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THE IN VITRO AND IN VIVO PERFORMANCE OF AQUEOUS BASED ENTERIC COATS OF NEUTRALISED HYDROXYPROPYL METHYL CELLULOSE PHTHALATE

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ABSTRACT

Prednisolone tablets, enteric coated with neutralised hydroxypropyl methylcellulose phthalate (HPMCP) were compared with Deltacortril tablets (Pfizer) by compendial *in vitro* testing and a pharmacokinetic study in 12 volunteers. Despite satisfactory compliance for both products with the specifications for enteric products of the European Pharmacopoeia and the United States Pharmacopoeia a significant difference in lag time before prednisolone was detected in plasma was observed between the products and only the Deltracortril tablet was concluded to exhibit true enteric properties.

The failure of the neutralised HPMCP coating probably results from incomplete gastric conversion to its acidic form due to the majority of subjects having gastric pH values in excess of those stipulated in the compendial *in vitro* tests. Alternative *in vitro* testing procedures are proposed.

INTRODUCTION

Aqueous based enteric film coatings are increasingly available and offer advantages in terms of cost, environmental impact, non flammability and reduced toxicity (1, 2). These advantages are achieved sometimes at the expense of technical problems relating to poor surface appearance, blockage of the spray gun, slower drying times and some tablet adhesion.

It has been reported (3) that some of these technical problems can be overcome for hydroxypropyl methylcellulose phthalate (HPMCP) by converting the majority of the carboxyl groups to the salt form with an alkali metal or an amine. After coating, full enteric properties are achieved by treatment with acid to convert the carboxyl groups to the acidic form. This work was extended by Stafford (4) who suggested through *in vitro* testing, after strictly controlled spray coating to avoid defects, that the acid treatment phase was unnecessary and that enteric properties could be achieved very rapidly after exposure to gastric fluid *in vivo*.

This approach is potentially very attractive in simplifying the production process but the satisfactory

TABLE 1

FORMULATION OF COATING SOLUTION

Component	% w/v	Source
HPMCP type HP-55	12.5	Shin-Etsu Chemical Co., Tokyo
Sodium hydroxide BP	1.0	Albright & Wilson, Cumbria, UK
Dispersed Red 11652	2.0	DF Anstead Ltd, Billericay, UK
Purified water	to 100	

in vivo conversion of neutralised HPMCP will be dependent upon the acidity of the stomach contents and it has been observed from studies in over 1500 subjects that 35% of gastric pH measurements were 6.0 or above and only 41% less than 3.5 (5).

In view of the reported wide inter and intra subject variations in gastric pH it was felt important to test the enteric properties of neutralised HPMCP *in vivo* by pharmacokinetic testing of tablets using prednisolone as a model drug and allowing comparison with a widely used commercial tablet form of enteric prednisolone.

MATERIALS AND METHODS

Dosage Forms

Deltacortril tablets, 5mg (Pfizer), batch number 4-007D.

Table 2

Operating Conditions for Spray Coating

PARAMETER	CONDITION
Drum rotation speed	12 rpm
Inlet air temperature	60 - 70° C
Outlet air temperature	35 - 40° C
Spray nozzle diameter	1mm
Spray on	30 secs
Spray off	5 secs
Spray rate	50g/min
Total coating time	3 hours
Average coat weight	10 mg

Prednisolone cores, 5mg, compressed from Precortisyl (Roussel) granules batch number 7R-172-1.

Preparation of Coating Solution

An aqueous coating solution of HPMCP was prepared according to the formula in Table 1.

The HPMCP was dispersed in the water by high speed mechanical mixing and the Sodium Hydroxide added as an aqueous solution. After hydration and solution of the HPMCP at 4°C for 16 hours the dye was added before coating.

Coating Procedure

A 10Kg charge was coated in a 24 inch Accela Cota, Manesty Machines Ltd, Liverpool UK, using a Walther

Pilot spray gun, Richard C Walther GmbH, Wuppertal, West Germany.

The operating conditions for the spray coater are given in Table 2.

