweight, the actual amount of drug released ranging from 81.69 to 116.5 mg per day.

The progression of erosion of this matrix over the 64 day medication period is illustrated in Plate 37.

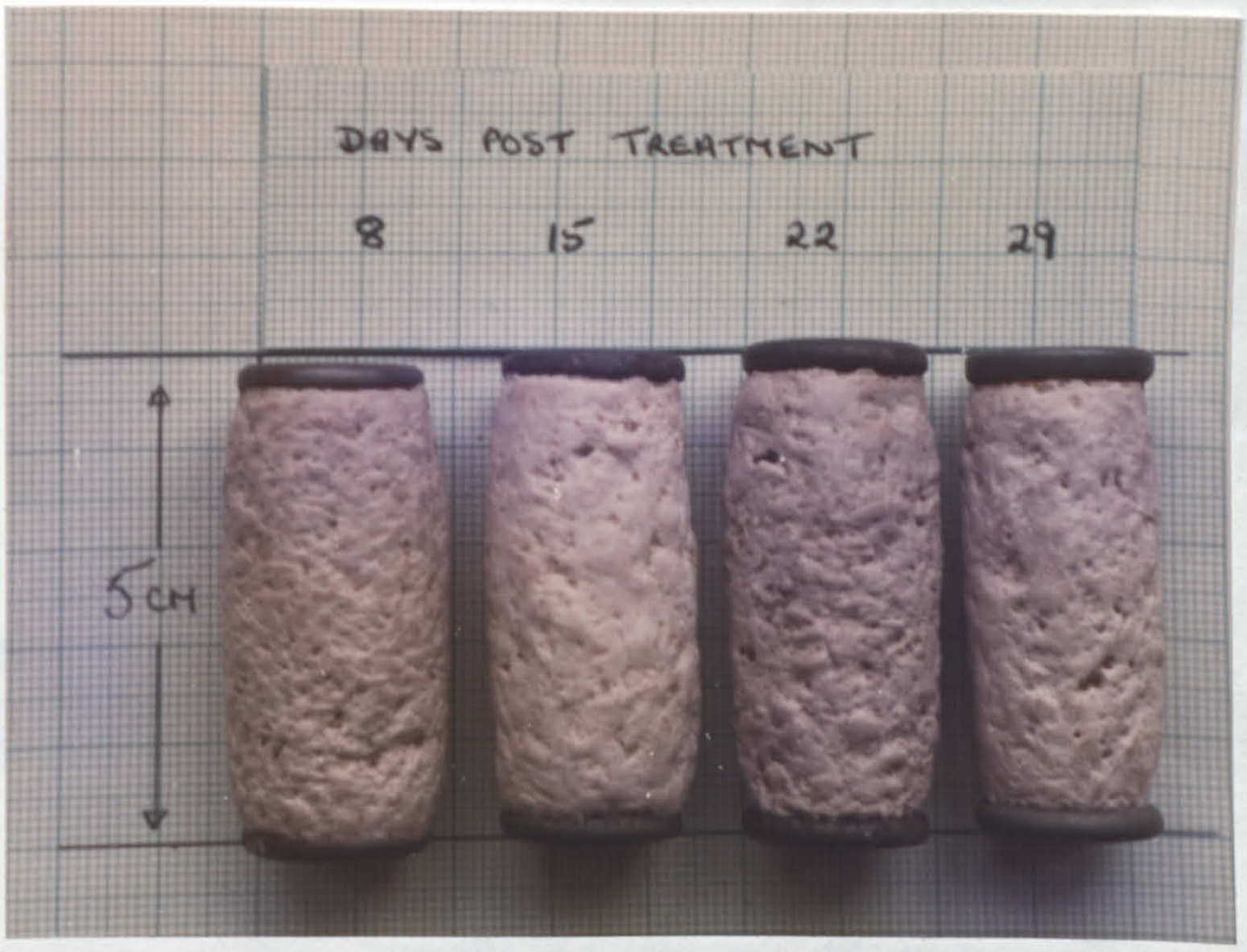
The mean diameters of the activity zones measured from excreted drug are shown in Fig.17. After the first two weekly recoveries (lambs 79 and 74) the readings from each lamb overlapped so the graphs are plotted alternatively in solid and stippled lines to distinguish between the sampling periods of each lamb. A solid vertical line at the end of the monitoring period indicates removal of the 'Dobbin' from the lamb.

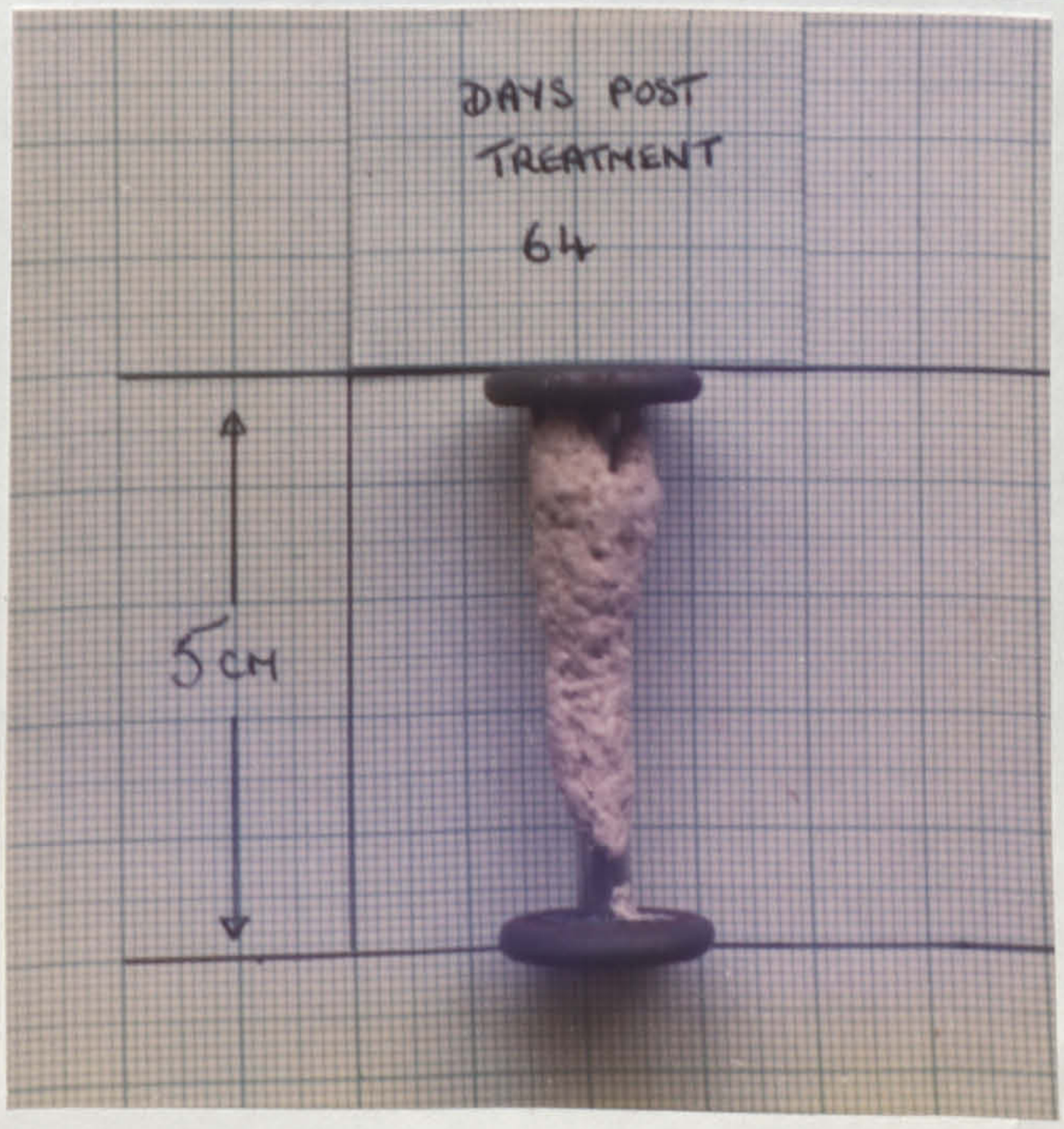
With the exception of one lamb (60) the readings monitored of the activity zone sizes remained fairly steady. The smaller zones recorded from lamb 60 were reflected in the lower drug release rate from the 'Dobbin' calculated at recovery.

TABLE 40 : Summary of the drug release rates achieved from the single dosed 'Dobbins'. Group 1. Experiment 11.

Lamb No.	Recovery day following dosing	Pre-dose 'Dobbin' weight (gms)	Recovery weight (gms)	Weight loss (gms)	Daily weight loss (mg)	Mg thiophanate per day	Lamb weight (kg)	Daily dosage received (mg/kg)
79	8	35.64	33.92	1.72	215.0	102.3	50.5	2.03
74	15	34.94	31.84	3.1	206.7	98.4	58.0	1.7
77	22	37.28	32.39	4.89	222.3	105.8	66.5	1.59
70	29	35.06	29.87	5.19	178.9	85.2	49.5	1.72
76	36	34.77	27.60	7.17	199.2	94.8	55.5	1.71
60	43	35.09	27.71	7.38	171.6	81.69	55.5	1.47
71	50	34.46	23.13	11.33	226.6	107.9	54.5	1.98
66	57	36.18	22.47	13.71	240.5	114.5	58.0	1.97
75	64	34.57	18.91	15.66	244.7	116.5	63.0	1.85

PLATE 37 : SINGLE TREATMENT PROGRESSION OF EROSION. Experiment 11





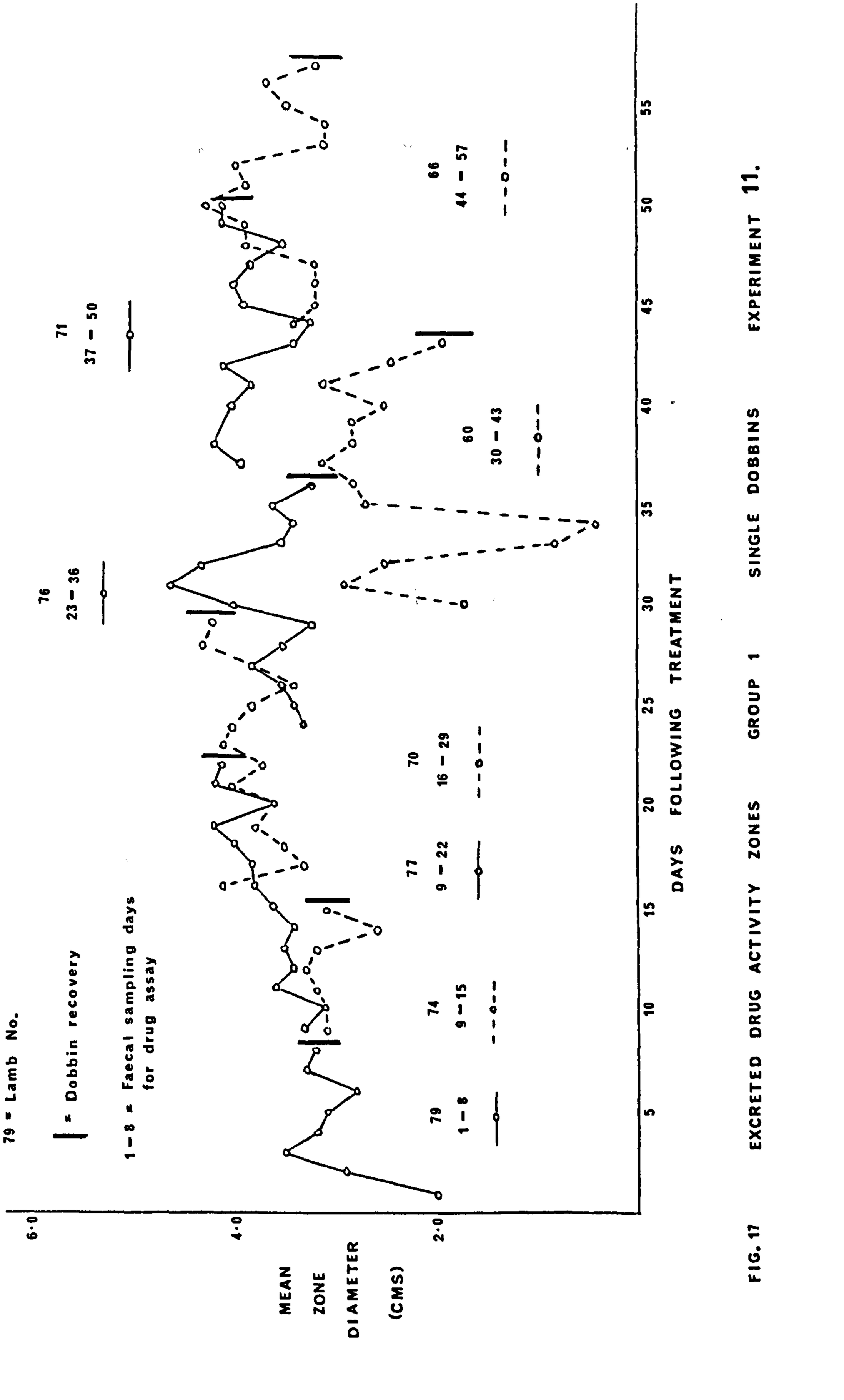

79 = Lamb
= Dobbins
1 — 8 = Faecal sampling days for drug assay
MEAN ZONE DIAMETER (CMS)
6·0
4·0
2·0
79
1 — 8
74
9 — 15
76
23 — 36
71
37 — 50
66
44 — 57
77
9 — 22
70
16 — 29
60
30 — 43
5
10
15
20
25
30
35
40
45
50
55
DAYS FOLLOWING TREATMENT
GROUP 1 SINGLE DOBBINS EXPERIMENT 11.
EXCRETED DRUG ACTIVITY ZONES

FIG. 17

The drug release rates obtained from Group 2 (pair dosed 'Dobbins') are summarised in Table 41.

The daily weight loss remained fairly steady throughout between the pairs and within the group with the exception of the last pair to be recovered (lamb No.80). The lambs bodyweights were in the range of 49 to 69 kgs. The final daily dosage of thiophanate received per lamb ranged from 2.2 to 3.1 mg per kg bodyweight, the actual amount of drug released ranging from 137.7 to 165.9 mg per day.

The progression of erosion of this matrix over the 63 day medication period is illustrated in Plate 38.

The mean diameters of the activity zones measured from the excreted drug are shown in Fig.18. The same procedure for plotting the readings was used as previously described for Group 1. The sizes of the zones measured were larger and appeared more variable than those obtained from the single dosed 'Dobbin'.

Fig.19 shows the diameter sizes of the activity zones measured from the assay of faeces collected from the same lamb throughout the medication period, one lamb from each group. The zone sizes were erratic ranging from 2.0 to 4.1 cms and 2.1 to 5.7 cms for Groups 1 and 2 respectively. A consistent positive recording was registered from all the faecal samples assayed throughout the experiment.

Table 41 : Summary of the drug release rates achieved from the pair dosed 'Dobbins'. Group 2. Experiment 11.

