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THE EFFECT OF MICROENCAPSULATION WITH DIKA WAX ON THE DEGRADATION AND DISSOLUTION OF ASPIRIN TABLETS

O.K. UDEALA AND S.A.S. ALY
Department of Pharmaceutical Technology
and Industrial Pharmacy
Faculty of Pharmaceutical Sciences
University of Nigeria, Nsukka.

ABSTRACT

Dika wax, an edible vegetable wax derived from *Irvingia gabonensis* was used for microencapsulating aspirin powder prior to compression. Both bees and carnauba waxes were respectively used as the basis for comparison. A bulking agent, Avicel PH 101 was added to the microcapsules prior to compressing each batch directly into tablets. A first order degradation pattern was obtained for tablets shelf-stored at 30°C. The degradation pattern of tablets stored under varying conditions of humidity and temperature deviated from the first order mechanism of reaction. The free wax acids were probably the main

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factor in the degradation of the shelf-stored aspirin tablets. The degradation observed under higher relative humidity is thought to be due to a combination of three factors, namely, the wax acids, moisture and temperature. The degradation of the microenacapsulated and tabletted drug conformed to what is known about the degradation of this drug in the solid state. The results indicate that the level of protection from hydrolysis offered by dika wax is higher than the protection offered by the other two waxes. Irrespective of the hydrophobic coat the tablets were rapidly disintegrating.

INTRODUCTION

The physico-chemical variables which affect the stability of aspirin have been the subject of extensive investigations. It was demonstrated by Yamamoto and Takahashi (1) and Lee et al (2) that both temperature and moisture accelerate the degradation of aspirin. The more important of the two factors in the hydrolysis of aspirin is obviously humidity (3). Other than humidity and temperature, a number of pharmaceutical excipients are known to promote the degradation of aspirin. The investigation of Kornblum and Zoglio (4) on the stability of aspirin in the presence of some lubricants demonstrated that certain type of lubricants

were bet er than others in formulations containing aspirin. The role of these and other pharmaceutical excipients in the hydrolysis of aspirin has been explained on the basis of pH within the system (5,6). Within a pH range of 5 and 8, a base catalysed isomerisation was assigned the rate determining step (7). Since moisture is easily the commonest agent that causes the hydrolysis of aspirin, a number of formulation techniques have been proposed as effective means of increasing the stability of this drug. Some of these techniques include coacervation with ethyle cellulose or polymethaacrylate (8,9), re-crystallisation (10) buffering and the addition of stabilising agents (11).

When dika wax was initially investigated as a tablet lubricant, there was some indication that it might not affect the stability of aspirin (12). Since dika wax is hydrophobic, it is reasonable to assume it would also protect a hydrolysable drug from the effects of moisture. In order to determine whether dika wax could offer protection to a hydrolysable drug, it was used in the microencapsulation of aspirin powder which was subsequently compressed into tablets. Bees and carnauba waxes were similarly applied. One of the earliest investigation on the degradation of aspirin in the solid state was carried out by Leeson and Mattocks(13). In that study, aspirin was subjected to varying conditions of humidity and temperature. In the present study, the microencapsulated tabletted drug was subjected

to similar conditions. Therefore the same mathematical model proposed by these workers was applied to the data obtained for the degradation of aspirin. The disintegration and dissolution data were examined for correlation. The effect of varying concentrations of wax used for microencapsulation on disintegration and dissolution was also investigated.

MATERIALS AND METHODS

Avicel PH 101, a brand of direct compression microcrystalline cellulose[1] was used as the direct compression vehicle. Aspirin and talc[2] were used as the active drug and lubricant respectively. Dika wax was obtained as described earlier(12) while bees wax[2] and carnauba wax[3] were used as procured from the manufacturers.

Microencapsulation of aspirin

Wax solutions of varying concentrations were prepared using absolute alcohol. The solutions were such that the concentration of a particular wax varying from 2 to 10 mg/ml could be obtained. The aspirin was dissolved in acetone to yield a 50% w/v solution. The desired concentration of wax in a given batch of microcapsules was obtained by mixing 15ml of the solution of aspirin in acetone and 100ml of wax solution of a known concentration. A stream of cold air which slowly evaporated the alcohol/acetone solvent system was directed to the mixture while being vigorously stirred. The microcapsules were deposited as the solvent system

evaporated. Thus, batches of microcapsules that varied from 0.05 to 0.3% w/w in their wax content were prepared with each wax. The microcapsules deposited after the vaporisation of the solvent system were transferred to a fluidised bed dryer[I] and dried at 40°C. The product was subsequently used for the preparation of tablets.

Compression of tablets

The direct compression vehicle, Avicel PH 101 was dried at 60°C for 24 h. The mix for compression was constituted to contain 200mg aspirin microcapsules, 290 mg. Avicel PH 101 and 10mg of acid-washed talc as lubricant. The mix was compressed into tablets using an F3 single[II] punch tabletting machine fitted with 13mm flat faced punches. Tablets with average weight of 500mg were produced in batches of 200 tablets. A batch of control tablets was also produced using untreated aspirin powder.

Disintegration time

The B.P. disintegration test apparatus[II] containing a 0.1N HCL maintained at 37° + 0.5°C was used for thee test. The average disintegration time for ten tablets from each batch was determined immediately after compression of the tablets.

Dissolution rate

The dissolution rate of the tablets was determined in a U.S.P. dissolution rate apparatus[III]. A 0.1N HCL constituted the dissolution medium. The revolution of the basket was set at 100 rpm. The amount of aspirin dissolved was assayed for at varying time intervals. The

dissolution rate for each batch of tablets was ascertained immediately after the compression of the tablets. The mean of five such determinations was obtained for each batch.

Stability studies

Each batch of the compressed tablets was divided into four samples. Each sample was subjected to defined temperature and humidity conditions over saturated salt solutions contained in desiccators maintained at the appropriate temperature were used for simulating the desired humidity and temperature conditions. Except the tablets shelf-stored at 30°C, the condition under which the other samples were stored were 40% and 80% RH at 40° and 60°C respectively. All tablets were assayed for their aspirin content at five days interval.