Tablet Testing

a) In vitro

For this study tablets were tested using the disintegration and gastro-resistance test of both the United States Pharmacopoeia and the European Pharmacopoeia. The dissolution of prednisolone from coated tablets followed the USP XXI procedure which involved monitoring drug release in a pH 6.8 phosphate buffer after 2 hours in 0.1M hydrochloric acid.

b) In vivo

Twelve (7 male and 5 female) healthy volunteers aged between 18 and 42 were studied in a single dose randomised cross over study of the two enteric coated tablets, each dose separated by at least six days. The volunteers who were ± 15% of ideal weight had no course of drug therapy within four weeks prior to the study or medicine of any type within 72 hours of the study or alcohol in the previous 24 hours. All volunteers underwent a full medical examination and blood and urine specimens were collected for routine

haematology, biochemistry and urinalysis tests. The dose was administered half an hour after completing a standard breakfast of cereal, toast, butter and marmalade with one cup of tea or coffee. The tablet was swallowed with 100ml of water and 20ml blood samples collected at 0.5, 1, 1.5, 2, 2.5, 3, 4, 6, 8 and 11 hours. Volunteers were not allowed to lie down for 2 hours after dosage and during this time no food or fluid was taken. The assay of prednisolone in plasma followed the radioimmunoassay method described by Chakraborty and English (6).

RESULTS AND DISCUSSION

The characteristics of the prednisolone tablets after coating with neutralised HPMCP and the Deltacortril tablets are summarised in Table 3.

The data from both batches of tablets are very comparable and comply with the current tests of the European Pharmacopoeia and the United States Pharmacopoeia with regard to enteric properties.

The plasma concentration of prednisolone in each volunteer together with the mean concentrations are provided in Table 4 for the neutralised HPMCP coated tablets and Table 5 for the Deltacortril tablets. The mean plasma levels as a function of time for both tablets are shown in Figure 1. The mean peak plasma levels are of the same order for both products as are

TABLE 3

Characteristics of Tablets Studied

PARAMETER	Neutralised HPMCP coated	Delta-Cortril
Diameter (mm)	6.5	7.5
Prednisolone assay (mg)	4.96	5.17
Disintegration (Ph Eur & USP Test for enteric products)	passes tests	passes tests
Dissolution: after 2 hours in 0.1M HCl	None detected	None detected
% released in pH 6.8 phosphate buffer at 10 mins	45	51
and after 20 mins	97	98

the mean areas under the plasma curves, being 694ng.hr.ml^{-1} for Deltacortril and 656ng.hr.ml^{-1} for the neutralised HPMCP coated tablet when extrapolated to infinity.

However, there is a very clear difference between the two products with regard to the lag time between drug administration and its first detection in the plasma (limit of detection 5ng/ml). The lag time for each volunteer is shown in Figure 2.

The mean time for prednisolone to appear in the blood was 4.2 hours (range 2 to 8 hours) for the Deltacortril product and 1 hour (range 0.5 to 1.5 hours) for the neutralised HPMCP coated product. There

TABLE 4

The Plasma Concentrations of Prednisolone (ng/ml) in 12 Volunteers (1-12) After a Single 5mg Dose of Prednisolone From Neutralised HPMCP Coated Tablets

TIME	VOLUNTEER NUMBER													
(h)	1	2	3	4	5	6	7	8	9	10	11	12	MEAN	SE
0.00	n.m.	n.m.	n.m.	n.m.	n.m.	n.m.	n.m.	n.m.	n.m.	n.m.	n.m.	n.m.	n.m.	
0.50	20	67	n.m.	n.m.	n.m.	n.m.	29	n.m.	41	n.m.	n.m.	n.m.	13	6.4
1.00	11	49	n.m.	13	n.m.	69	113	14	71	n.m.	11	96	37	11.7
1.50	22	61	12	38	21	59	132	27	75	10	33	156	54	13.6
2.00	71	66	36	140	80	45	137	40	83	40	81	162	82	12.4
2.50	63	50	44	110	41	52	150	58	73	48	103	128	77	10.6
3.00	63	55	111	98	72	43	128	67	73	68	96	116	83	7.7
4.00	57	49	76	85	53	42	117	79	55	60	83	94	71	6.3
6.00	44	34	41	66	35	50	98	94	38	69	74	64	59	6.4
8.00	25	19	24	32	27	31	74	66	21	57	48	37	38	5.3
11.00	22	10	n.m.	n.m.	12	20	52	34	12	34	26	22	20	4.3

Results below the limit of determination (5ng/ml) are signified as n.m. (not measurable).