Lamb No.	Recovery day following dosing	Pre-dose 'Dobbin' weight (gms)	Recovery weight (gms)	Weight loss (gms)	Daily weight loss (mg)	Total loss (mg)	Mg thiophanate per day	Lamb weight (kg)	Daily dosage received (mg/kg)
84	7	31.83 33.14	30.96 32.24	0.87 0.9	124.3 128.6	252.9	131.7	51.5	2.56
78	14	32.13 33.27	30.38 31.32	1.75 1.95	125.0 139.3	264.3	137.7	62.0	2.21
90	21	30.47 32.24	27.46 29.22	3.01 3.02	143.3 143.8	287.1	149.6	49.0	3.1
85	28	32.21 32.11	28.06 28.30	4.15 3.81	148.2 136.1	284.3	148.1	61.5	2.41
89	35	33.74 33.29	28.74 27.88	5.0 5.41	142.8 154.6	297.4	154.9	56.5	2.74
87	42	31.88 31.96	25.79 25.5	6.09 6.46	145.0 153.8	298.8	155.6	50.0	3.1
81	49	30.68 31.19	23.23 24.32	7.45 6.87	152.0 140.2	292.2	152.2	54.0	2.8
83	56	31.31 33.39	23.72 26.14	7.59 7.25	135.5 129.5	265.0	138.0	61.5	2.2
80	63	31.18 31.17	23.19 19.1	7.99 12.07	126.8 191.6	318.4	165.9	69.0	2.4

PLATE 38 : PAIRED TREATMENT PROGRESSION OF EROSION Experiment 11.

Recovery days following treatment

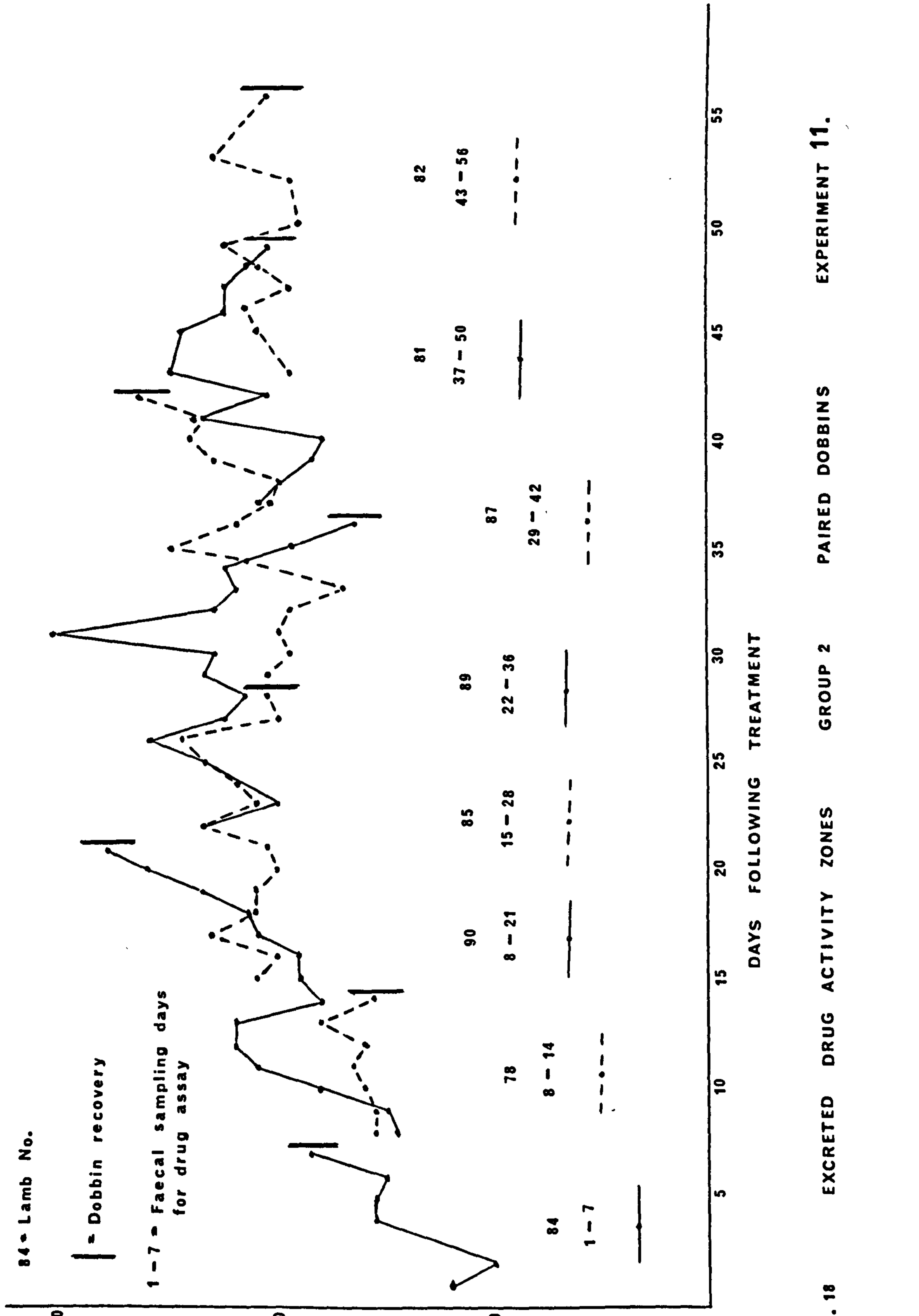


FIG. 18 EXCRETED DRUG ACTIVITY ZONES

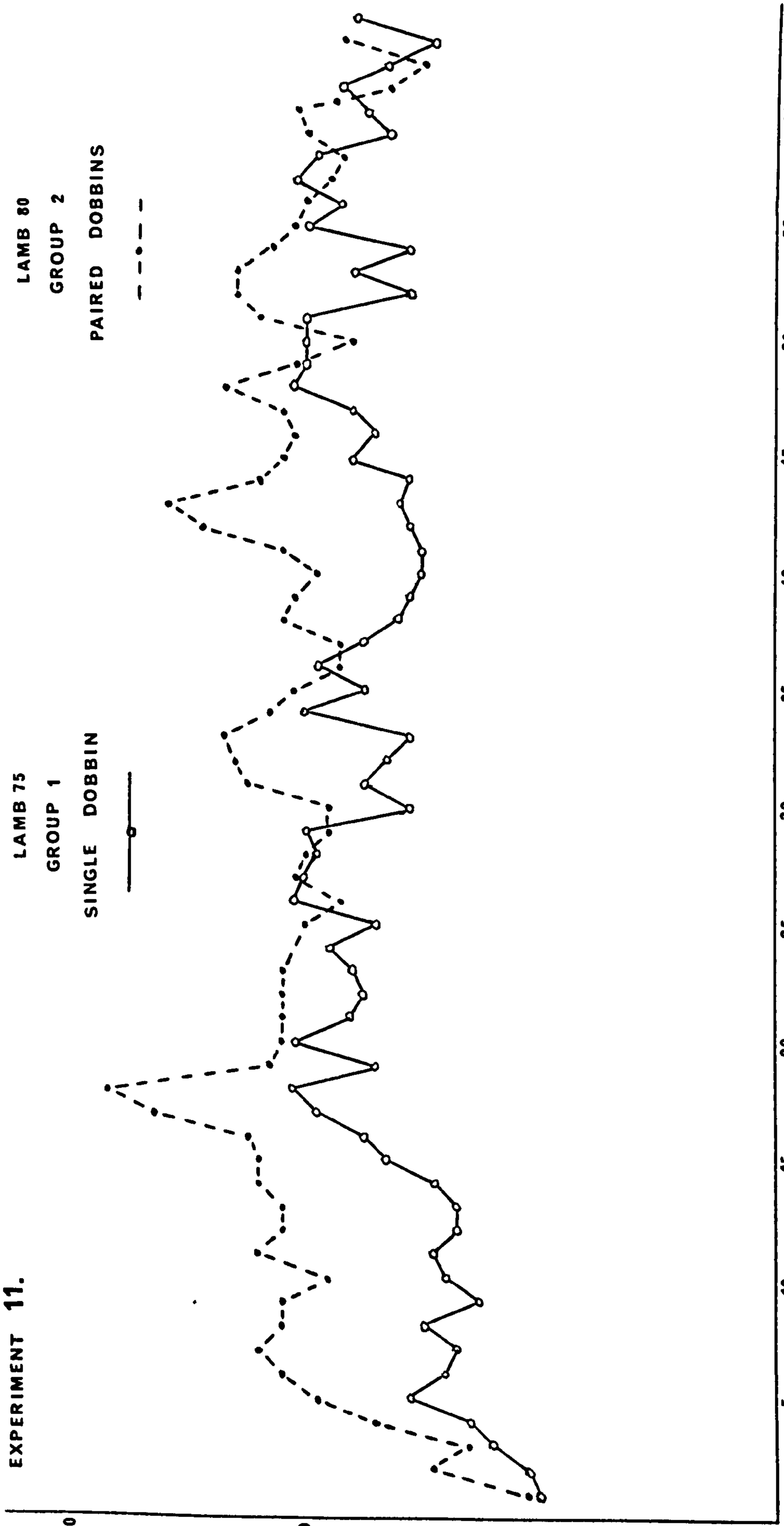


FIG.19 EXCRETED DRUG AC

11.3. Discussion

In Group 2 the drug release rate from one of the paired 'Dobbins' recovered at 63 days was higher than average. At recovery, the matrix was found to have cracked in half, possibly with the breaking away of some slivers causing a larger amount of drug to be released. This may account for the erratic levels of excreted drug recorded from this lamb (No.80, Fig.19).

From the activity zone sizes obtained (Figs.17, 18 and 19) and as noted from the infusion studies, an accumulative effect was not observed in the amount of drug being excreted. Anderson, Laby, Prichard & Hennessy (1980) observed that the plasma levels in sheep of the anthelmintic oxfendazole reflected the rate of matrix dissolution indicating that the rate of drug clearance was not increased as a result of prolonged exposure to host tissues.

If the activity zone sizes from the excreted drug results are compared to those obtained from the infusion studies in Section A, a daily dose rate of 3.0 to 4.0 mg thiophanate per kg bodyweight from a single dosed 'Dobbin' and 4.5 to 5.0 mg per kg from a pair should have been recorded in this experiment.

By referring back to the lambs on the infusion studies in Section A, and studying the actual daily amount of thiophanate infused, the lambs treated in this experiment were seen to be heavier in bodyweight so consequently the dose rate was lower. The infusion lambs treated with 3.0 and 4.0 mg per kg received an average of 96 and 153 mg thiophanate respectively per day. A single 'Dobbin' released an average of between 82 and 116 mg drug per day and may have recorded a higher release rate on occasions; therefore the activity zones obtained from the faecal samples could be in accordance with those obtained in the infusion studies. The paired 'Dobbins' released an average of 138 to 166 mg thiophanate which was equivalent to that received by the

infusion lambs on a daily dose rate of between 3.0 and 4.5 mg per kg bodyweight. This rate was lower, however, than indicated from the activity zone sizes of the excreted drug at this dose rate in the infusion study. The excreted drug levels measured in this experiment were erratic and it is possible that the amount of drug released could, on occasions, have risen to the level recorded from the infusion study of 216 mg thiophanate.

From the results reported in this experiment, there appears to be a possible correlation between the activity zone sizes measured from the excreted drug and the amount of thiophanate actually received by the ruminant but not with the dose rate as calculated in relation to the lamb's bodyweight.

This correlation was verified by examination of the activity zone sizes recorded from previous experiments.

The zone sizes measured in Experiment 7 were too erratic to draw any conclusions from, but those recorded in Experiment 9, although still variable, were comparable (Fig.16). The boluses dosed to lambs 1 to 4 released a daily amount of 133, 214, 135 and 158 mg thiophanate respectively. The drug activity zone sizes from all four lambs, on average, agreed with those obtained in the infusion studies for these levels of drug. The lambs treated in Experiment 9 were, however, of different bodyweights so consequently the final dose rates received in relation to lamb bodyweight were higher or lower. For example, from the zone sizes obtained, lamb 1 should have received a daily dose rate of between 3.0 and 4.0 mg per kg in relation to the infusion studies but a rate of 4.5 mg per kg was recorded during the first half of the experiment. Similarly, lamb 2 should have received 5.0 mg per kg but actually received 6.5 mg per kg. However, during the second half of the experiment, the actual dose rates received by lambs 1 and 3 were in agreement to those indicated by the activity zone sizes, that is, between 3.0 and 4.0 mg thiophanate

per kg bodyweight.

It could therefore be concluded that if a steady erosion rate is obtained from a ruminal bolus, the drug release rate calculated as mg thiophanate per day could be estimated by the plate assay method but this reading would not necessarily correlate with the daily dose rate calculated in relation to the lamb's bodyweight.

12. GENERAL DISCUSSION AND CONCLUSIONS

The results which form the basis of this work have proved that the slow release concept could be an efficient means of anthelmintic medication. However, some indication for further studies did emerge.

Many factors have to be taken into account when analysing results obtained from experiments involving an intra-ruminal slow release bolus of the type studied here, that is, where the matrix is exposed to rumen mechanics and its bacterial population.

One major consideration is the animal's diet. All the studies undertaken with the selected matrix (paraffin wax) were in housed, experimentally infected sheep fed twice daily on concentrate rations with hay. The bacterial population of the rumen responds to the continuous input of a particular polymer by developing a stable component of species that can adhere to and digest that polymer (Cheng & Costerton, 1980). The rate of erosion and dissolution of the matrix could therefore vary, depending on the diet. For example, when a ruminant has been maintained on a forage diet it is dependent on a stable population of cellulose-digesting bacteria for its digestive function. A decrease in this species and an increase in the amylase-producing species would occur in ruminants fed on a concentrate diet. Also, in grazing stock, large quantities of saliva are produced and forages are ensalivated to a sludge before being swallowed. On the other hand, meals and pelleted diets, being easy to swallow, are consumed so rapidly that much less saliva is added. This will adversely influence ruminal digestion by the inadequate regulation of pH and maintenance of fluid flow (Kay, 1983). The turnover rate in the rumen of dry matter in hay fed animals is two to three times as slow as for pasture fed sheep (Egan, Walker, Nader & Storer, 1975; Corbett, Pickering & Perez, 1979),

and the limitation of access to food induces an increase in the eating rate and a reduction of ruminating efficiency (Welch & Smith, 1969; Dulphy, Remond & Theriez, 1980). These factors would affect the extra erosive process achieved by the paired 'Dobbin' treatment, that is, less ruminal movement, less rubbing friction between 'Dobbins'. A comparable experiment should therefore be undertaken to assess the rate of erosion and or dissolution of the various matrices when administered in pairs to pasture grazed stock and the anthelmintic activity assessed under conditions of a natural worm challenge. The difference, if any, of the speed of dissolution of the matrices loaded onto a single dosed 'Dobbin' should also be studied in animals at pasture. Anderson, Laby, Prichard & Hennessy (1980) found that the oxfendazole release rate from treated sheep in a pen experiment was lower than those anticipated on the basis of calculations from the release rates previously obtained in grazing cattle. It was suggested that most of the difference could possibly be accounted for by the diet which, being chaff, would lead to a slightly higher pH of rumen liquor and a consequent slower dissolution of the basic matrix.