Analysis of aspirin

The absorbance of aspirin dissolved in 0.1N HCL was measured at a wavelength of 229 nm using an SP6-450 specrophotometer (Pye Unicam). Ten tablets from a given batch were pulverised immediately after compression, during or at the termination of the stability study. An amount of the powder equivalent to 10mg of aspirin was transferred into a suitable vessel containing some 0.1N HCL. This was filtered into a 100-ml volumetric flask. The residue was thoroughly washed with several portions of the solvent. The filtrate was then made up with 0.1N HCL to a final volume of 100ml. The absorbance of the solution was measured and the concentration of

aspirin calculated from a calibration curve prepared with the pure sample of drug. Five such analyses were carried out for each batch of the tablets. The absorbances of samples withdrawn from the dissolution medium were similarly measured.

Determination of acid values

The B.P. method for determining the acid values of fats and waxes was adopted. The acid values were calculated according to the standard method.

RESULTS AND DISCUSSION

One of the many applications of microencapsulations in pharmaceutics is the protection of most drugs from the deleterious effect of atmospheric oxygen and moisture. The microencapsulating materials are as varied as the techniques. In the present investigation, the microencapsulating materials, bees, carnauba and dika waxes were applied by a differential solvent technique.

A graph of per cent aspirin decomposition against time in days for the shelf-stored tablets is shown in Fig. 1. This depicts first order degradation pattern. The stability data for these tablets are also presented in Table 1. Both Fig. 1 and Table 1 show that the control tablets prepared with unencapsulated aspirin powder acquired the highest reaction rate of 13.29×10^{-4} mg h^{-1} The tablets prepared with aspirin microencapsulated with dika wax had the highest level of stability in that these tablets showed the least reaction rate constant. While

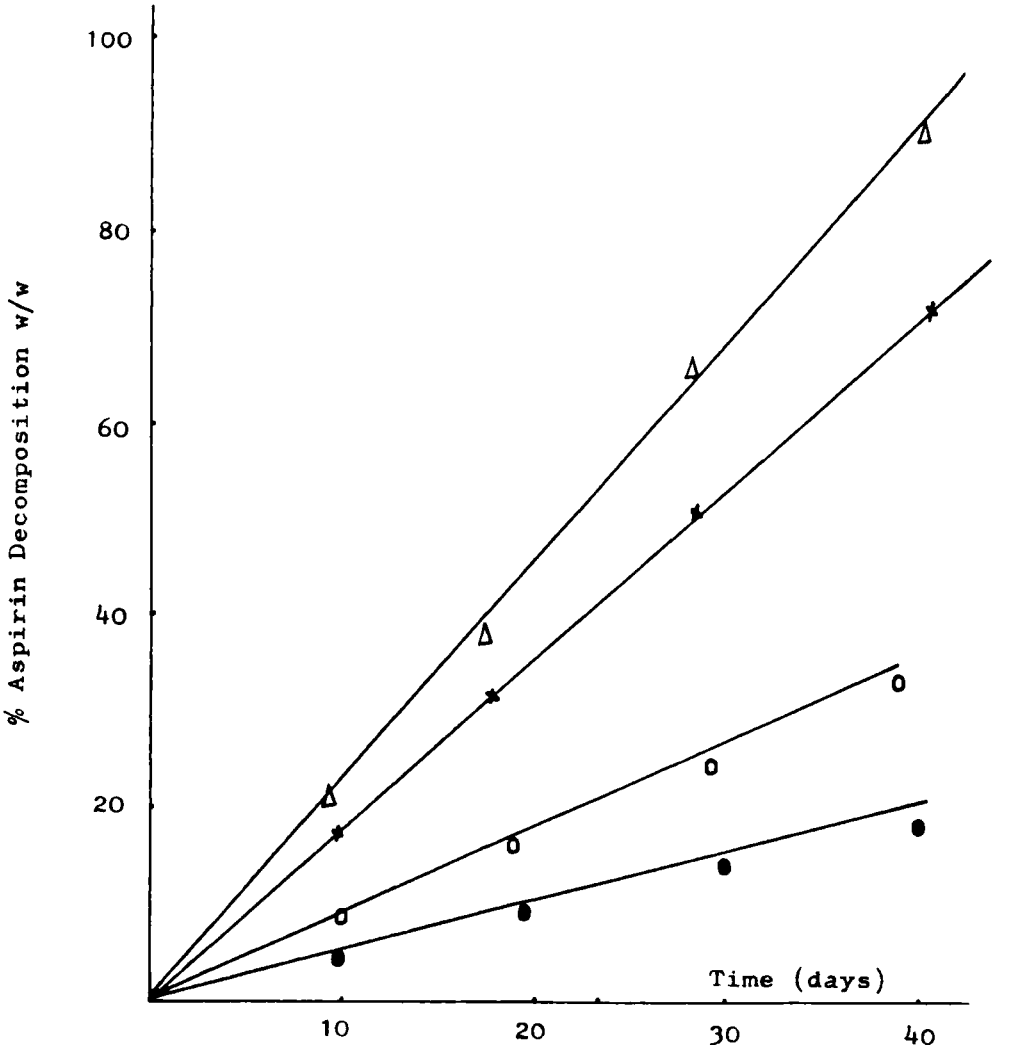

Fig. 1 First order pattern of Aspirin degradation in its tablets compressed from Avicel and Aspirin microencapsulated with 0.3% w/w of ● Dika wax ○ Bees wax, × carnauba wax, △ control.

TABLE 1: Some stability parameters of microencapsulated aspirin in its directly compressed tablets from Avicel PH 101 shelf store (30°C)

Applied Name	Wax Conc.% W/W	No % W/W	Nt % W/W	KX10^{-4} h^{-1}	$t_{\frac{1}{2}}$ days	t10% days
	00.00	119.21	32.25	13.29	21.7	3.3
CW	0.2	104.11	90.16	1.95	148.1	22.64
	0.25	113.20	64.4	5.73	50.41	7.70
	0.3	116.50	41.2	10.57	27.33	4.18
BW	0.2	112.0	80.5	3.36	85.96	13.14
	0.25	104.0	83.81	2.20	131.59	20.11
	0.3	122.0	103.17	1.72	167.93	25.66
DW	0.2	102.12	81.11	2.34	123.43	18.86
	0.25	104.20	87.15	1.82	158.7	24.25
	0.3	100.0	88.12	1.30	227.18	33.9

the reaction rate constant decreased with increase in the concentration of either dika or bees wax, it increased with increase in the concentration of carnauba wax. Since a thicker wax coat will exclude more moisture. The chemical nature of this wax, perhaps its high free acid content, contributed significantly to the degradation of aspirin.