TABLE 5

The Plasma Concentrations of Prednisolone (ng/ml)in 12 Volunteers (1-12) After a Single Dose of Deltacortril tablets (Pfizer) (5mg)

TIME	VOLUNTEER NUMBER													
(h)	1	2	3	4	5	6	7	8	9	10	11	12	MEAN	SE
0.00	n.m.	n.m.	n.m.	n.m.	n.m.	n.m.	n.m.	n.m.	n.m.	n.m.	n.m.	n.m.	n.m.	
0.50	n.m.	n.m.	n.m.	n.m.	n.m.	n.m.	n.m.	n.m.	n.m.	n.m.	n.m.	n.m.	n m.	
1.00	n.m.	n.m.	n.m.	n.m.	n.m.	n.m.	n.m.	n.m.	n.m.	n.m.	n.m.	n.m.	n.m.	
1.50	n.m.	n.m.	n.m.	n.m.	n.m.	n.m.	n.m.	n.m.	n.m.	n.m.	n.m.	n.m.	n.m.	
2.00	n.m.	n.m.	19	n.m.	18	n.m.	n.m.	n.m.	n.m.	n.m.	n.m.	n.m.	n.m.	
2.50	n.m.	n.m.	28	n.m.	63	n.m.	n.m.	n.m.	n.m.	n.m.	34	n.m.	10	5.9
3.00	n.m.	53	35	n.m.	68	n.m.	n.m.	n.m.	n.m.	n.m.	64	126	29	11.9
4.00	45	57	137	n.m.	39	34	n.m.	n.m.	n.m.	n.m.	49	128	41	13.9
6.00	54	52	121	56	37	78	110	n.m.	n.m.	63	68	126	64	11.9
8.00	47	39	61	161	19	57	86	n.m.	76	64	45	84	62	11.6
11.00	26	15	35	75	n.m.	47	60	95	63	51	28	44	45	7.6

Results below the limit of determination (5ng/ml) are signified as n.m. (not measurable).

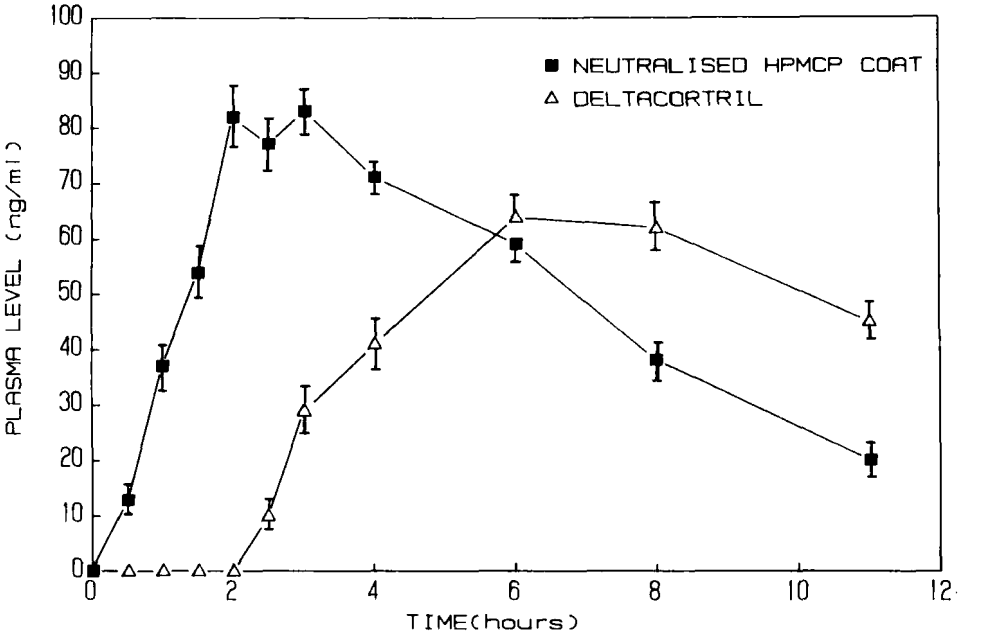

FIGURE 1
MEAN PLASMA PROFILES OF TWO 5mg PREDISOLONE E.C. TABLETS

is no overlap in the ranges and the difference is absolute.