Where regular treatment of an animal is required each year, for example, in breeding ewes, the effect of the residual empty 'Dobbin' framework on the drug release rate of a newly administered bolus should be studied. The results obtained in Experiment 7 seem to indicate that the empty "carrier" will affect the erosion rate of a loaded one by maintaining the drug release rate equivalent to that individually achieved from a pair of loaded 'Dobbins'.

The use of a slow release bolus in the field, administered at various times under various management conditions requires monitoring to achieve the greatest potential from such a product.

A number of practical applications can be envisaged where sustained release of anthelmintics from a ruminal bolus would be advantageous. For example, the pre-lambing treatment of the breeding ewe to prevent the post-parturient rise, would prepare the pastures with the minimum of contamination for the newly weaned lambs. Given sufficient information on the epidemiology of nematode infections, intra-ruminal boluses provide a means of reducing the worm egg output over an extended time before or during periods of weather favourable for the development, survival and transmission of the free-living stages of helminths. In lambs, the use of such a bolus administered at weaning could reduce the anthelmintic treatment to a single preventative application each year, thus considerably reducing the amount and cost of labour associated with parasite control programmes. If the anthelmintic incorporated into the bolus is also ovicidal at the low daily dosages used, then pasture contamination would also be reduced and the number of larvae overwintering would be minimal.

Whilst the work reviewed in this thesis was being undertaken, a slow-release anthelmintic bolus - Paratect* - was marketed for cattle. It was first described by Jones (1981) as a cylindrical sintered polythene outer shell, 7.6 cm long and 2.5 cm in diameter, impregnated with cellulose acetate. This outer shell contained an inner stainless steel sleeve to increase the density and which, in turn, contained holes of finite number and dimension to control the rate of drug released. The bolus is filled with a blend of active ingredient (the anthelmintic morantel tartrate), polyethylene glycol and sodium metaphosphate and has a density of 2.4. Many reports have since been published of the use of this bolus for controlling gastro-intestinal nematode infestations and in achieving an advantageous bodyweight gain in calves

*Paratect Sustained Release Bolus. Pfizer Ltd.

during their first grazing season in Great Britain (Jones, 1981; Jacobs, Fox, Walker, Jones & Bliss, 1981; Armour, Bairden, Duncan, Jones & Bliss, 1981) and abroad (Borgsteede, Oostendorp, Burg, Harmsen & Tarrij, 1981; Brunsdon & Vlassoff, 1981, Burger, Jones & Bliss, 1981). A general review has also been published (Bliss & Jones, 1983) incorporating reports from various workers covering the use of the bolus when administered under various grazing management systems to first and second season grazing stock; its continued annual use with the possible effect on inducing drug resistance and its compatability with Dictol* lungworm vaccine. Overall, the "Paratect Bolus System" has proved conclusively that the concept of intra-ruminal continuous low-level medication is effective.

The published work on the retention of heavy objects in cattle and the marketing of "Paratect" necessitates the assessment of the potential activity in calves of the 'Dobbin' when scaled up to a suitable size, weight and density.

Another new concept has just recently been marketed for the restoration to and maintenance of the normal values of the blood concentration of copper and selenium. This bolus** for cattle and sheep is based on a soluble glass and opens up a complete new field for sustained release medication. The manufacture of soluble glass has been reported previously (Harvey, 1978) and its use incorporating an anthelmintic is highly feasible.

* "Dictol". Oral Husk Vaccine, Living BP (Vet). Glaxovet Ltd.

** "Cosecure". Contains 13.4 per cent copper, 0.3 per cent selenium and 0.5 per cent cobalt. Chance Pilkington and The Wellcome Foundation Ltd.

In conclusion, the results obtained in this thesis from studies with an intra-ruminal bolus indicate that a bolus with a density equal to or greater than 2, utilizing the 'Dobbin' as the "carrier" and incorporating the anthelmintic thiophanate is effective against a single mixed nematode infection when administered in a pair. With further experimentation, confirmation of the anthelmintic activity using a single 'Dobbin' treatment could be demonstrated.

The incorporation of the metal framework "carrier" may, however, not be always practical, economic or acceptable for use in the field. By investigating other bolus systems available, for example, the compressed bolus based on a high-density, non-toxic metal derivative as used by Byford, Riner & Hair (1980) or the soluble glass concept, an effective system may be found where no residual material remains within the rumen after the active ingredient has been completely released.

Finally, it should also be mentioned that such a system could find many other applications within the Animal Health field, for example, with growth promotants, insecticides, coccidiostats and hormones.

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APPENDIX

FAECAL DRUG ASSAY

Thiophanate, as well as being an anthelmintic is also marketed as a fungicide* and as such has shown to be active against Penicillium. This fact was used to design a test to detect the presence of excreted drug in the faeces of treated animals.

A known weight of faeces (up to 25 gms) was soaked overnight in chloroform. After filtering, the liquid was evaporated to dryness and stored at 4°C until required for assay.

Sterilised biological assay plates, 30.5 cms square, were plated with 200 mls of potato dextrose agar to which 6 mls of a suspension of Penicillium expansium had been added.

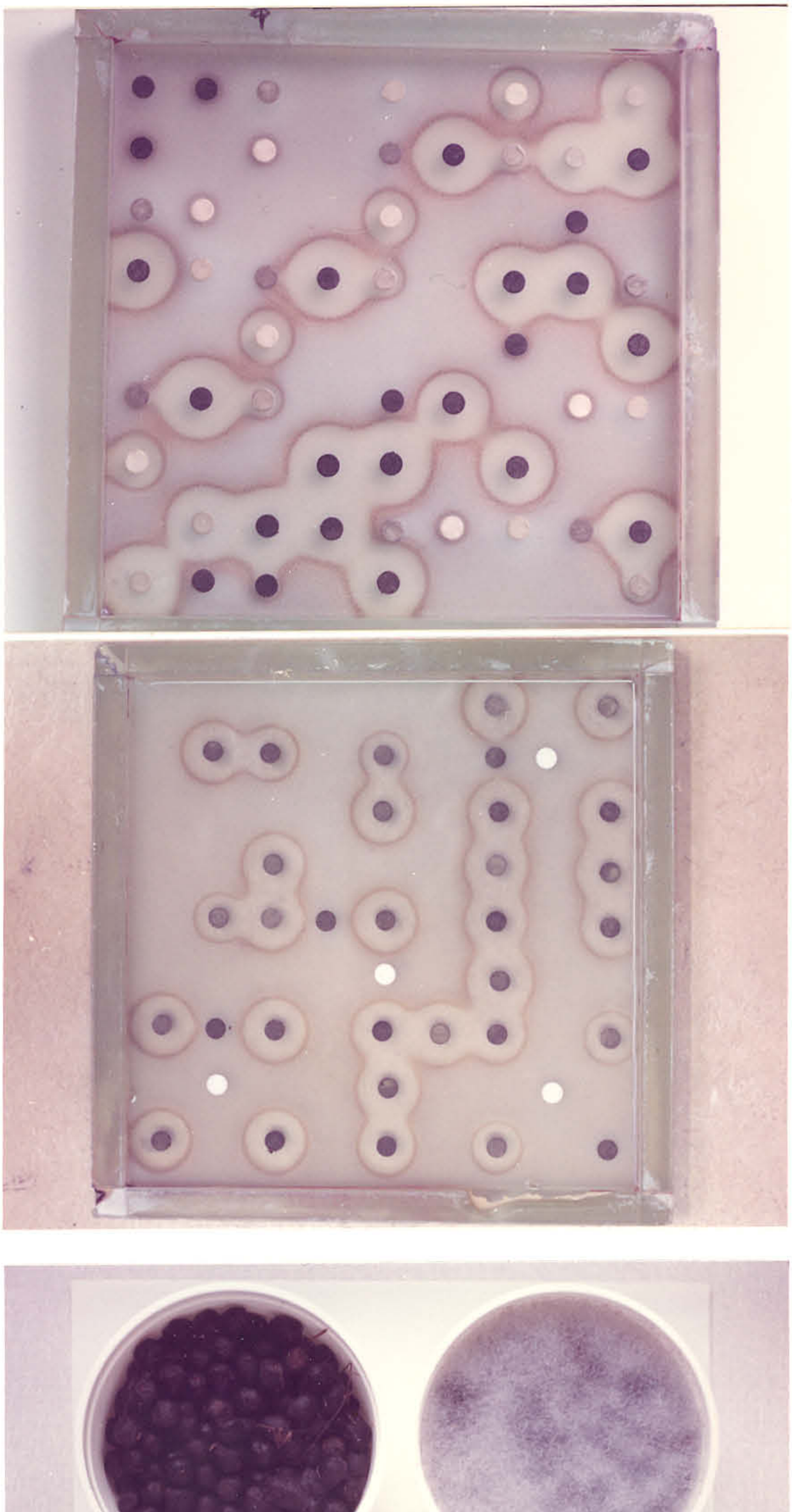
The evaporated faecal extract was reconstituted in 1 ml of chloroform and by absorption onto a 12 mm diameter paper disc, samples were laid on the agar, using a latin square formulation. Four replicate discs for each sample were used.

After incubation at 22°C for 3 days, zones of activity which developed around the discs were measured.

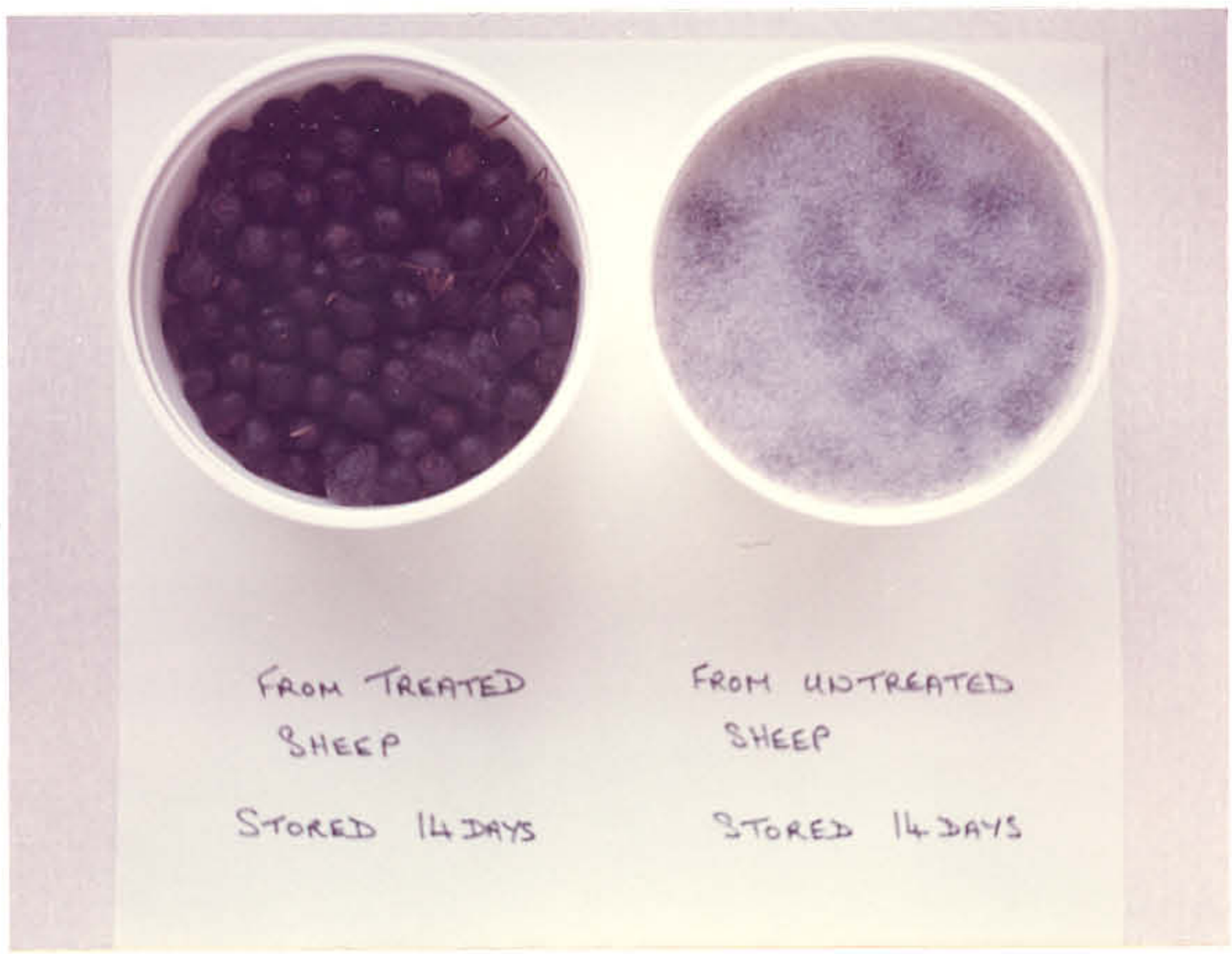
Plate 39 illustrates the type of zones achieved from faecal extracts and thiophanate's fungicidal properties in the faeces.

* 'Mildothane' - May & Baker Ltd., Dagenham, Essex.

PLATE 39 : EXCRETED DRUG PLATE ASSAY



Assay plates after 3 days incubation at 22°C



Stored faecal samples illustrating the fungicidal property of the anthelmintic thiophanate

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Experimental and field studies with thiophanate in pigs

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Thiophanate, administered at a dosage of 50 mg per kg to artificially infected pigs, removed 96 to 99 per cent of adult *Oesophagostomum spp*, *Hyostrongylus rubidus* and *Trichuris suis*. Activity was also high against larval stages of these nematodes, except for 26-day-old *T suis*. Thiophanate also showed ovicidal and larvicidal activity against *H rubidus* and *Oesophagostomum spp*. At 50 mg per kg thiophanate administered alone was inactive against *Ascaris suum* and *Metastrongylus apri*, the former species also being refractory at 200 mg per kg.

Field trials confirmed these efficacy results in naturally infected animals. Pellet formulations providing mean dosages of 63 mg thiophanate per kg for adult pigs and 75 mg thiophanate per kg with 83 mg piperazine base per kg for growing pigs were highly effective in reducing the faecal output of *Oesophagostomum spp*, *H rubidus* and *T suis* eggs. In growing pigs, *A suum* was controlled by the thiophanate/piperazine product. No palatability or tolerance problems were observed when thiophanate or thiophanate/piperazine mixtures were administered at recommended dosage or multiples thereof in experimental or field studies.

THIOPHANATE (diethyl 4,4'-o-phenylene bis (3-thioallophanate) (United Kingdom patents numbers 1191406 and 1307250) has been extensively studied as an anthelmintic for ruminants. Experimental studies (Eichler 1973, 1974) and field trials have shown thiophanate to be a safe and effective compound for the treatment and control of parasitic gastroenteritis. The compound has subsequently been tested in pigs and the results of experimental and field work conducted in this species are reported here.

Materials and methods

EXPERIMENTAL STUDIES

Activity

In a preliminary experiment (experiment 1), three pigs (large whites) were each infected with 20,000 infective larvae of *Oesophagostomum spp* cultured from the faeces of infected sows. Sixty days later two animals were dosed with thiophanate at a dosage of 50 mg per kg and one at a dosage of 25 mg per kg, the anthelmintic being mixed with dry pig meal. The medicated meal was consumed within 20 minutes. Faecal egg counts, using the modified McMaster technique (Ministry of Agriculture 1972), were carried out two days before dosing and three to six days after dosing in order to detect anthelmintic activity by faecal egg suppression.

