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Pharmacokinetics and dissolution of two crystalline forms of carbamazepine

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Summary

The dissolution, crystal growth in aqueous milieu and pharmacokinetics of carbamazepine, as the dihydrate and anhydrate, have been studied. The only difference in pharmacokinetics between the two forms was a somewhat higher absorption rate for the dihydrate. The slower absorption of the thermodynamically more active anhydrous form was attributed to rapid transformation, in aqueous milieu, of this form to the dihydrate, resulting in a fast growth in particle size.

Introduction

Differences in physical forms have, for a relatively long time, been considered as important factors when the influence of the physicochemical properties of pharmaceuticals on absorption from the gastrointestinal tract have been discussed. Crystalline modifications of solid drug substances can, according to Haleblian (1975), be either polymorphs or molecular adducts. Stoichiometric forms of adducts are solvates. They are not molecular compounds but are defined as molecular complexes which incorporate solvent molecules in their crystal lattice.

Hydrates are the most common solvates encountered in pharmacy. The dissolution behaviour of hydrated and anhydrous forms are dissimilar, the latter usually having greater aqueous solubilities and faster dissolution rates. The absorption of drugs often correlates positively with these parameters; for example, the studies with ampicillin (Poole et al., 1968a and b; Ali and Farouk, 1981) suggest that the anhydrous form of ampicillin would be better absorbed than the trihydrate which was attributed to the greater water solubility and faster dissolution rate of the

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anhydrous form. Some other studies on ampicillin, however, have not confirmed these observations and other factors affecting the bioavailability of this antibiotic have been claimed to be more important (Bauer et al., 1974; Hill et al., 1975).

Carbamazepine, used since in the early 1960's as an antiepileptic drug, exists as an anhydrous form and as the dihydrate. Furthermore, polymorphic forms have been reported (Pohlman et al., 1975). The transition between the two first-mentioned forms is highly dependent on the temperature and the relative humidity. So, the manufacturing conditions for carbamazepine tablets and their storage must be carefully considered and controlled (Stahl, 1980).

Carbamazepine is available as a 2% aqueous suspension or as tablets. When the bioavailabilities of these dosage forms have been compared, the absorption from suspension has been found to be faster than that from tablets (Meinardi et al., 1975; Morselli et al., 1975; Wada et al., 1978). The most obvious reason for the faster absorption from suspension is the small particle size of carbamazepine in this dosage form as compared with that in tablets. However, the difference in absorption might also be partly attributed to the different crystal modifications. In tablets the anhydrous form is used while in aqueous suspension carbamazepine exists as the dihydrate.

The importance of crystalline modifications to the bioavailability of drugs is undisputed. Therefore, although the possible differences in the pharmacokinetic behaviour of the anhydrous and dihydrate forms of carbamazepine most probably have no practical consequences, a comparison of their absorption and dissolution may give useful information about the influence of crystal modifications on the bioavailability of drugs.

Materials and methods

Absorption studies

Eight adult ambulatory volunteers, 3 females and 5 males, with medical histories devoid of evidence of any gastrointestinal or hematological problems, weighing between 64 and 85 kg, participated in the study. No drugs, other than the required doses of carbamazepine, were permitted for one week before and during the study, which was carried out following a cross-over design with one week's wash-out period between the experiments.

For the study the subjects fasted overnight at least 10 h before the test and were not permitted to eat until 4 h after the dosing.

The volunteers received a single 847 μmol dose of carbamazepine at 08.00 h as hard gelatin capsules with 100 ml of tap water. Drug levels in serum were followed by taking blood samples before administration and at 1, 2, 3, 4, 5, 6, 8, 12, 24, 32, 48, 72 and 96 h after dosing. Serum was separated by centrifugation and stored frozen (-20°C) until analyzed.

Serum carbamazepine concentrations were determined fluorometrically by the method of Meilink (1974) modified by us (Anttila et al., 1979). Accordingly, carbamazepine metabolites do not interfere significantly with the determination of

unchanged carbamazepine in the single-dose studies. The lower limit of detection is 0.2 $\mu mol \cdot l^{-1}$ and the reproducibility is better than 4% (relative standard deviation) in the concentration range of 1–25 $\mu mol \cdot l^{-1}$.

In the pharmacokinetic calculations a one-compartment open model with first-order kinetics was utilized. The serum level data obtained fitted the model tolerably well. The fitting was not acceptable for the curve of one subject (AL) when receiving anhydrous carbamazepine.

The elimination rate constants (k_e) were determined by the use of log-linear regression analysis of data in the post-absorption phase and the absorption rate constants (k_a) were determined by the method of residuals. The apparent volume of distribution (V_d) was calculated by dividing the dose by C_0 or the serum concentration extrapolated to zero time. The body clearance (Cl_{tot}) was calculated by multiplying the apparent volume of distribution by the elimination rate constant.

The maximum serum levels ($C_{max\text{-}obs}$) and time of peak concentrations ($t_{max\text{-}obs}$) were read from the concentration–time curves. Theoretical values of these parameters based on absorption and elimination rates ($C_{max\text{-}calc}$ and $t_{max\text{-}calc}$) were calculated utilizing the formula given by Gibaldi and Perrier (1975). The area-under-the-curve ($AUC_{0\text{-}\infty}$) was determined by the trapezoidal approximation with extrapolation to infinity.