Gastric emptying of non disintegrating tablets is variable, particularly after food (7) and will be affected by product size (8). However, gamma camera studies have shown that after a light meal mean gastric residence times of 3 to 4 hours can be expected (9). These findings would support the conclusion that the Deltacortril plasma profile is consistent with that of an adequately enteric coated tablet.

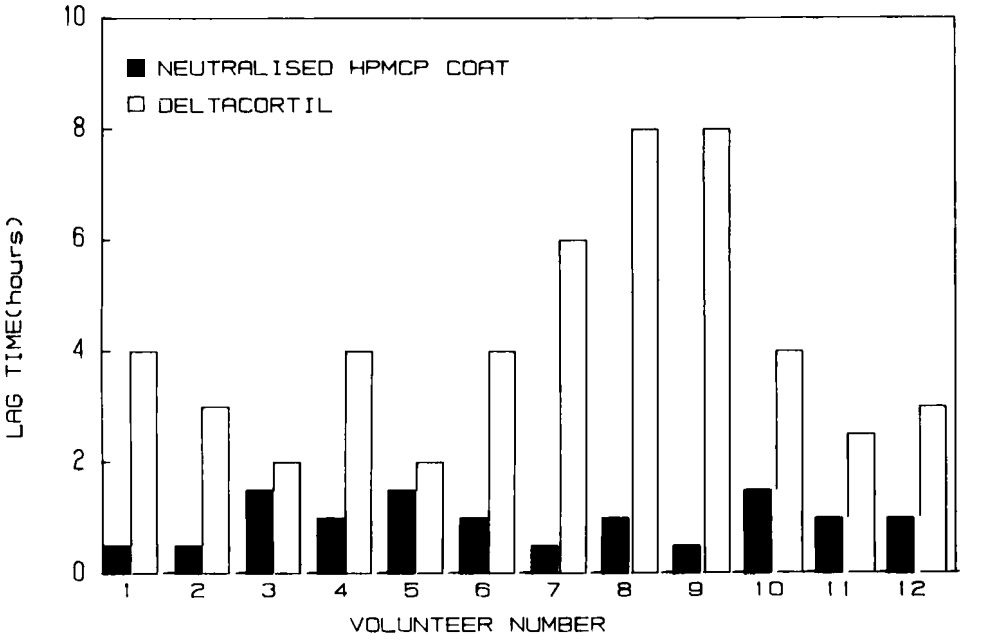

FIGURE 2.
LAG TIMES TO ABSORPTION FOR TWO ENTERIC COATED PREDISOLONE TABLETS

In a properly controlled study it is improbable that the volunteers, whilst under study with the HPMCP coated tablet, would show consistently faster gastric emptying than when under study with Deltacortril, particularly when the tablet diameter is of the same order for each product.

Similarly, although gastric pH can vary widely (5) and a high gastric pH would be expected to accelerate drug release and absorption, a high gastric pH bias in favour of the HPMCP volunteers is also improbable.

Infra-red analysis of the coat on the Deltacortril tablets used in this study indicated that the enteric polymer was cellulose acetate phthalate (CAP).
This finding can be supported by other work on Deltacortril tablets (10). Both CAP and HPMCP have very similar pKa values, in the region of 4.5, however, changes in dissolution rates as a function of pH for different materials of similar pKa have been reported (11). This is due to the negative charges produced after partial dissociation impeding the dissociation of remaining carboxylic acid groups due to an increased attraction for hydrogen ions. The magnitude of these effects depends on the proximity of adjacent phthalate groups. Davis (11) calculated this distance as 8.5A for HPMCP and 7A for CAP and attributed the slower dissolution rate of CAP to this dimensional difference. Although this difference in dissolution rate between CAP and HPCMP may contribute to the observed difference in lag times in vivo it is unlikely to be the major cause. It is more probable that the observed differences in vivo are primarily due to inadequate conversion of the neutralised HPMCP to the acidic form under the prevalent gastric pH conditions.

The sensitivity of adequate conversion of neutralised HPMCP to the acidic form was assessed by examining the disintegration and dissolution characteristics as a function of pH. Deltacortril tablets were examined in a similar manner and comparative disintegration data are presented in Table

TABLE 6

Disintegration Times (mins) of Neutralised HPMCP Coated Tablets and Deltacortril Tablets as a Function of pH.