A critical experiment (experiment 2) was carried out using five weaned pigs (large whites) harbouring mixed natural infections which included *Ascaris suum*, *Trichuris suis* (identified by their eggs), and *Oesophagostomum spp* and *Metastrongylus apri* (identified by examination of worms expelled or found at autopsy). During the first week, faeces were collected from each animal to determine whether or not natural worm loss occurred to a degree which could be misinterpreted as anthelmintic activity after dosing. Only one pig (no 2) passed *T suis* on the seventh day. On the eighth day, one pig was dosed with thiophanate at 25, three at 50 and one (harbouring *A suum*) at 200 mg per kg using the same method as in experiment 1. Each pig was penned separately and total faecal output was collected daily. The expelled worms were counted and identified. The pigs were killed and autopsied seven days after treatment and the alimentary tract and lungs removed from each animal. The stomach was examined for presence of *Hyostrongylus rubidus* or evidence of a previous infection, the small intestine for *A suum*, and the caecum and colon for *T suis* and *Oesophagostomum spp*. Lungworms (*M apri*) were recovered by cutting open the air passages with fine scissors to facilitate extraction. The numbers of worms found at autopsy were compared with those expelled after dosing with thiophanate.

A controlled test (experiment 3) was carried out according to the prodedure of Gibson (1964) using 25 worm free weaned pigs (large white cross-breed) each of which was artificially infected with *H rubidus* (4300 infective larvae), *T suis* (4000 embryonated eggs) and *Oesophagostomum* spp (5400 infective larvae). At autopsy, worm burdens of the last named genus in the controls were found to comprise on average 93 per cent *O dentatum* and 7 per cent *O quadrispinulatum*. The infected pigs were divided into groups of four. Each group was dosed with thiophanate at either two, eight, 15, 26 or 55 days after infection. A group of five pigs acted as controls. Individual faecal samples were collected from the last group to be treated one day before treatment, on the day of treatment and on six occasions up to 72 hours after treatment. Egg hatchability was determined and the recovery rate of third stage (infective) larvae from faeces mixed with vermiculite and incubated for six days at 25°C was assessed. All animals were killed and autopsied 61 days after infection and the residual worms in the alimentary tract counted. For each genus the worm counts in each treated group were compared with those in the control group.

Tolerance

Eleven weaned pigs, 10 to 15 weeks old, were housed in pens with concrete floors. Two groups of three were dosed with thiophanate and a group of five served as controls. One group of three received thiophanate mixed in dry meal at a concentration of 1·5 per cent w/w which was consumed over a period of 30 minutes to give a mean intake of test material of 600 mg per kg. The second group of three animals received a concentration of 2·0 per cent w/w which was consumed over a period of 20 minutes to give a mean intake of 800 mg per kg. For the following 29 days, all animals were given approximately 2 kg of plain pig meal per head per day. Daily observations were carried out for adverse clinical signs, and each animal was weighed at seven day intervals until 28 days after dosing. Frequent observations on appetite were carried out at the twice daily feeds during this period.

FIELD TRIALS

Animals and trial sites A series of field trials was conducted on commercial pig farms in Essex, Kent and Buckinghamshire

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TABLE 1: Experiment 2: Number of worms recovered after treatment of pigs with thiophanate—individual worm counts

Pig No	Dose rate (mg/kg)	Nematode genus	No of worms recovered after treatment: No expelled in faeces on Day: +1	+2	+3	+4	+5	+6	No recovered at postmortem
1	25	Oesophagostomum	0	116	8	1	2	0	9
		Trichuris	38	69	62	8	11	13	21
		Ascaris	0	0	0	0	0	0	0
		Metastrongylus	—	—	—	—	—	—	264
2	50	Oesophagostomum	6	122	23	2	3	0	0
		Trichuris	123	110	138	15	13	0	0
		Ascaris	0	0	0	0	0	0	0
		Metastrongylus	—	—	—	—	—	—	46
3	50	Oesaphagostomum	52	15	2	0	0	0	0
		Trichuris	0	0	0	0	0	0	0
		Ascaris	0	3	1	1	0	0	30
		Metastrongylus	—	—	—	—	—	—	0
4	50	Oesophagostomum	50	47	0	1	0	0	0
		Trichuris	0	0	0	0	0	0	0
		Ascaris	0	0	0	0	0	0	6
		Metastrongylus	—	—	—	—	—	—	62
5	200	Oesophagostomum	2	15	1	0	0	0	0
		Trichuris	52	7	1	2	6	0	0
		Ascaris	0	0	0	0	0	0	6
		Metastrongylus	—	—	—	—	—	—	0

in collaboration with practising veterinary surgeons. A total of 118 adults and 481 growing stock was treated with thiophanate.

Formulations of thiophanate used After preliminary palatability work two cereal-based formulations were selected for trials:

(1) Pellets containing 10 per cent w/w thiophanate for adult stock (Nemafax sow wormer pellets, May & Baker). Use rate, 1 oz per 100 lb liveweight (25 g per 40 kg liveweight) as a single dose. Mean dosage 62·5 mg thiophanate per kg.

(2) Pellets containing 6 per cent w/w thiophanate and 15 per cent w/w piperazine phosphate for growing/fattening pigs (Nemafax P wormer pellets, May & Baker). Use rate, 1 oz per 50 lb liveweight (25 g per 20 kg liveweight) as a single dose. Mean dosage 75 mg thiophanate per kg and 83 mg piperazine base per kg.

Pellets were administered either alone or with the normal ration for a single meal. Growing pigs were medicated in groups, adults either individually or in groups.

Trial design Comparable groups of adult or growing pigs were selected and medicated with either the appropriate thiophanate formulation at recommended or multiple dosage, or a standard product containing 4 per cent w/w thiabendazole (Thiprazole sow wormer, Merck, Sharp & Dohme) (adult pigs) or 4 per cent w/w thiabendazole and 8 per cent w/w picadex (Thiprazole weaner wormer, Merck Sharp & Dohme) (growing pigs) at recommended dosage or given an unmedicated diet. Animals were observed at the time of medication for any signs of unpalatability and for up to seven days subsequently for tolerance purposes.

In one trial, groups of growing pigs were medicated with thiophanate/piperazine pellets at one, two and three times recommended dosage. Their weight gains over three weeks after medication were compared with an untreated control group and a group treated (recommended dosage of thiabendazole/picadex).

In two adult and three growing pig trials, where faecal examinations showed a worm burden to be present, efficacy was assessed on the basis of faecal egg counts. The basic trial design was as above and in addition faecal samples were taken from a proportion of the animals in each group at intervals before and after treatment. Eggs were counted by the modified McMaster technique and cultured in vermiculite for six days at 25°C for subsequent larval identifications (Taffs 1967).

TABLE 2: Experiment 3: Anthelmintic efficacy of thiophanate at 50 mg/kg in experimentally infected pigs (four pigs per group)

Species	Age of infection when treated (days)	Postmortem worm burdens: Mean	Range	Percentage efficacy
H rubidus	2	58	20-120	95
	8	98	30-150	92
	15	170	70-260	86
	26	55	0-130	96
	55	15	0-40	99
	Control	1218	720-1170	—
Oesophagostomum spp	2	15	0-20	95
	8	80	60-90	75
	15	60	20-100	81
	26	20	0-40	94
	55	5	0-20	98
	Control	320	140-440	—
T suis	2	35	20-80	90
	8	113	80-140	69
	15	20	0-30	95
	26	293	180-460	20
	55	15	0-40	96
	Control	365	200-460	—

Results

EXPERIMENTAL STUDIES

In experiment 1 (activity), thiophanate at a dose-rate of 50 mg per kg caused suppression of the faecal egg output of *Oesophagostomum* spp in two pigs. Two days before dosing egg counts of 900 and 3100 eggs per gram (epg) were detected. Counts of less than 50 epg of faeces were recorded for both animals four, five and six days after dosing. The faecal egg count of the single animal dosed at 25 mg per kg rose from 200 epg two days before dosing to 12,250 epg six days after dosing.

In experiment 2 (activity), using five pigs carrying patent natural infections, thiophanate was tested against several nematode species. The results are given in Table 1. Thiophanate at a dosage of 50 mg per kg was effective in removing *Oesophagostomum* spp and *Trichuris suis*. A measure of activity against these two species was also seen at 25 mg per

TABLE 3: Experiment 3: Individual faecal egg counts, hatchability data and larval recoveries

Observation	Treatment	No of pigs	Time before/after treatment when faecal sample taken (hours): −24	0	+2	+4	+6	+24	+48	+72
Mean and range of faecal egg counts of *Oesophagostomum* spp and *H rubidus* (epg)	Controls	5	638 (250-950)	570 (150-900)	570 (150-950)	520 (50-1100)	650 (50-400)	540 (50-1100)	500 (150-1150)	680 (250-1250)
	Thiophanate	4	1688 (250-3900)	525 (200-1100)	713 (250-1550)	913 (150-2550)	725 (150-1950)	450 (50-750)	100 (50-250)	50
Mean and range of egg hatchability (per cent hatch)	Controls	5	99·9 (99·4-100·0)	100·0	98 8 (96 5-100·0)	99 3 (96·3-100·0)	97 8 (95 0-98 5)	97 8 (95 5-100·0)	97·7 (94 8-100·0)	98 6 (96·3-100·0)
	Thiophanate	4	98·3 (97·0-100·0)	97·5 (93·7-100·0)	93 5 (81·2-100 0)	96·7 (92 8-100 0)	95·2 (93·3-97 8)	9 0 (0-36·1)	5·0 (0-10·0)	—
Total number of larvae recovered	Controls	5	>2000	>2000	>2000	>2000	>2000	>2000	>2000	>2000
	Thiophanate	4	>2000	>2000	>2000	>2000	<100	<10	<10	<10

TABLE 4: Experiment 4: Observations on the weights of weaner pigs treated with thiophanate mixed in dry pig-meal

No of pigs	Concentration of thiophanate in pig-meal (per cent)	Approximate dosage of thiophanate (mg/kg/pig)	Mean and range of weights (kg) on following days after treatment					Overall weight gain (kg)
			0	7	14	21	28	
3	1·5	600	56·7 (55-59)	58·7 (57-61)	62·0 (60-65)	65·7 (64-68)	69·0 (67-71)	12·3 (12-13)
3	2·0	800	29·0 (18-39)	31·7 (19-43)	35·7 (20-48)	38·7 (23-51)	42·0 (26-55)	13·0 (8-16)
5	Controls		36·6 (29-49)	39·2 (32-51)	43·4 (35-56)	46·4 (38-59)	48·6 (39-61)	12·0 (10-15)

TABLE 5: Field trials: weight gains of growing pigs

Group (No of pigs)	Mean initial liveweight (±SE) of pigs (kg)	Mean liveweight gain (±SE) of pigs over following periods (kg)		
		Days −5 to 0 (Medication Day 0)	Days 0 to 7	Days 0 to 21
Untreated controls (26)	29·9±1·0	5·4±0·3	3·5±0·1	10·2±0·2
Thiophanate/ piperazine 1 × dosage (31)	31·5±1·0	3·6±0·1	3·5±0·1	11·8±0·2
Thiophanate/ piperazine 2 × dosage (19)	30·8±1·2	3·6±0·1	2·7±0·1	10·1±0·2
Thiophanate/ piperazine 3 × dosage (17)	30·4±1·2	2·7±0·1	3·2±0·1	11·7±0·3
Thiabendazole/ Picadex 1 × dosage (20)	29·8±1·2	3·0±0·1	3·0±0·1	12·1±0·2

kg. However, thiophanate administered alone was inactive against *Ascaris suum* and *Metastrongylus apri* at 50 mg per kg and the former species was refractory at 200 mg per kg.

The results of the controlled test (experiment 3) are summarised in Table 2. They show high levels of activity against the mature stages of the three species tested (96 to 99 per cent) as well as most immature stages. Some variation in response was evident, however, against eight day *Oesophagostomum spp* and *T suis* (75 per cent and 69 per cent), 15-day *H rubidus* and *Oesophagostomum spp* (86 per cent and 81 per cent), and 26-day *T suis* (20 per cent). Ovicidal and larvicidal activity against *H rubidus* and *Oesophagostomum spp* was also demonstrated, the results being shown in Table 3.

Change of bodyweights in experiment 4 (tolerance) are given in Table 4. No adverse effects due to treatment were recorded. No adverse clinical signs or inappetence were apparent at any time during the course of the experiment.

FIELD TRIALS

Palability was satisfactory for both thiophanate containing formulations when administered in all types of feed. The growing pig pellets were readily consumed even at three times recommended dosage. The thiabendazole/picadex product at recommended dosage was similarly palatable. Both products could be successfully fed to growing pigs without accompanying feed but observation suggested that this method caused greater individual variation in intake than when pellets were given with other feed.

In adult pigs individual variations in rates of feeding were greater whether medicated pellets were fed alone or with the normal feed, The great majority of pigs readily consumed the ration but one sow each refused thiophanate pellets and the thiabendazole product.

Tolerance of both thiophanate formulations was excellent. After treatment of 118 adult pigs (81 at recommended dosage and 37 at double dosage), including sows at all stages of pregnancy and sows suckling young pigs, and 481 growing pigs of varying ages (320 at recommended dosage, 144 at double dosage and 17 at three times dosage), the only untoward effect observed was transient inappetence in two growing pigs medicated with thiophanate/piperazine pellets. A similar effect was observed in one adult sow medicated with thiabendazole. Appetite and feed consumption in all cases had returned to normal 24 hours after medication.

Where the weight gains of growing pigs were studied for three weeks after medication, statistical analysis by Student's "t" test showed no significant differences in weight gains of the groups over the three weeks after medication (Table 5).