The degradation pattern of aspirin tablets stored under varying humidity and temperature is shown in Fig. **2**(a-c). The graphs deviate from those shown in Fig.1. This is indicative that the over all degradation of aspirin under varying humidity and temperature is different from the degradation under shelf-storage. The factors responsible

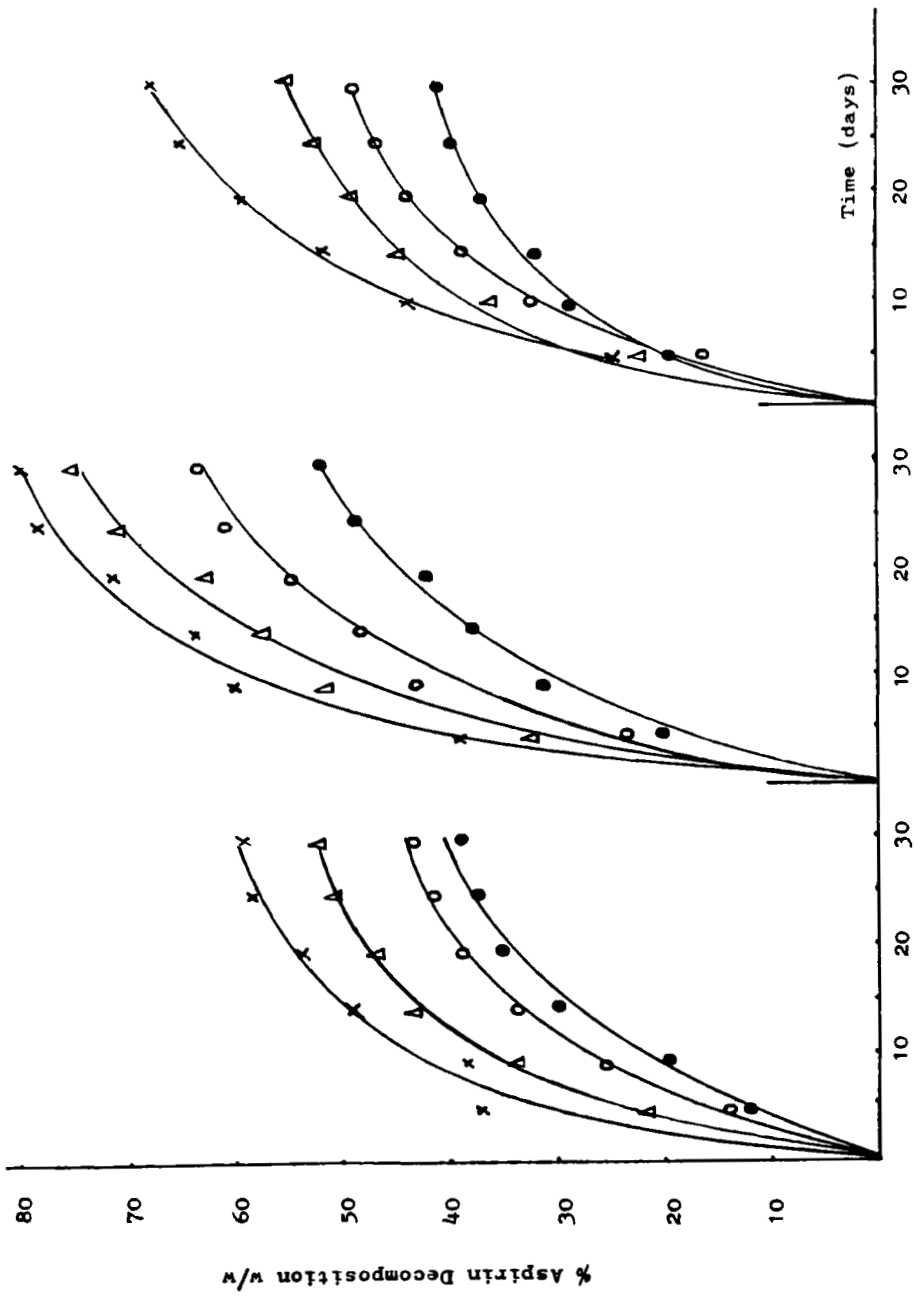

Fig. 2(a-c) Degradation of Aspirin in its tablets directly compressed from Avicel and Aspirin microencapsulated with 0.3% w/w of ● Dika wax ○ Bees wax △ carnauba wax and x control and stored at 'a' 60°C - 40% RH 'b' 60°C - 80% RH and 'c' 40°C - 80% RH.

for the degradation reaction under this condition were the acidity of the waxes, the rate of moisture uptake through the wax coat and temperature. The decomposition of aspirin in the solid state subjected to similar physical conditions was investigated by Leeson and Mattocks(13). These authors calculated the parameters for aspirin degradation by applying the following expression,

$$\log \left(a_o^{\frac{1}{2}} + c^{\frac{1}{2}}\right)/a = \frac{\left(a_o^{\frac{1}{2}} K\right) P \frac{3h}{2} t}{2.3} \qquad \text{Eq. (1)}$$

where a_o represents the initial concentration of aspirin; a, concentration of aspirin remaining after time, t; c, concentration of salicylic acid; k, reaction rate constant and p, the vapour pressure. The parameter, n is the order of the sorption reaction with respect to p as given in Freundlich isotherm equation. A plot of the left hand term of Eq. 1 vs time, t is presented in Figs. 3 & 4 (a-b) The curves of the control tablets prepared with untreated aspirin powder are shown in Fig. 4b. These curves conform to the model of degradation obtained by Leeson and Mattocks for loose aspirin powder subjected to similar conditions(13). The curves shown in Figs. 3 & 4(a-b) are similar but differ in that the curves, except those for the control tablets do not pass through the origin. There is a break with the portion extrapolated to the origin. It was assumed that the degradation in the extrapolated section of the curves followed a course similar to the degradation in the shelf-stored tablets and the control tablets subjected