Product	pH						
	1.2	2.0	2.5	3.0	4.0	5.0	6.0
Neutralised HPMCP Tablets	>120	90–120	60–120	30–60	30	20	15
Deltacortril	>120	>120	>120	>120	>120	>120	60

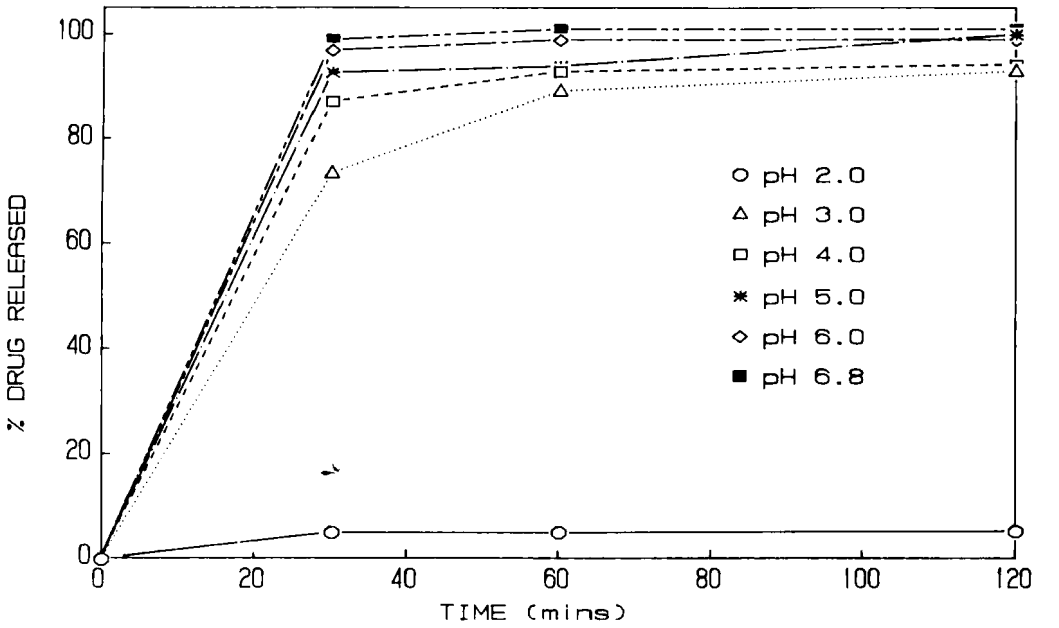

FIGURE 3.