Faecal egg count data from the field trials are given in Tables 6 (adult pigs) and 7 (growing pigs). The first of these shows that the thiophanate formulation effectively reduced faecal egg counts of *H rubidus* and *Oesophagostomum* spp in adults and compared favourably with the thiabendazole product. In the growing pig trials the nematode genera present were more variable, as were the levels of infection even between groups in adjacent pens. Both products were effective in controlling *Oesophagostomum* spp. In trial GP12 *T suis* was satisfactorily controlled by thiophanate/piperazine. Only in trial GP6 was any residual egg count after medication with thiophanate/piperazine apparent, this being due almost entirely to *A suum* in one pig. A similar occurrence was noted in the thiabendazole/picadex group of trial GP2. Piperazine is known (Gibson 1975) to be highly effective against the stages of *A suum* in the gut and the generally low levels of

TABLE 6: Field trials: Faecal egg counts—Adult pig trials

Trial	Day of trial (Medication day 0)	Mean and range of faecal egg count (epg)			Nematodes present
		Thiophanate	Thiabendazole	Untreated controls	
AP3	−7	950 (750-1100)	1350 (450-2250)	1350 (600-2100)	*Oesophagostomum spp* *H rubidus*
	0	1050 (600-1800)	750 (50-1300)	1650 (200-3050)	
	7	<50	150 (<50-350)	1700 (200-3150)	
	21	<50	200 (<50-600)	900 (100-1650)	
AP4	−7	2950 (300-6600)	3750 (500-9950)	3800 (50-11800)	*Oesophagostomum spp*
	0	3950 (1150-9400)	6850 (1250-14600)	4450 (400-9500)	
	7	<50	250 (<50-900)	2000 (50-3900)	
	21	<50	1950 (100-9350)	5300 (250-11800)	

TABLE 7: Field trials: faecal egg counts—growing pig trials

Trial	Day of trial (Medication day 0)	Mean and range of faecal egg count (epg)								
		Thiophanate /piperazine phosphate			Thiabendazole/Picadex			Untreated Controls		
		Oesophagostomum spp	*A suum*	*T suis*	*Oesophagostomum spp*	*A suum*	*T suis*	*Oesophagostomum spp*	*A suum*	*T suis*
GP2	—7	325 (<50-1050)	95 (<50-900)	<50	<50 (<50-200)	755 (<50-2000)	<50	<50	295 (<50-2050)	<50
	0	550 (<50-1300)	300 (<50-1750)	<50	<50	640 (<50-5550)	<50	<50	675 (<50-1900)	<50
	7	<50 (<50-50)	<50	<50	<50	150 (<50-850)	<50	<50	250 (<50-1100)	<50
	21	<50	<50	<50	<50	<50 (<50-250)	<50	<50	345 (<50-1250)	<50
GP6	—7	185 (<50-600)	1250 (<50-3300)	<50 (<50-50)	865 (50-5100)	75 (<50-350)	<50 (<50-50)	<50	160 (50-350)	<50
	0	135 (<50-300)	1000 (<50-4050)	<50	1400 (<50-2250)	<50	<50	<50	<50 (<50-50)	<50
	7	<50	210 (<50-1550)	<50	<50	<50	<50 (<50-50)	<50	<50 (<50-50)	<50
	21	<50	<50 (<50-100)	<50	<50	<50	<50	<50	<50 (<50-100)	<50
GP12	—7	274 (<50-1400)	80 (<50-300)	100 (<50-200)				<50 (<50-50)	<50	60 (<50-100)
	0	<50 (<50-200)	56 (<50-300)	106 (<50-300)				<50	<50	50 (<50-100)
	7	<50	<50 (<50-50)	<50				<50	<50	50 (<50-200)
	21	<50	<50	<50				<50	<50 (<50-50)	50 (<50-200)

post treatment faecal egg counts of this parasite in the present trials suggest that piperazine gave good control of *A suum* when combined with either thiophanate or thiabendazole.

The length of the post medication period which could be monitored in the field trials was such that the results confirm the efficacy of thiophanate against adult and larval stages of *H rubidus* and the adult and later larval stages of those parasites, *Oesophagostomum* spp and *T suis*, with longer prepatent periods.

Discussion

The experimental efficacy results for thiophanate at a dosage of 50 mg per kg show the compound to be an effective anthelmintic for all stages of *H rubidus* and *Oesophagostomum* spp and for adult and most larval stages of *T suis*. This is borne out by the results of field trials. The high degree of activity against the early stages of *H rubidus* and *Oesophagostomum* spp is noteworthy since Taffs (1966, 1968a) showed thiabendazole at a dosage of 66 mg per kg to have low activity against these stages. Variable activity of oral or subcutaneous levamisole (7·5 mg per kg) against two to three and seven to eight day old *H rubidus* has been demonstrated by Probert and others (1973). Taffs (1968b) also showed oral tetramisole (15 mg per kg) to be ineffective against 5-day-old *Oesophagostomum* spp infections and to be somewhat variable in activity against adults. Pecheur and others (1971) demonstrated that parbendazole (30 mg per kg) had markedly lower activity (46·8 per cent) against 14-day *H rubidus* than against adults (93·7 per cent). A recent study by Stewart and others (1975) has shown coated and uncoated dichlorvos formulations to be effective against adult *H rubidus* but to have little or no activity against five or 15 day old worms. On the present results, therefore, and in the absence of a direct comparison, thiophanate appears to show higher and more consistent activity than some other anthelmintics particularly against the early parasitic stages of *H rubidus* and *Oesophagostomum* spp.

Davidson and others (1968) found that, in naturally infected sows treated with thiabendazole at 50 mg per kg, residual egg counts of *H rubidus* and *Oesophagostomum* spp remained after treatment in some cases. This was apparent with thiabendazole, but not with thiophanate (63 mg per kg), in adult pig trials reported here. The difference may reflect the superior activity of thiophanate against some stages of the nematodes, and also a more consistent level of efficacy provided by a higher mean dosage of the thiophanate product relative to the minimum effective dosage.

The efficacy of thiophanate against *T suis* is also of interest since Taffs (1969) in reviewing the effective anthelmintics against this parasite concluded that, of the presently widely used compounds, only dichlorvos (Beer and others 1971) could be recommended. Parbendazole (Taffs 1970) is now also known to be effective and thiophanate can be added to this list. The potential pathogenicity of *T suis* to pigs has been noted by Beer (1971) and Beer and others (1971) so that activity of a broad spectrum pig anthelmintic against this parasite is obviously of value. The reason for the relatively refractory nature of the 26 day old infection to thiophanate treatment in the controlled test is not apparent.

The ovicidal effect of thiophanate on *H rubidus* and *Oesophagostomum* spp is similar to that of thiabendazole (Taffs 1968a) and parbendazole (Taffs 1970). The poor activity of thiophanate administered alone against *A suum* and *M apri* resembles that of thiabendazole for both parasites and of parbendazole for the latter. The piperazine included in the growing pig pellet, however, provides good control of *A suum*.

The palatability and tolerance studies show thiophanate and thiophanate/piperazine pellets to be well accepted and tolerated by adult and growing pigs respectively. It is therefore concluded that the thiophanate formulations tested are safe and effective anthelmintic presentations for use in pigs.

Acknowledgements.—We gratefully acknowledge the technical assistance of Mr M. H. Wormald with the experimental work and Mr P. Lake with the field trials. Thanks are also due to the farmers and veterinary surgeons who collaborated in the field trial programme.

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Thiophanate as a low daily dosage anthelmintic in sheep

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Veterinary Record (1978) 130. 131-134

Thiophanate administered daily at low dosages reduced nematode faecal egg output, egg hatchability and parasitic worm burdens in treated lambs and ewes.

Six daily doses of 1 or 3 mg per kg thiophanate (approximately 1/25th to 1/75th of the median therapeutic dose), given to lambs experimentally infected with *Trichostrongylus colubriformis*, were partially effective in suppressing faecal egg output and egg hatchability. Six doses of 5 mg per kg per day were effective in lambs infected with *Haemonchus contortus* and *Nematodirus spathiger*. Daily doses of thiophanate (50 or 200 mg per head) given over 14 weeks to lambs grazing contaminated pasture resulted in improved productivity (the higher dosage) and suppression of output of viable eggs and reduced worm burdens (both dosages). Reduced output of viable eggs was also obtained in housed, lactating ewes receiving 5 or 7 mg per kg thiophanate dispersed daily in the feed for 11 or nine weeks respectively after lambing.

THIOPHANATE has been shown to possess broad spectrum anthelmintic activity in sheep and cattle (Eichler 1973) and to be well tolerated by these species (Eichler 1974).

An important attribute for the preventive use of anthelmintics is an ability to sterilise worm eggs in the host's gut. This prevents further pasture contamination, which may otherwise occur after the death of the worms, arising from eggs passed in the faeces for a period of 12 hours or longer.

Thiabendazole and parbendazole have been shown to have such ovicidal activity in ruminants (Southcott 1963, Gordon 1964, Johns and Mendel 1969). Phenothiazine also possesses this characteristic and has been incorporated into feedblocks and other carriers to provide a self-medication system.

This paper describes experiments conducted to establish the daily dose rate of thiophanate required to markedly reduce the output of viable nematode eggs, in lambs and ewes, by ovicidal activity and other means, thereby controlling pasture contamination.

Materials and methods

The ovicidal activity of thiophanate was determined in a preliminary experiment using 16 worm-free, weaned, Welsh cross lambs experimentally infected with *Haemonchus contortus* and *Trichostrongylus colubriformis*. When infection was patent, eight lambs were treated with a standard therapeutic dose of 50 mg thiophanate per kg body-weight, the remaining eight acting as untreated, infected controls. Individual faecal samples were collected one, three, six and 24 hours after treatment. The nematode eggs, recovered from each sample by centrifugation in saturated saline on to a microscope cover slip, were incubated in distilled water for four days at 24°C and their hatchability assessed by microscope examination of embryonation.

Following this, experiments were conducted to establish the minimum dosage, administered daily, to control the output of viable ova by infected sheep. Egg counts were conducted by the modified McMaster technique (Ministry of Agriculture 1971) and hatchability assessed as above.

Although phenothiazine is now only occasionally used in practice, much information exists on its anthelmintic properties, including its effect on the hatchability of nematode ova. As this property was studied in comparison with that of thiophanate, phenothiazine is an appropriate reference standard.

Experimentally infected lambs.—The effects of daily dosing with thiophanate on faecal egg output and egg hatchability were tested in worm-free, weaned, cross-bred lambs experimentally infected either with *T colubriformis* or with *H contortus* and *Nematodirus spathiger*. Treatment was given orally as an aqueous suspension for six days at the rate of 1, 3 or 5 mg per kg per day. Individual faecal samples were collected before and during treatment, and for up to 28 days thereafter.

Lambs grazing infested pasture.—The effect of daily dosing on the faecal egg output, egg hatchability, parasite burden, body-weight and incidence of clinical helminthiasis were tested in groups of five weaned, worm-free, cross-bred lambs, of the same age and balanced for weight, sex and breed, grazing together on pasture contaminated with mixed species of infective nematode larvae.

The lambs were drenched orally with thiophanate at 50 or 200 mg per head or phenothiazine at 500 mg per head in aqueous suspension immediately before entering the pasture and then daily for 14 weeks during the months June to

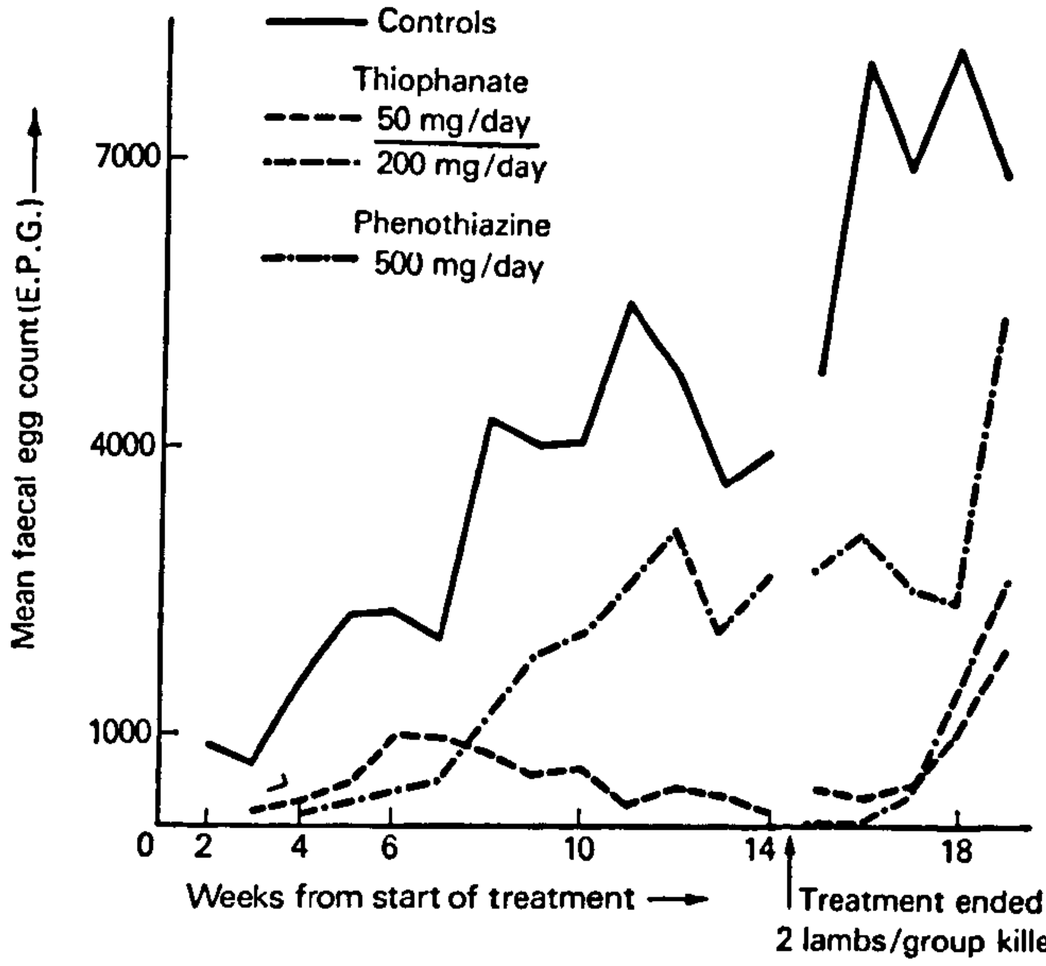

FIG 1: Mean faecal egg count—naturally infected lambs on daily treatment

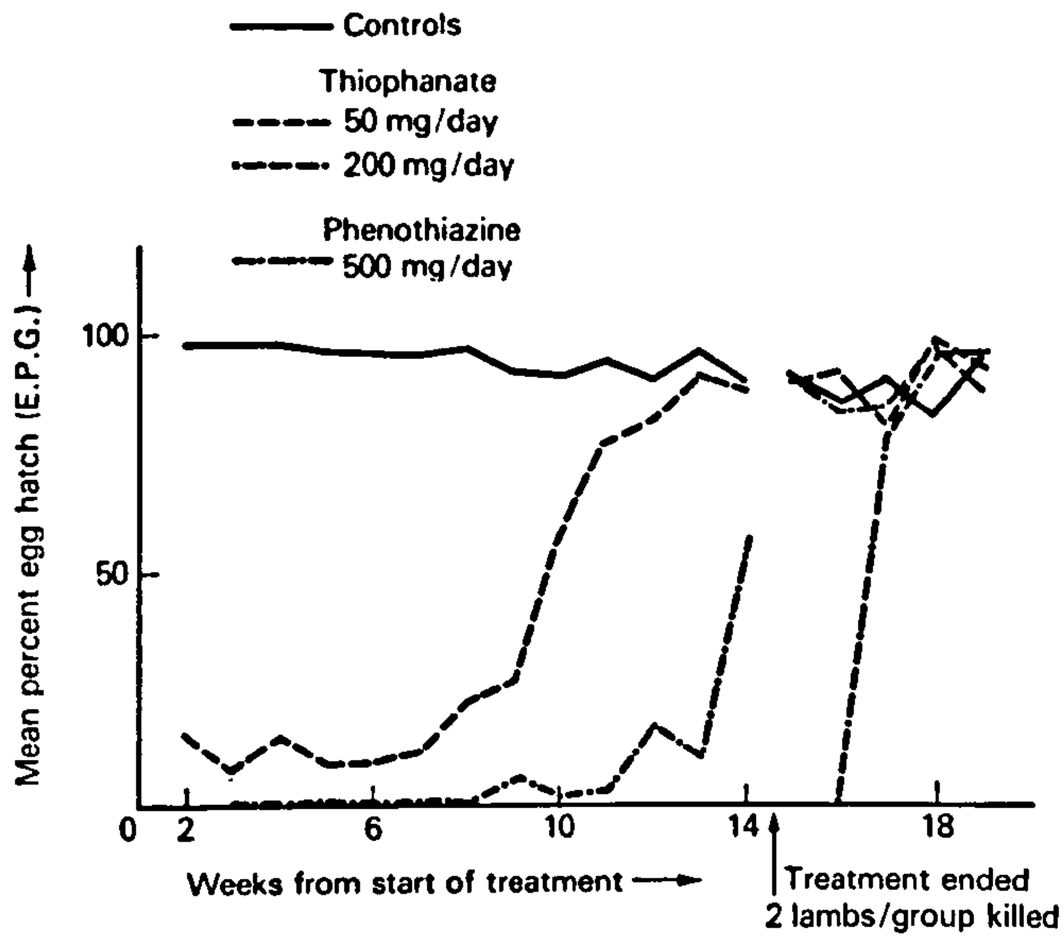

FIG 2: Mean percent egg hatch—naturally infected lambs on daily treatment

September. One group of lambs was untreated throughout and served as an unmedicated control group. Each lamb was weighed at weekly intervals and individual faecal samples were collected twice weekly for egg counts and hatchability tests. At cessation of treatment, two lambs from each group were killed and the remainder housed on concrete floored pens for five weeks to allow any immature parasites to mature.