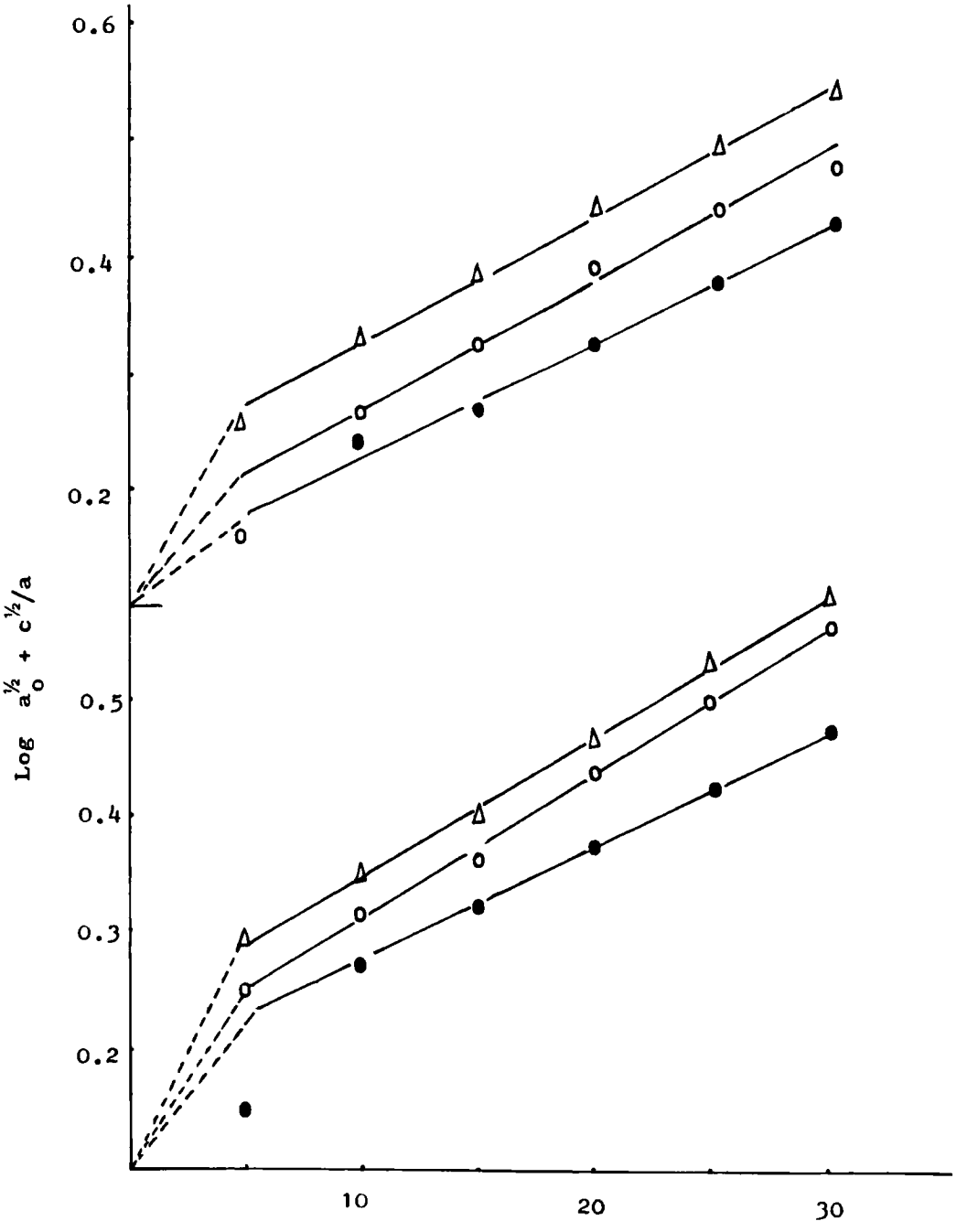

Fig. 3(a-b) Log $a_o^{\frac{1}{2}} + c^{\frac{1}{2}}/a$ as a function of time for Aspirin tablets prepared from microencapsulated Aspirin with 0.3% w/w of ● Dika wax, O Bees wax and Δ carnauba wax.

a for tablets stored at 40°C - 80% RH

b for tablet stored at 60°C - 40% RH.