PERCENT OF DRUG RELEASED IN DIFFERENT pH MEDIA FOR NEUTRALISED HPMCP COATED TABLETS

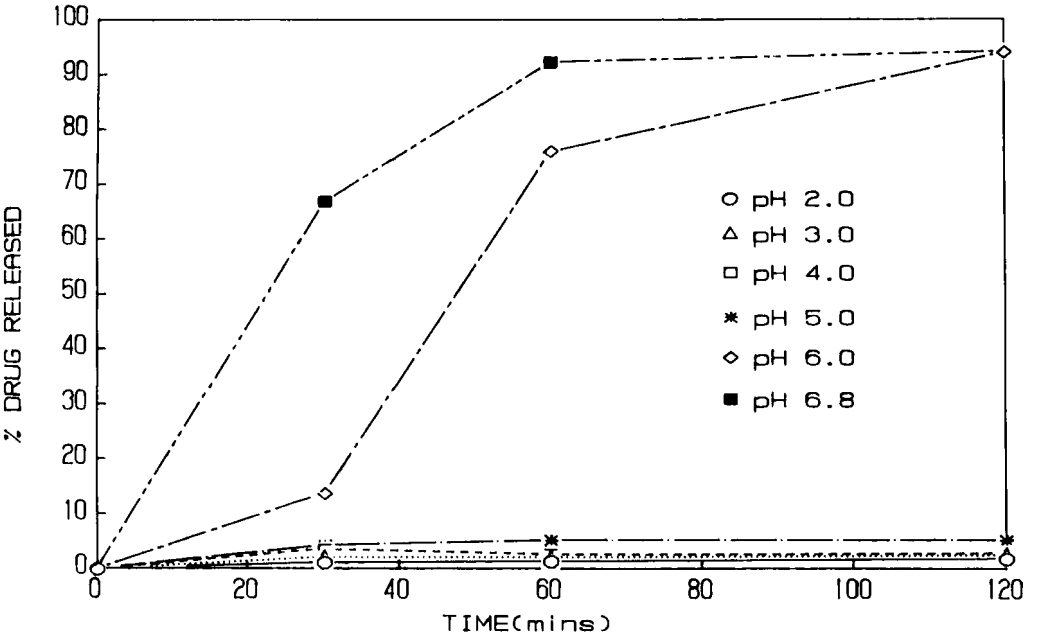

FIGURE 4.
PERCENT OF DRUG RELEASED IN DIFFERENT pH MEDIA FOR DELTACORTIL TABLETS (5mg)

6 and dissolution data in Figures 3 and 4. The neutralised HPMCP coat did not offer 2 hours protection from disintegration above pH 1.2 whilst the Deltacortril tablet showed an adequate performance up to pH5.

The dissolution performance closely reflected the disintegration characteristics and was independent of coating weights between 5 and 25mg for the neutralised HPMCP tablet.

This study supports other work (12) suggesting that the pH of the stomach can influence the rate of drug absorption from enteric formulations and that contemporary compendial testing does not recognise gastric pH variations and its place in bioavailability.

In order to propose more realistic in vitro conditions for disintegration or dissolution testing, it is important to have a good understanding of the inter and intra subject gastric pH profile and a better knowledge of the relationship between in vitro testing and in vivo performance.

The work of Kuna (5) giving an average gastric pH of 4.5 (range 2.0 to 7.2) is complemented by that of Shibuya (13) who reported pH values of the resting stomach from 30 subjects in the range 2 to 5.5. With this wide gastric pH profile it will be difficult to propose a universally acceptable in vitro pH test which will ensure, for the whole population, both gastric protection and subsequent rapid and complete absorption in the small intestine.

However, a gastric pH test at 4.5 would make a significant improvement in the discrimination of the in vitro test for gastric protection. This value is in broad accord with the apparent critical pH for dissolution of enteric tablets proposed by Kaniwa (12) but it must be recognised that disintegration in the stomach could occur in subjects with clear anacidity.

In making the gastric pH test more discriminating it is important to ensure that the product will release drug promptly in the small intestine and a reduction in the time for disintegration at pH 6.8 to 30 minutes is probably also now appropriate. In addition, in view of our improved knowledge of gastric emptying times, the testing period at pH 4.5 might be extended to 3 hours, particularly for larger dosage forms administered with or after food.

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REFERENCES

1. K. S. Murthy, N. A. Enders, M. Mahjour and M. B. Fawzi, Pharm. Technol. 10:36 (1986).

2. F. Gumowski, E. Doelker and R Gurny, Pharm. Technol, 11: 26 (1987)

3. United States Patent 4, 017, 647 (1977).

4. J. W. Stafford, Drug Development and Industrial Pharmacy, 8: 513 (1982).

5. Kuna S, Arch. Int. Pharmacodyn et Ther. 151: 79 (1964)

6. J. Chakraborty and J English, Brit. J. Clin. Pharmacol. 3: 903 (1976).

7. S. S. Davis, J. G. Hardy and J. W. Fara, Gut 27: 886 (1986)

8. N. Kaniwa, N. Aoyagi, H. Ogata, A. Ejima, H. Mokoyama and H. Yasumi, J. Pharmacobio. Dyn. 11:571 (1988).

9. J. G. Hardy, D. F. Evans, I. Zaki, A. G. Clark, H. H. Tonnesen and O. N. Gamst, Int. J. Pharm. 37: 245 (1987).

10. R. G. Henderson, T. Wheatley, J. English, J. Chakraborty and V. Marks, Brit. Med. J. 1: 1534 (1979)

11. M. Davis, I. Tchikawa, E. J. Williams and G. S. Banker, Int. J. Pharm. 28: 157 (1986)

12. N. Kaniwa, H. Ogata, N. Aoyagi, M. Koibuchi, T. Shibazaki and A. Ejima, Chem. Pharm. Bull. 33: 3899 (1985).

13. T. Shibuya, Nikon Shoukakibyougakkai Zasshi 69: 783 (1972).