Naturally infected ewes.—Three groups each of 10 Border Leicester cross ewes, freshly lambed and suckling, were removed from grazing infested pasture and housed in groups of five on concrete floored pens. A mean daily dose of 3, 5 or 7 mg per kg thiophanate dispersed in the concentrate feed was fed, using one group for each treatment, for nine to 11 weeks after lambing. Each treatment group was maintained with a separate unmedicated control group. Egg counts and hatchabilities were measured in individual faecal samples collected once weekly.

Results

The percentage hatchability of the eggs recovered from the faeces was reduced from 97·1 to 38·7 within three hours of a single drench with thiophanate at 50 mg per kg bod-yweight. By six hours after treatment hatchability was almost completely inhibited (7·5 per cent) and at 24 hours was negative in seven out of eight sheep.

Repeated daily dosing for six days with 5 mg per kg thiophanate suppressed the faecal egg output of *H contortus* and *N spathiger* both during and after the course of treatment. Daily dosing with 3 mg per kg per day reduced the egg output of *T colubriformis* by 83 per cent and, during the period of treatment only, reduced egg hatchability by more than 56 per cent. Six daily doses of 1 mg per kg had a slight effect on *T colubriformis* egg output (44 per cent reduction) but egg hatchability was unaffected.

In lambs exposed to natural infection on pasture the faecal egg output was almost completely suppressed (>98 per cent) by dosing with 200 mg thiophanate and >80 per cent with 50 mg thiophanate, 500 mg phenothiazine being less effective (63 per cent) (Fig 1). After five weeks off medication when the remaining lambs were housed on concrete, the mean faecal egg counts showed mean per cent reductions of 86, 87 and 69 respectively relative to the original counts. Egg hatchability was markedly reduced during treatment (Fig 2) giving an actual mean output of viable eggs (mean faecal egg count × hatchability) by these treatments of 0, 267 and 228 respectively (controls = 3069). One lamb died of parasitic gastroenteritis in each group, except that receiving 200 mg thiophanate per head. The mean weight gain of the lambs which received 200 mg thiophanate was significantly higher than that of the lambs in the control group (Table 1). Both

TABLE 1 Effect of daily treatment for 14 weeks with either thiophanate or phenothiazine on the weight gains of first year lambs after grazing contaminated pasture

	Mean weight gain from Day 0 (kg)																		
	Weeks during treatment														Weeks off medication (3 lambs per group remaining)				
Group	1	2	3	4	5	6	7	8	9	10	11	12	13	14	1	2	3	4	5
Controls	2·3	2·1	2·4	3·3	2·8	2·4	1·4	1·9	1·9	2·0	2·0	1·25	1·25	0·9	4·0	3·7	5·0	4·5	5·2
50 mg per day Thiophanate	2·7	1·0	–0·2	0·4	0·5	0·3	0·1	0·4	1·1	2·2	2·7	3·2	4·1	4·4	5·0	6·2	7·3	8·5	9·0
200 mg per day Thiophanate	3·6	2·1	2·1	3·5[4]	3·7[5]	3·6	3·6	4·1	5·3[5]	6·4	7·1[5]	8·1[1,5]	9·7[2,6]	10·3[2,6]	11·2[4]	12·0[1]	13·8[1,5]	15·0[5]	15·3[1]
500 mg per day Phenothiazine	3·6	2·6	3·6	4·8t	4·6t	4·1	3·6	4·1	4·1	4·9	4·7	4·4	5·0	5·0	9·5	10·7	13·2	13·2	13·0

Significant values
Treatments compared with controls
1 P > 0·02
2 P > 0·01
3 P = 0·05

200 mg thiophanate compared with 50 mg thiophanate
4 P = 0·05
5 P > 0·02
6 P > 0·01

500 mg phenothiazine compared with 50 mg thiophanate
7 P > 0·02

TABLE 2: Effect of daily treatment for 14 weeks with either thiophanate or phenothiazine on the worm burdens found in first year lambs after grazing contaminated pasture

Group	Mean dose rate (mg per kg per day) (Range) Week 0	Week 14	Two lambs per group killed at end of treatment: Main genera present	Mean worm burden	Mean efficiency (per cent) (Range)	Three lambs per group killed five weeks after treatment*: Main genera present	Mean worm burden	Mean efficiency (per cent) (Range)
Control	—	—	*Ostertagia*	8022·0		*Haemonchus*	1148·7	
			Trichostrongylus[1]	11084·0		*Ostertagia*	2680·7	
			Nematodirus	689·0	—	*Trichostrongylus*[1]	11011·0	—
						Nematodirus	1583·0	
			Total	19810·0		Total	16453·0	
			Range	8520-21100		Range	9820-21110	
50 mg per day Thiophanate	4·9 (2·9-7·7)	3·4 (2·9-4·5)	*Haemonchus*	237·0		*Haemonchus*	377·0	
			Ostertagia	4424·0	73·3	*Ostertagia*	2417·0	71·4
			Trichostrongylus[2]	293·5	(57·2-89·3)	*Trichostrongylus*[1]	1194·4	(55·4-87·6)
			Nematodirus	331·5		*Nematodirus*	651·7	
			Total	5295·0		Total	4700·0	
			Range	2110-8480		Range	2040-7340	
200 mg per day Thiophanate	15·3 (11·1-23·5)	8·5 (6·2-12·9)	*Ostertagia*	580·0		*Haemonchus*	263·3	
			Trichostrongylus[2]	10·0	96·8	*Ostertagia*	1820·0	83·0
			Nematodirus	35·0		*Trichostrongylus*[2]	16·7	
					(93·8-99·8)	*Nematodirus*	653·3	(72·9-90·8)
			Total	625·0		Total	2790·0	
			Range	30-1220		Range	1520-4460	
500 mg per day Phenothiazine	30·8 (27·0-100·0)	23·5 (16·7-52·5)	*Ostertagia*	10086·0		*Haemonchus*	196·7	
			Trichostrongylus[1]	5312·0	19·3	*Ostertagia*	3893·3	0
			Nematodirus	587·0	(8-30·6)	*Trichostrongylus*[1]	12971·0	(0-5·4)
						Nematodirus	939·0	
			Total	15985·6		Total	17160·0	
			Range	13750-18223		Range	15550-19030	

*Survivors removed to concrete floored pens and treatment discontinued. 1 = *T axei* and *T colubriformis* present
2 = *T colubriformis* only

thiophanate treatments, but not phenothiazine, resulted in lower worm burdens than in untreated controls (Table 2).

In the lactating housed ewes, egg output was controlled by 7 mg per kg per day, while 5 or 7 mg per kg per day markedly reduced the output of viable nematode eggs. Three mg per kg per day had a partial effect based on these parameters (Figs 3 and 4).

Discussion

The experiments described in this paper show that treatment with thiophanate reduces both egg output and egg hatchability when it is administered as a single therapeutic dose or continuously at a low dosage over several days. The net effect is prevention of or reduction in the pasture contamination.

Treatment of lambs with 200 mg per head per day thiophanate (mean daily intake of approximately 12 mg per kg) protected against clinical helminthiasis and resulted in a statistically significant improvement in weight gain when compared with that of untreated controls. These results were obtained under conditions of set stocking when the pasture challenge increased considerably (number of larvae per kg of herbage varied from 10 in late May to 119 in mid-September). The group treated with 50 mg per head per day thiophanate (given a mean daily intake of approximately 4 mg per kg) failed to show a weight response during the first two months when the intake was relatively high and the pasture challenge relatively light. Under these conditions an initial daily dosage higher than 50 mg per head is probably required for young susceptible lambs and this can be reduced as resistance to nematode infestation is acquired.

Prevention of pasture contamination by medication of the lambs with thiophanate was achieved with 200 mg per head per day because detectable faecal egg output was completely suppressed. In the 50 mg per head per day group, faecal egg output and hatchability were both reduced and resulted in a considerable lowering of pasture contamination relative to the untreated controls.

Phenothiazine suppressed pasture contamination with

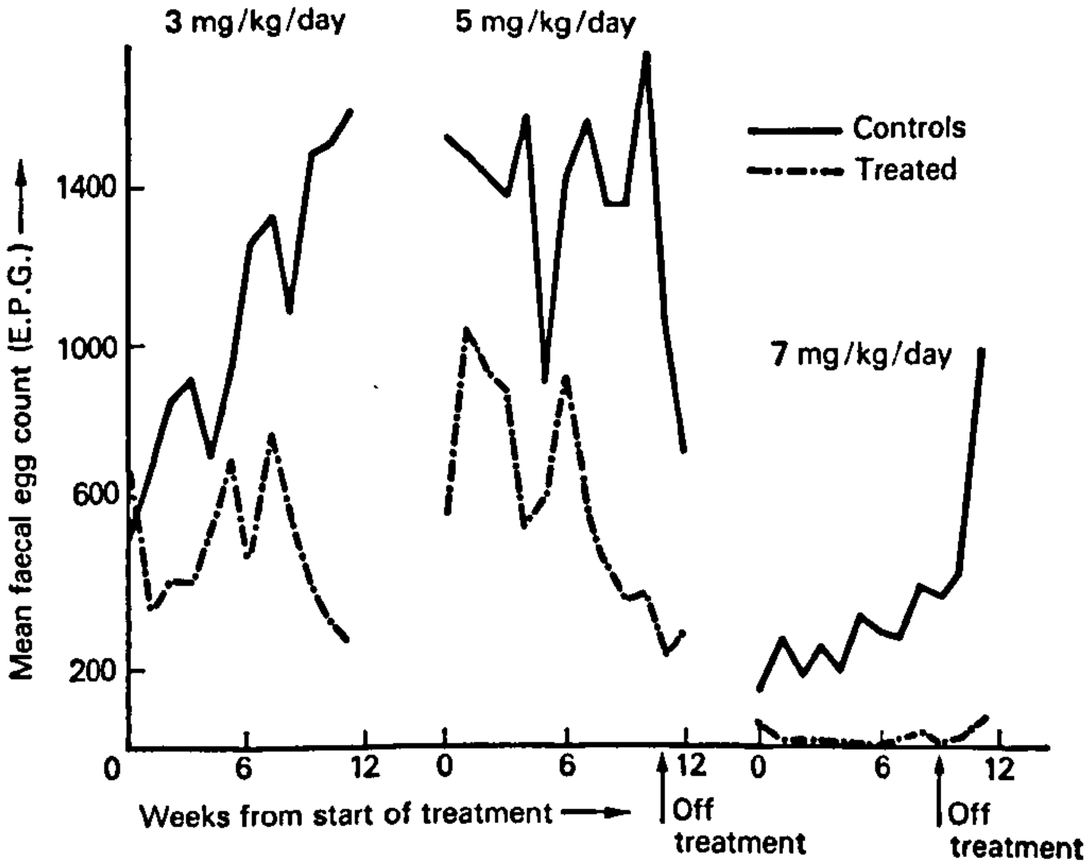

FIG 3: Mean faecal egg count—lactating ewes on in-feed daily treatment

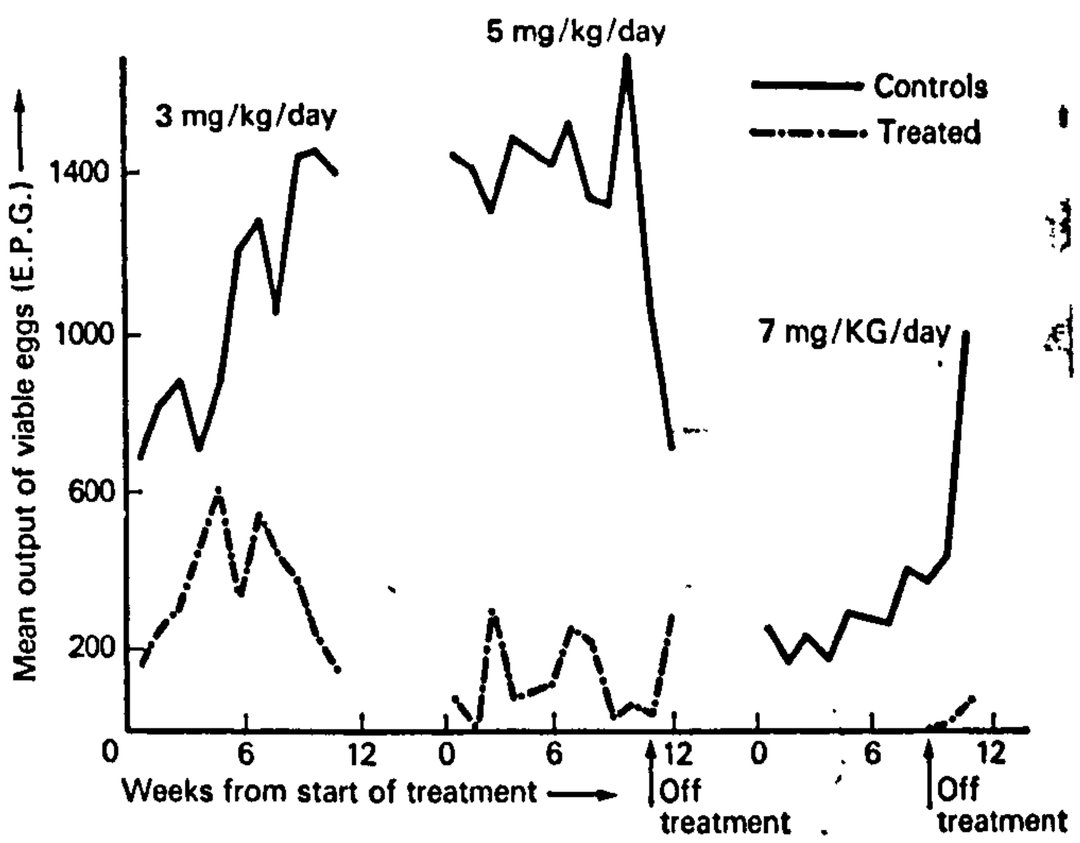

FIG 4: Mean output of viable eggs—lactating ewes on in-feed daily treatment

moderate efficiency, due to its effect on hatchability, but did not prevent clinical helminthiasis.