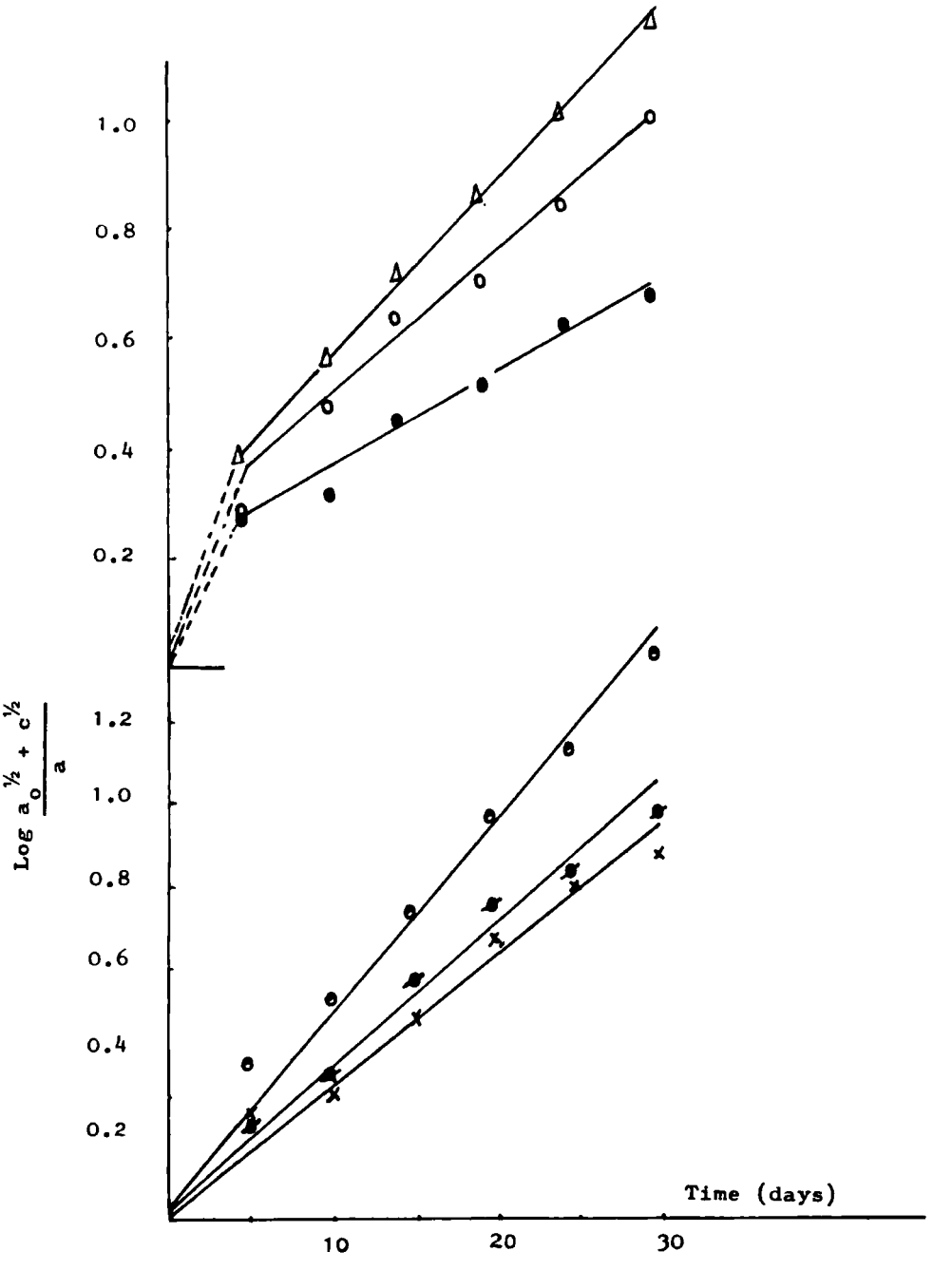

Fig. 4(a-b) Log $\frac{a_o^{\frac{1}{2}} + c^{\frac{1}{2}}}{a}$ as a function of time for Aspirin tablets (a) prepared from microencupsulated Aspirin with 0.3% w/w of ● Dika wax, ○ Bees wax and △ carnbauba wax stored at 6°C - 80% RH (b) for control tablets stored at × 6°C - 40% RH, ●— 40°C - 80% RH and ◓ 60°C - 80% RH

to varying humidity and temperature. Prior to sorption of enough moisture, the acidity of the waxes and the ambient temperature contributed to the degradation reaction. When enough moisture had penetrated through the wax coat, the degradation reaction would change and would be reflected in changes in rate constant and slope, The slope, α , of each of the experimental curves is related to the vapour pressure, p under which the experiment was carried out by the following expression,

$$\log \alpha = 3\frac{n}{2} \log p - \log \frac{(a_o^{\frac{1}{2}} K)}{2.3} \qquad \text{Eq. (2)}$$

A plot of log α vs log p is presented in Fig. 5. The order of sorption n with respect to p may be calculated from the slope of the curves while K the overall reaction rate constant is obtained from the intercept. The values of n and K respectively are presented in Table 2.

According to the theory of chemisorption, the value of n should be unity. This would be understandably so if the conditions relate to loose aspirin powder fully exposed to moisture. The value of 0.2 obtained for n in each case may be accounted for by the limited surface area provided by the tablets. However, the value obtained for n implies that the order of sorption in each batch of the tablets was the same. The values and the order of magnitude for K obtained seem reasonable and logical. The control tablets prepared with untreated aspirin has

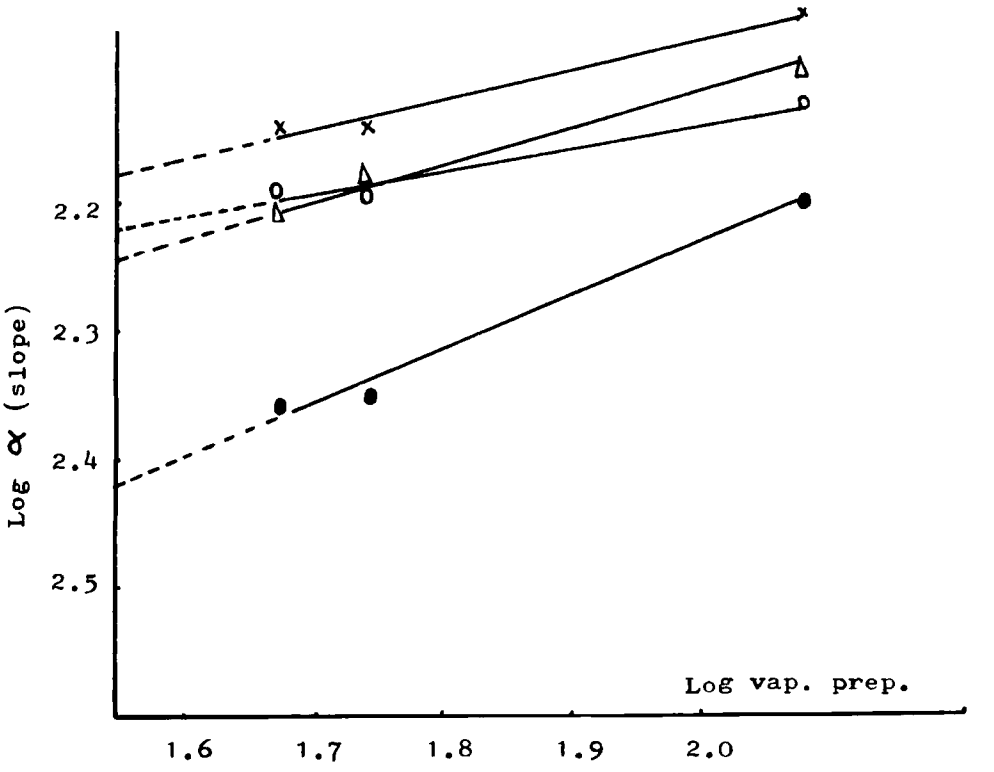

Fig. 5 Log log relationship between α and vapour pressure for various Aspirin batches according to Eq. 2.

Key: ● Dika wax ○ Bees wax, △ carnauba wax × control

TABLE 2: Values of n and K obtained for aspirin microencapsulated with 0.3% w/w wax and compressed into tablets

Material	n	K x 10^{-4} h^{-1}
Control	0.20	0.71
CW	0.17	0.631
BW	0.24	0.50
DW	0.20	0.355

the highest value for K (0.71×10^{-4} mg h^{-1}). Those tablets prepared with aspirin microencapsulated with dika wax showed the lowest value for K. The level of protection offered by each of these waxes would follow logically from their acid values, which are 13.0, 17.9 and 20.1 for dika, bees and carnauba waxes respectively. The amount of potassium hydroxide consumed by each wax during the determination of acid values was equated to the hydrogen ion concentration. This was calculated as the pH of the wax systems. Garette(14) has shown that there is a relationship between log reaction rate constant, K and pH at which the hydrolysis of aspirin takes place. Fig. 6a shows a plot of log K vs pH expected in each system containing 0.3% w/w of wax. This curvesis similar to those obtained by Garette(14). Obviously, the pH contributed by dika wax was 3.05. This pH is known to be favourable for the maximum stability of aspirin(14). This further explains why dika wax, in contrast to bees and carnauba waxes respectively offered the highest level of protection to aspirin.

With limited amount of moisture as in the shelf-storage condition and the condition that generated the extrapolated sections of the curves in Figs.3(a-b), aspirin would degrade mainly as a result of temperature and wax acids. Fig. 6b shows an Arhenius plot constructed with k values derived from shelf-storage at 30°C and the extrapolated region of the curves obtained at 40° and 60°C respectively. In Table 3 are presented

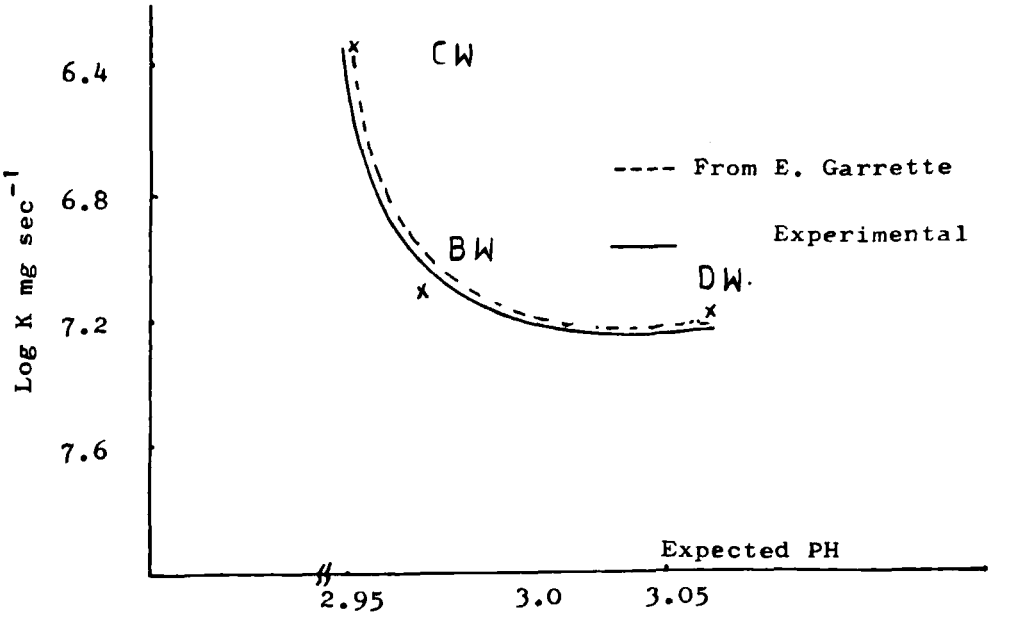

Fig. 6a Log K as a function of PH offered by different waxes.

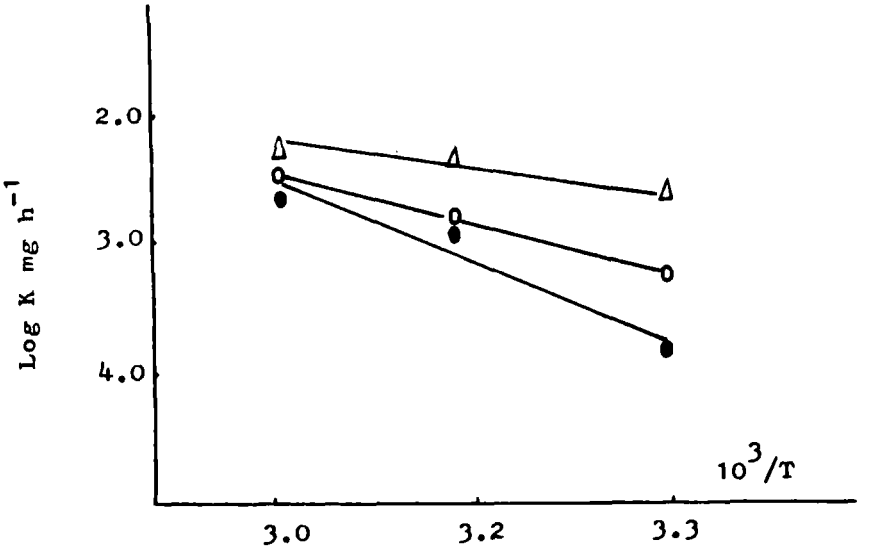

Fig. 6b Arrhenius plot, log k as a function of $10^3/T$. The values of K were calculated from graphs in Fig. 1 and the extrapolated portions of the graphs in Figs. 3(a-b)

Key: See Fig. 5

TABLE 3: The activation energy calculated for Aspirin microcapsules compressed into tablets

Material	E Cal./Mol
Control	-
CW	980.58
BW	2135.5
DW	2640.0

the calculated activation energy E for aspirin degradation.

Those tablets prepared with aspirin microencapsulated with carnauba wax have the lowest activation energy. The value of E for tablets treated with dika wax is the highest. This is consistent with the proposed participation of free wax acids in the degradation reaction and the level of protection offered by each of the waxes. The higher the concentration of wax acid, the less the energy required for the degradation reaction.