Faecal egg count increased after completion of treatment with 200 mg thiophanate per head per day when the lambs were removed from pasture, and moderate numbers of worms were recovered at autopsy. This suggests that, except for *T axei* which was completely removed, treatment was incompletely nematocidal and faecal egg count suppression was due to a reduction in egg laying and/or the selective removal of adult worms. The faecal egg count which reappeared after the cessation of treatment may have arisen from maturation of larvae picked up during the late stage of treatment and thus having undergone little exposure to thiophanate. Similar factors were probably responsible for the effect in the lactating ewe experiments and in this case no marked resurgence of egg counts occurred within two weeks of the end of treatment at 7 mg per kg per day.

Acknowledgements.—I wish to thank Mr A. B. Notman for rearing and housing the lambs and ewes.

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Repeat dosing of ruminants over limited periods with the anthelmintic thiophanate

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Studies in experimentally infected sheep and calves showed that repeated daily doses of 3·5 to 10 mg per kg live-weight of the anthelmintic thiophanate, for periods of seven to 28 days, reduced the output of viable nematode eggs to low levels, with no marked resurgence after completion of treatment. There was a variable vermicidal effect although many worms remaining after treatment appeared to be sterile. A dosage of 2·5 mg per kg twice daily to sheep for 10 or 20 days produced similar effects on viable egg output. It also produced a more complete and consistent worm kill of most gastrointestinal nematode species tested than did the once daily regimes.

In a field trial on commercial premises, thiophanate was made available in a feedblock carrier to ewes over the lambing period, the daily dosage being approximately 4 to 5 mg thiophanate per kg. The post parturient rise in faecal egg count was markedly lowered in comparison with that of untreated controls and the number of larvae recoverable from the cultured faeces of treated animals was very low.

Experimental and field studies showed the high vermicidal effect of 20 mg per kg per day for five days in sheep and the efficacy of such a regime in arresting faecal egg count in cattle receiving thiophanate in their feed.

EXPERIMENTAL and field studies with thiophanate (UK patent numbers 1191406 and 1307250) have shown that in single treatments at dosages of 50 mg per kg and above, it is an effective and safe broad spectrum anthelmintic for use in ruminants and pigs (Eichler 1973, 1974, Baines and others 1976, Baines and Colegrave 1977). Additionally, experimental studies in which thiophanate was used at repeated low daily dosage showed that viable faecal egg output was suppressed (Dalton 1978).

The present paper is a report of the results of further experimental work and field trials in sheep and cattle in which thiophanate was administered at low daily dosages in various regimes and the effects during and after the conclusion of medication recorded.

Materials and methods

EXPERIMENTAL STUDIES

Four studies were conducted in experimentally infected worm-free weaned crossbred lambs and Friesian calves as follows:

Experiment 1.—Groups of four lambs were infected with 5000 *Haemonchus contortus* and 20,000 *Nematodirus battus* infective larvae and treated from 27 days post infection with single daily doses of thiophanate according to the following regimes: 3·5 mg per kg per day for 28 days; 5 mg per kg per day for 20 or 28 days; 7 mg per kg per day for 20 days; or left untreated. Two animals per group were killed at the completion of medication and worms in the abomasum and small intestine counted. Additionally, a proportion of the nematodes recovered post mortem was fixed in Carnoy's fluid and examined microscopically.

Experiment 2.—Groups of five calves were infected with 15,000 *Ostertagia ostertagi* and 15,000 *Cooperia oncophora* infective larvae and treated from 25 days post infection with single daily doses of 5 mg per kg per day for 14 or 20 days or with 10 mg per kg per day for seven or 14 days or left untreated. One tracer calf per group was killed three to five days after completion of medication, the worms being examined as in experiment 1.

Experiment 3.—Groups of two lambs were infected with 5000 *H contortus*, 15,000 *O circumcincta*, 15,000 *Trichostrongylus colubriformis* and 15,000 *Nematodirus spathiger* infective larvae and treated from 21 days post infection with doses of 2·5 mg per kg twice daily for 10 or 20 days. A group of four was similarly infected but left untreated. All the lambs were killed at 20 days after completion of medication and worms examined as in experiment 1.

Experiment 4.—Groups of four lambs were infected with 500 *H contortus*, 1000 *O circumcincta*, 2000 *T. colubriformis* and 2000 *N spathiger* infective larvae per day on days –6 to –3 inclusive or, alternatively, with similar numbers and species of larvae daily on days –21 to –13 inclusive. In both cases, two lambs were treated from day 0 onwards with single daily doses of 20 mg per kg per day for five days and two left untreated. Therefore, assuming normal development, third and fourth stage larvae were present at the time of treatment in the first case and pre-adults and adults in the second. All the lambs were killed at 21 days after the completion of infection, and worm counts conducted.

In the experiments where different groups of treated animals were killed on different days, untreated control animals were killed on each of these days.

Infective larvae were administered per os. In each case thiophanate was administered as Nemafax suspension containing 20 per cent w/v thiophanate (May & Baker Ltd) either alone (experiment 4) or diluted to 10 times the volume with water to provide a larger dose volume when lower dosages were used (experiments 1, 2 and 3).

Individual faecal samples were collected from the lambs or calves at intervals before, during and for up to 34 days after the completion of medication in those experiments involving adult parasites. Faecal egg counts were conducted by the modified McMaster technique and most faecal samples collected during treatment were examined for assessment of egg hatchability and larval viability. Hatchability was assessed by recovering eggs from the faeces and examining these microscopically after culturing in distilled water at 25°C for three days. Faeces were also cultured in vermiculite for six days at 25°C before identification and estimation of numbers of larvae.

FIELD TRIALS

Administration via a feedblock carrier to parturient ewes

Thiophanate (as Nemafax wettable powder containing 70 per cent w/w thiophanate) was incorporated into feedblocks at a level calculated to provide intakes by ewes of approximately 5 mg per kg per day based on expected consumption of the blocks. The blocks used contained 15 per cent protein plus urea equivalent to 7·5 per cent protein. Groups of 80 naturally infected housed Colbred ewes on commercial premises in Essex were allowed free access to either the thiophanate-medicated blocks or to similar unmedicated blocks, from four weeks before the expected start of lambing until seven weeks after this time. The block consumption of

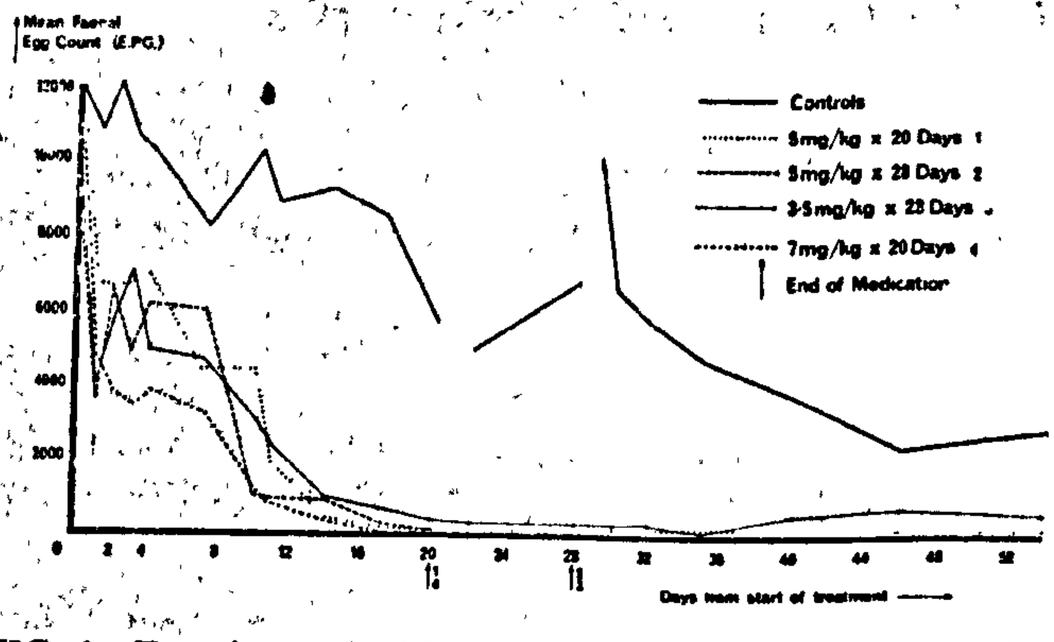

FIG 1: Experiment 1—Mean faecal egg counts (*Haemonchus contortus*)

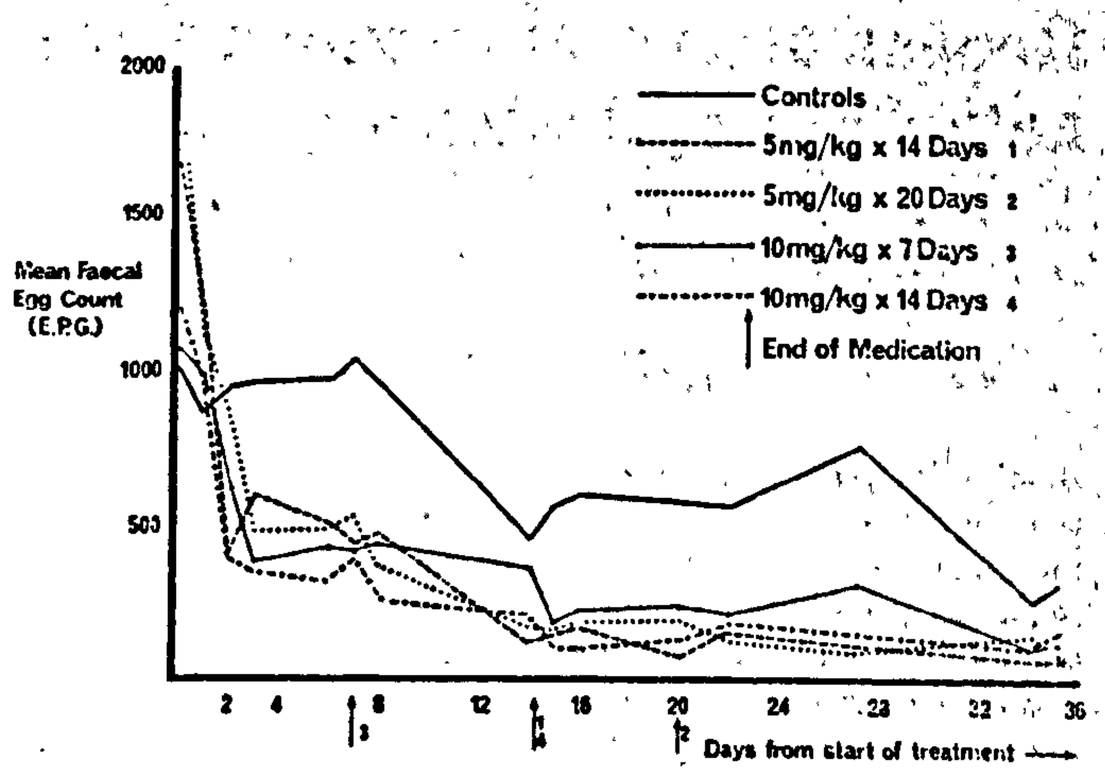

FIG 2: Experiment 2—Mean faecal egg counts

each group was estimated from the numbers of fresh blocks supplied and from this, for the medicated group, the thiophanate intake was calculated.

Individual faecal samples were collected from a proportion of the ewes in each group at weekly intervals throughout the period of medication and for five weeks after. These samples were used for egg counts and, during medication and for one week after, for assessment of egg hatchability and larval viability after culture.

At the end of the medication period the ewes together with their lambs were turned to permanent pasture heavily grazed the previous autumn. Faecal egg counts were also conducted on faecal samples collected from the lambs during this period.

Administration in-feed to housed cattle

A medication regime of 20 mg per kg per day for five days was tested in naturally infected steers of mixed breeds on a commercial farm in Essex. The animals were housed for the winter having spent the summer at grass. Two groups each of 12 animals housed in adjacent pens were used for the trial: one was medicated on days 0 to +4 inclusive with thiophanate (as Nemafax pellets containing 10 per cent w/w thiophanate) sprinkled on the morning feed at a level calculated to provide a mean dosage of 20 mg thiophanate per kg per day; the other was unmedicated. Faecal samples were collected from a proportion of the animals in each group on days 0, +4, +11 and +25 and used for egg counts and cultured for larval identifications.

Results

EXPERIMENTAL STUDIES

Experiment 1

Mean faecal egg counts of *H contortus* are shown in Fig 1. All treatment regimes caused counts to drop to very low levels by approximately 14 days after the start of treatment. No resurgence of egg count occurred in any group for up to 34 days after the end of medication. When the viable faecal egg output (total faecal egg output × percentage hatchability/100) was considered, this was found to decline to low levels in all treated groups within three days of the start of medication.

Egg counts of *N battus* were low in all groups and, therefore, more difficult to interpret. The same essential features were however exhibited.

Worm counts on lambs killed in this experiment are shown in Table 1. These demonstrate that, although there was a degree of vermicidal effect, this was not complete, there being little dose response. Microscopic examination of worms recovered post mortem showed that, particularly for *H contortus* females, there was evidence of sterilisation, the reproductive tract being extensively damaged. Comparable damage was seen in a proportion of *H contortus* males also, but was not apparent in a superficial examination of *N battus* males and females in this experiment, although eggs in utero were rare in the females.

TABLE 1: Experiment 1—Post mortem worm counts

Treatment	Post mortem worm counts: *Haemonchus contortus* Mean (range)*	Per cent reduction	*Nematodirus battus* Mean (range)*	Per cent reduction
5 mg per kg per day x 20 days	2330 (1880-2780)	0	3425 (1750-5100)	45·3
7 mg per kg per day x 20 days	1170 (1130-1210)	42·2	2355 (150-4560)	62·4
5 mg per kg per day x 28 days	1410 (1210-1610)	30·4	3125 (2340-3910)	50·1
3·5 mg per kg per day x 28 days	855 (610-1100)	57·7	105 (10-200)	98·3
Untreated controls	2025 (1980-2070)	—	6265 (4210-8320)	—

*Two animals per group. One untreated control was killed on each of days 20 and 28.

Experiment 2

Mean faecal egg counts are shown in Fig 2. As in experiment 1 all treatments caused a progressive decrease in total faecal egg counts to low levels by the end of treatment. During periods of up to 35 days after the end of medication, little resurgence of egg count was seen except, to a limited extent, in the 10 mg per kg per day for seven days regime. Egg hatchability was greatly reduced from the first day of treatment so that viable egg output was very low during treatment. After completion of treatment egg hatchability returned to normal and, therefore, most eggs present hatched.