The microencapsulation of aspirin powder with waxy materials would be expected to delay both disintegration and dissolution of the compressed tablets. The effect of varying concentrations of the microencapsulating wax on the disintegration time and dissolution rate of the tablets is shown in Table 4.

The disintegration of the coated tablet bears a log - normal relationship with the concentration of the applied

TABLE 4: The mean disintegration times and (t50) of tablets formulated with aspirin microcapsule containing varying concentrations of waxes.

Conc.% of Wax w/w	CW		BW		DW	
	Dt	t50	Dt	t50	Dt	t50
	(Min)					
0.05	15.8	24.7	15.6	30.2	13.3	22.5
0.10	18.1	32.5	17.1	31.9	13.5	27.2
0.15	18.4	35.4	18.0	36.2	14.2	29.1
0.20	19.2	35.9	19.2	37.0	14.5	30.5
0.25	20.4	38.9	20.4	45.8	15.6	33.6
0.30	22.8	48.6	22.8	4.87	16.9	38.2

*The presented value is the mean of five determinations.

coat. A plot of log D_t vs wax concentration is presented in Fig. 7a. The effect of applying varying concentration of wax on the disintegration constant **D of the tablets** be evaluated using the expression

$$\log D = A - NC \qquad \text{Eq. (3)}$$

where A is the disintegration constant of tablets prepared with unencapsulated aspirin powder; N is the slope and C is the concentration of wax. The disintegration constant, **D** increases with increase in the concentration of the applied wax.

Brossard et al (15) fitted the dissolution and disintegrations constants for coated tablets in the following expression.

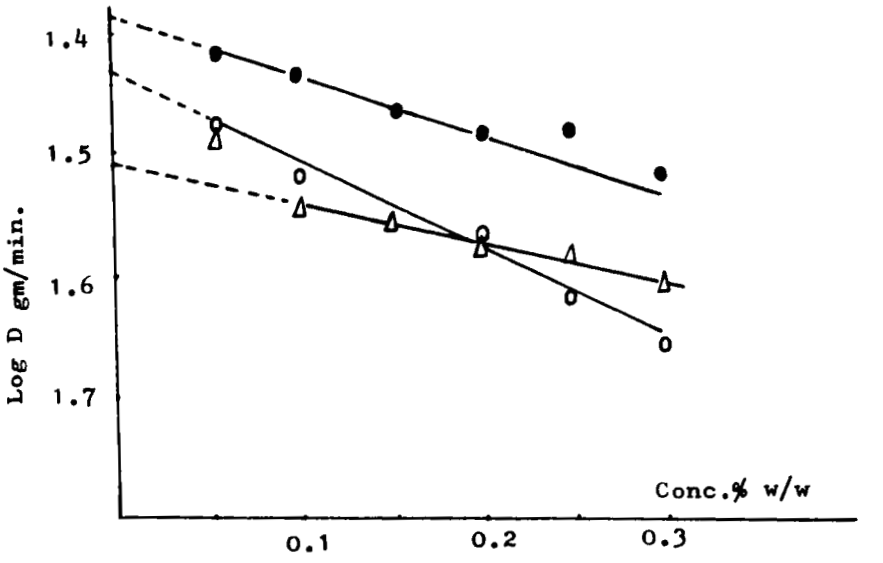

Fig. 7a Log D of Aspirin tablets prepared from microencapsulated Aspirin powder and Avicel as a function of wax concentration.

Key: ● Dika wax, ○ Bees wax and △ Carnauba wax.

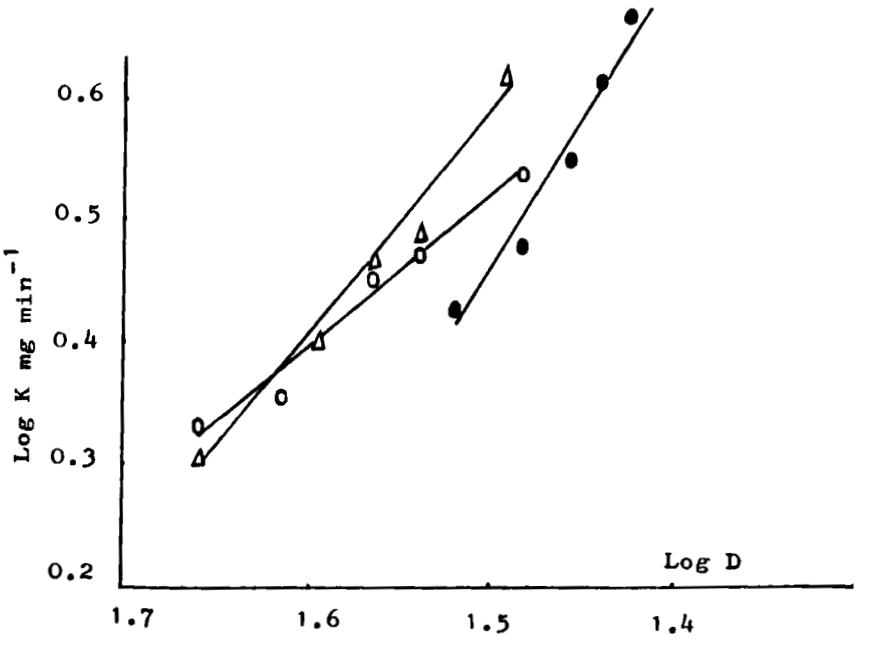

Fig. 7b log k (mg min^{-1}) of Aspirin tablets compressed from microencapsulated Aspirin and Avicel as a function of disintegration constant (D).

Key: ● Dika wax, ○ Bees wax and △ Carnauba

$$\text{Log } K = a + n \log D \qquad \text{Eq. (4)}$$

where K is the dissolution rate constant; D, the disintegration constant; a and n are constants. A graph of log K vs log D is shown in Fig 7b. The linearity of the curves indicates that the relationship holds for the wax-treated aspirin powder compressed into tablets. This also indicates that the tablets are rapidly disintegration its presence obviously countered the water-proofing effect of the waxes. A statistical analysis of the data obtained from the disintegration and dissolution studies showed that the correlation coefficient "r" were 0.91, 0.89 and 0.88 for dika, bees and carnauba waxes respectively.