Culture of faeces during treatment revealed that very few larvae could be recovered from treatment groups. This demonstrates a probable larvicidal effect of the drug since

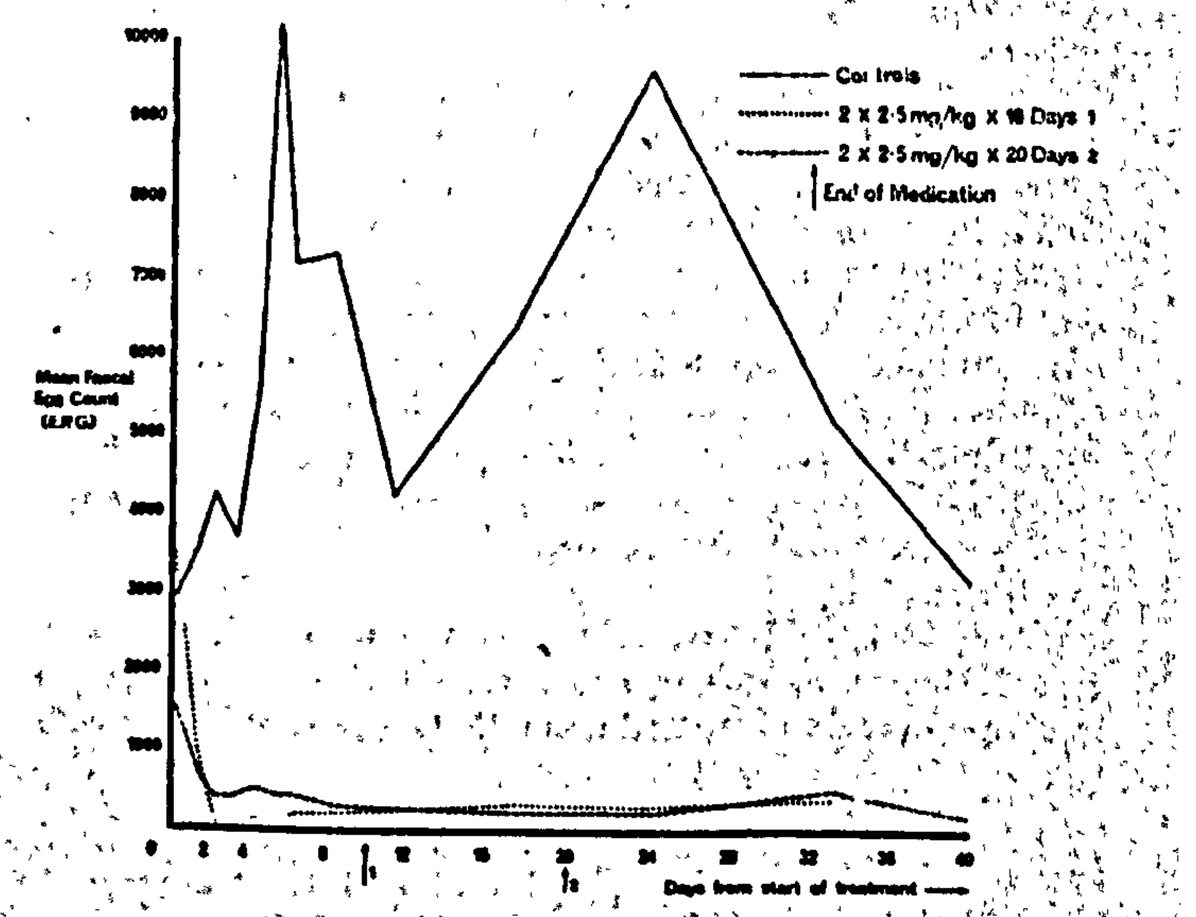

FIG 3: Experiment 3—Mean faecal egg counts

TABLE 2: Experiment 3—Post mortem worm counts

Treatment	Post mortem worm counts							
	Haemonchus contortus		*Ostertagia circumcincta*		*Trichostrongylus colibriformis*		*Nematodirus spathiger*	
	Mean (range)	Per cent reduction	Mean (range)	Per cent reduction	Mean (range)	Per cent reduction	Mean (range)	Per cent reduction
2·5 mg per kg twice daily x 10 days	80 (60-100)	95·1	3320 (2760-3880)	0	40 (20-60)	99·6	50 (20-80)	97·2
2·5 mg per kg twice daily x 20 days	0	100	4120 (60-8180)	0	210 (20-400)	97·6	730 (380-1080)	82·7
Untreated controls—group 1	1630 (100-3160)	—	2140 (660-3620)	—	9800 (7760-11,840)	—	1800 (1260-2340)	—
Untreated controls—group 2	1840 (380-3300)	—	2750 (1460-4040)	—	8790 (7980-9600)	—	4230 (1260-7200)	—

Untreated controls—group 1 killed on the same day as the 10 day treatment group, untreated controls—group 2 killed on the same day as the 20 day treatment group. Percentage reductions for the treatment groups relate to untreated controls killed on the same day.

the numbers of larvae recovered were even lower than those expected from consideration of the viable faecal egg count. After completion of medication, larvae were recovered from all treatment groups, but in much lower numbers than in controls. The ratio of ostertagia:cooperia larvae in treated groups was approximately 1:8 to 1:14 compared to 1:3 for the control group indicating a possible differential effect, ostertagia being more susceptible than cooperia.

Post mortem worm counts conducted on one animal per group showed that none of the treatment regimes had an appreciable vermicidal effect in this experiment. No morphological effect on male or female worms was detected on microscopic examination although few eggs were present in utero in females.

Experiment 3

Mean faecal egg counts are shown in Fig 3. In both treatment groups the faecal egg counts were reduced to a very low level from two days after the start of treatment and viable egg output was almost completely suppressed from the first day of treatment. No marked increase in faecal egg count occurred in periods of up to 20 days after the cessation of treatment. During medication no larvae were recovered from the faeces of treated groups after the second day.

The post mortem worm counts (Table 2) suggested that both treatments were effective against *H contortus* and *T colubriformis*. This was confirmed by the marked reduction in the output of viable eggs and the disruption of the reproductive tracts of the few remaining female worms. Less consistency, but still a high level of effect, was shown against *N spathiger*. *O circumcincta* was not removed by the 10- or 20-day regimes although there was an apparent reduction in numbers in one of the two animals in the 20-day group. Female worms of all species recovered post mortem showed abnormalities of the reproductive tract and few eggs were present in utero. Less effect was noted in males.

Experiment 4

The results are shown in Table 3. Post mortem worm counts showed that treatment had a high vermicidal effect against all stages of the parasites tested. Additionally, during the early stages of treatment when a faecal egg count was still present, the hatchability of these eggs was reduced to extremely low levels.

FIELD TRIALS

Administration via a feedblock carrier to parturient ewes

The mean thiophanate intake per ewe in the treated group was approximately 4 mg per kg per day during the pre-lambing period. After lambing, until the blocks were withdrawn, there was a steady increase in block consumption, so that the dosage of thiophanate reached almost 8 mg per kg per day per "ewe unit" (ewe plus twin lambs) at the end of medication. However, it was observed that the lambs were consuming increasing amounts of block. It is impossible to estimate the extent of this precisely but it seems unlikely that ewe intakes of thiophanate were markedly above 5 mg per kg per day at any stage.

Mean faecal egg counts in the two groups of ewes are shown in Fig 4. In the unmedicated controls a marked post parturient rise was seen with a peak at approximately four weeks after lambing. No such rise was seen in the medicated group where faecal egg counts remained at a low level throughout and no marked increase in egg count occurred when treatment was withdrawn. The faecal egg counts in both control and treated groups showed a tendency slightly to increase at the very end of the trial. This could be attributed to new larvae picked up from the contaminated pasture after the end of block medication and subsequently maturing. This is supported by evidence that, at the same time, the lambs running with the ewes first showed faecal egg output.

Examination of egg hatchability and larval recoveries after culture showed that, during the period of medication, the

TABLE 3: Experiment 4—Post mortem worm counts, egg output and hatchability

Developmental stage	Treatment	Post mortem worm counts								Mean faecal egg counts in eggs per gram and (per cent hatchability) on following days after start of treatment			
		Haemonchus contortus		*Ostertagia circumcincta*		*Trichostrongylus colubriformis*		*Nematodirus spathiger*					
		Mean (range)	Per cent reduction	Mean (range)	Per cent reduction	Mean (range)	Per cent reduction	Mean (range)	Per cent reduction	0	1	2	3
3rd and 4th stage larvae	20 mg per kg per day x 5 days	0	100	5·0 (0-20)	99·8	0	100	10·0 (0-20)	99·6				
	Untreated controls	1377·5 (40-2420)	—	2125·0 (880-3000)	—	3527·5 (3580-5880)	—	2345·0 (560-5100)	—				
Early adults and adults	20 mg per kg per day x 5 days	10·0 (0-20)	99·7	5·0 (0-20)	99·8	5·0 (0-20)	99·9	0	100	2837·5 (96·6)	500·0 (10·4)	62·5 (–)	25·0 (–)
	Untreated controls	3305·0 (2800-4020)	—	3210·0 (2020-5120)	—	5880·0 (4900-7320)	—	6535·0 (1700-11,720)	—	6462·5 (97·0)	6112·5 (97·1)	7512·5 (97·7)	9200·0 (97·7)

(–) = ≤ 10 larvae or eggs found in sample.

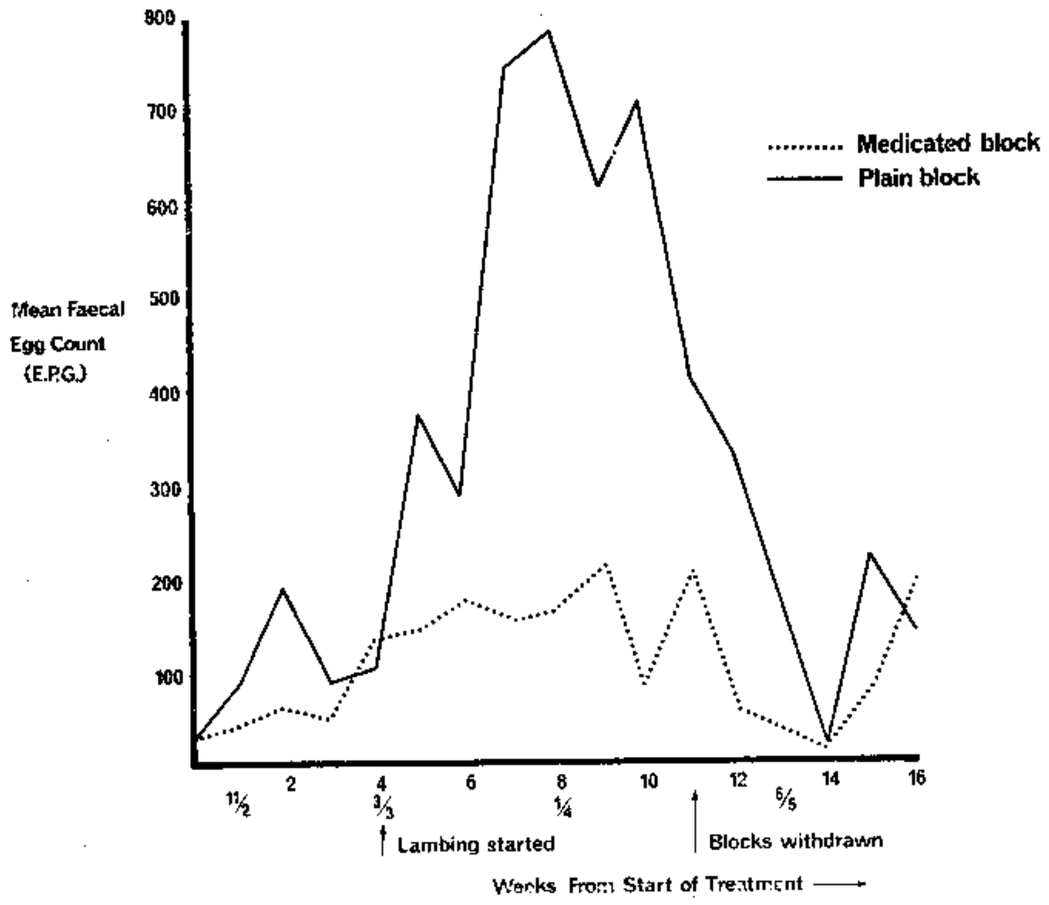

FIG 4: Field trials—Administration via a feedblock carrier to parturient ewes. Mean faecal egg counts

viable egg output and larval viability in the treated group were extremely low throughout while those in the control group were as expected from the faecal egg count.

Administration in-feed to housed cattle

A mean dosage of 20 mg per kg per day for five days resulted in reduction of faecal egg count to low levels by the end of medication and this remained so for three weeks after the completion of treatment (Table 4). Faecal culture showed *C oncophora* to be the predominant parasite in both treated and control groups with lower numbers of *O ostertagi* present.

Discussion

Previous studies (Dalton 1978) defined the anthelmintic effects of low-level administration of thiophanate to ewes or lambs over prolonged periods. The present results indicate that shorter term administration of the anthelmintic at dosages of 3·5 to 10 mg per kg per day (the median therapeutic dosage of thiophanate is 75 mg per kg as a single dose) suppresses faecal egg count (during and after treatment) and egg hatchability and larval viability (during treatment) and has a degree of vermicidal effect. Increasing the daily dosage to 20 mg per kg per day and shortening the medication period results in a very high degree of suppression of faecal egg output and also an almost complete vermicidal effect.

With potential carriers for self-medicaments, such as feedblocks, animals frequently feed more than once a day. From comparison of the effects of 5 mg per kg per day for 20 days and 2·5 mg per kg per twice daily for the same period (or for 10 days) in sheep, it is evident that an increase in the frequency of medication using the same total daily dosage results in an increase in the vermicidal effect of thiophanate against most adult nematodes, as well as reducing faecal egg count more effectively during the early stages of medication. It appears that longer term medication using this twice a day dosage may be necessary for consistent removal of *O circumcincta*.

Evidence of the permanent suppression of faecal egg output is provided by the fact that surviving adult worms were sterilised, particularly where twice a day dosing was used (Dalton, unpublished).

In the application of low level medication in the field, the marked ovicidal/larvicidal activity of thiophanate is a most useful attribute, since this ensures that little pasture contamination occurs during the early stages of medication when worm eggs may still be present in faeces.

The control of the post parturient rise is an obvious application for low level in-feed medication since supplementary feeding is often given at this time, providing a suitable vehicle for the anthelmintic. The principal practical advantage of this form of medication is that it avoids the need to handle the ewes, thus eliminating the attendant risks and providing a substantial saving in time and labour. The field trial result as well as those of experiments previously reported (Dalton 1978) show that low level medication with thiophanate can conveniently and successfully be applied at this time.

TABLE 4: Field trials—Administration in-feed to housed cattle. Faecal egg counts

	Mean and range of faecal egg counts	
Day of trial	Medicated group*	Untreated controls
0	250·0 (50-450)	40·0 (50-100)
4	30·0 (<50-50)	130·0 (<50-250)
11	12·5 (<50-50)	80·0 (<50-300)
25	12·5 (<50-50)	30·0 (<50-100)

*20 mg thiophanate per kg per day on days 0 to 4 inclusive.

Under some conditions, eg, in growing animals, it will be desirable to achieve a high degree of vermicidal effect quickly, or the feeding period which can be economically employed may be relatively short. In these circumstances, shorter term-higher dosage regimes using thiophanate, such as 20 mg per kg per day for five days, show considerable promise experimentally and in the field.

Thiophanate has suitable properties and sufficient adaptability as an anthelmintic, in terms of dosage and period of medication, to be applied using various dose regimes in conditions where drug intake on a "self help" basis can be obtained.

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