In order to determine the effect of the wax coat on dissolution, the disintegration constants for both wax treated (Eq. 4) and untreated tablets (Eq. 3) must be known. If the value of log D in Eq. 3 is inserted into Eq. 4, the latter becomes.

$$\log K = a + n \quad (A - NC) \qquad \text{Eq. (5)}$$

with (a + nA) written as A' and nN as N', Eq. 5 becomes

$$\log K = A' - N'C \qquad \text{Eq. (6)}$$

This is an exponential equation of the form

$$K = A' \exp (- N'C) \qquad \text{Eq. (7)}$$

with this equation only the dissolution rate constant, K need be determined. A linear curve as shown in Fig. 8 is obtained if the disintegration and dissolution are related. The calculated and experimental values of N'

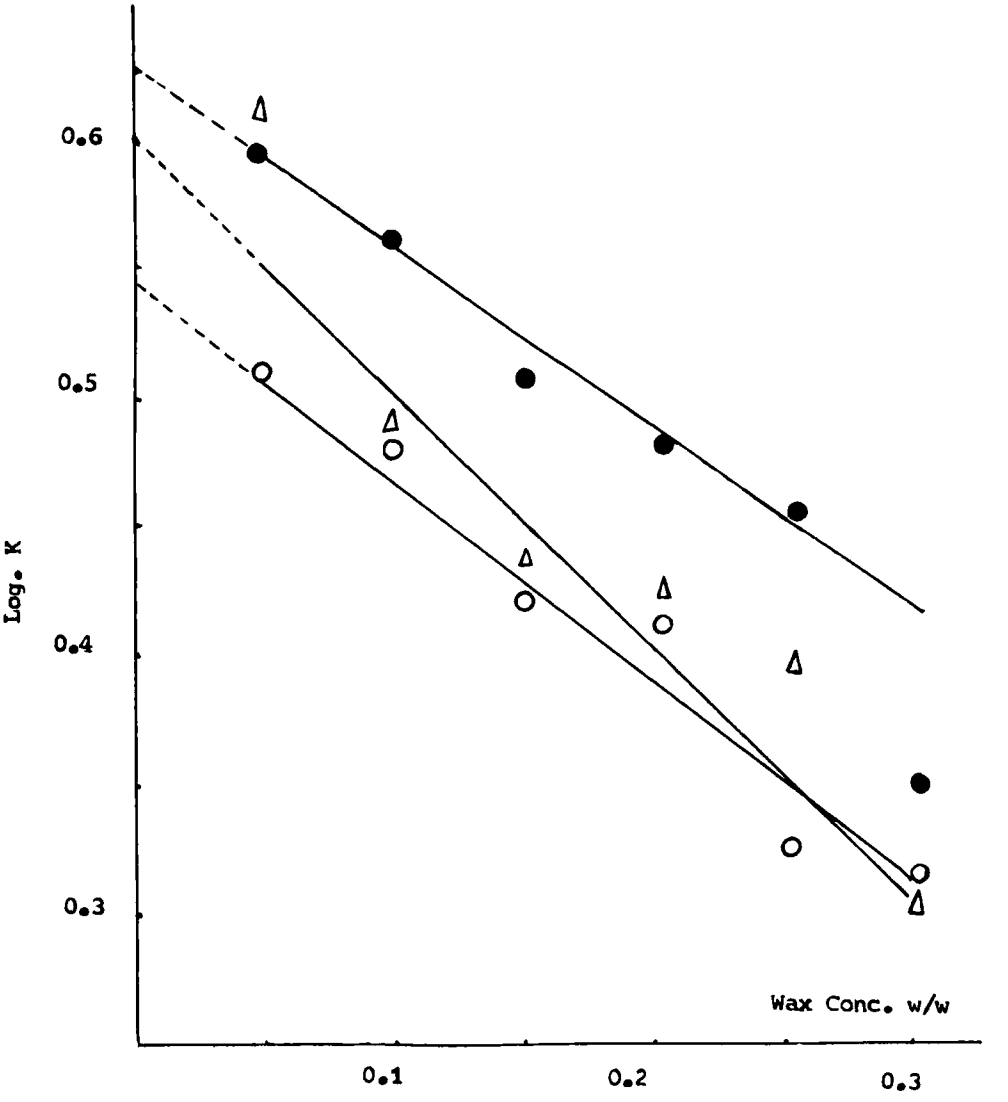

Fig. 8: Log K of Aspirin Microcapsules from its tablets as a function of wax concentration

Key: See Fig. 7

TABLE 5: The estimated and experimental values of N'.

Wax	N'	
Used	Estimated	Found
Dika	- 0.722	- 0.75
Bees	- 0.887	- 1.05
Carnauba	- 0.710	- 0.85

are presented in Table 5. The closeness of the values confirm the validity of Eq. 7.

CONCLUSION

In order to acnieve some measure of stability in tabletted aspirin, the drug was, prior to tabletting, microencapsulated with varying concentrations of dika wax. The performance of this wax was compared with that of bees and carnauba waxes respectively. Other than moisture and temperature which normally influence the hydrolysis of aspirin, the free wax acids were thought to be largely responsible for the first order degradation of the shelf-stored aspirin tablets. Under accelerated stability testing, the over-all reaction was no longer first-order. However the degradation reaction conformed to the mathematical model given by Leeson and Mattock(13). The break in the curves obtained for the accelerated stability tests is attributable to the initial limited ingress of moisture into the tablet core and microcapsules.

The results show that the mathematical expression applied to loose aspirin powder may be applied, with modification to tabletted dosage form. As much the expression would be given as

$$\log \; a_o^{\frac{1}{2}} + c^{\frac{1}{2}}/a \; - \; \frac{Ktf}{2.303} \; = \; a_o^{\frac{1}{2}} K \frac{K}{2.303} P \frac{3n}{2} \; (t-tf)$$

where K is the first order reaction rate constant and tf represents the time required for moisture. penetration through the tablet core and the micro-capsules. Microencapsulation with low concentrations of dika wax while serving as a water-proofing coat, does not prolong the disintegration of the tablets.

FOOTNOTES

1. FMC Corp. Pensylvania USA
2. Merck Damstadt
3. Halowood Chemicals, England.

I PRL Engineering Ltd. Model FBD

II Manesty Machines Ltd.

III Erweka Apparatabeau, West Germany Model DT-D.

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