Statistical significance of differences was assessed by Student's *t*-test for paired data.

In vitro studies

To study the crystal growth of the two carbamazepine forms 2% suspensions of both forms were prepared by dispersing them in 0.1 M hydrochloric acid and in 0.1 M hydrochloric acid with 0.05% polysorbate 80. The mean particle length of carbamazepine was 3 μm.

At various time intervals the suspensions were shaken thoroughly and samples transferred to a microscope slide. The length, which was defined as the particle size, of 100 particles was measured utilizing a light microscope. The procedure was repeated 5 times at the same time interval.

The dissolution behaviour of anhydrous and dihydrate forms at 37°C was followed utilizing a flow-through cell dissolution apparatus (Disotest, Sotax AG, Basle) with a flow rate of 16 ml/min. 0.01 M dihydrochloric acid either with 0.01% of polysorbate 80 as wetting agent or without any surfactant served as dissolution media. Before beginning the test, the carbamazepine samples were gently mixed with equal amounts of lactose.

At periodic intervals samples were withdrawn, diluted appropriately and absorbances measured at 285 nm in a UV-spectrometer. The carbamazepine concentration in solution was determined from the standard Beer's law plot prepared previously and the amount dissolved calculated. Each dissolution profile is the average of 3 individual determinations. The ranges are indicated in the graphs.

For statistical comparison Student's *t*-test was utilized.

Results

Fig. 1 shows the serum levels of carbamazepine attained in two subjects (KL and MJ) which had the lowest and the highest $C_{max\text{-}obs}$ values. The kinetic parameters determined from serum concentrations versus time curves are presented in Table 1.

The pharmacokinetic parameters obtained in the study are in accordance with those given in the literature (Morselli and Frigerio, 1975; Hvidberg and Dam, 1976; Bertilson, 1978; Pynnönen, 1979). In most subjects at least two maxima occurred in the concentration–time curves, the second one existing in connection with eating. This rather common phenomenon when following carbamazepine serum levels by single-dose studies has been suggested to be due to the solubilization of the drug by bile secreted following a meal or extensive enterohepatic cycling (Levy et al., 1975). It explains the discrepancy between observed and calculated t_{max} values. E.g., as can be seen from Fig. 1 and Table 1 the highest level in the concentration–time curve ($t_{max\text{-}obs}$) of KL when taking carbamazepine dihydrate is reached at 12 h after dosing. Another, lower maximum can be observed at 4 h after dosing. This maximum as well as the calculated and observed peak value measured for MJ correlate quite well with the calculated value so it is obvious that the $t_{max\text{-}obs}$ values in this study are not very usable when assessing the absorption rates of the crystal forms studied. The $t_{max\text{-}obs}$ have also been defined at the first time the maximum concentration appears for any subject. However, the use of a 'true' peak concentration as $t_{max\text{-}obs}$ demonstrates that this value does not necessarily reflect the (initial) absorption rate.

When comparing the different forms studied it is obvious that the pharmacokinet-

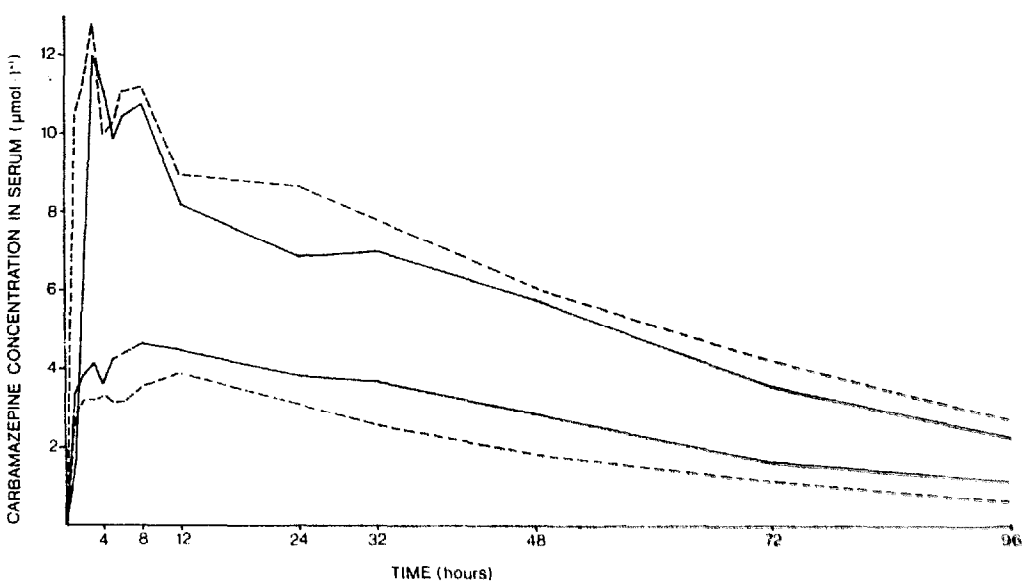

Fig. 1. Plots of carbamazepine concentrations in serum versus time in two subjects (KL lower curves and MJ higher curves) following a single oral 847 mmol dose of different crystal forms. Solid lines = anhydrous form; dotted lines = dihydrate.

TABLE I

CALCULATED AND OBSERVED PHARMACOKINETIC PARAMETERS OF ANHYDROUS AND DIHYDRATE FORMS OF CARBAMAZEPINE IN HEALTHY VOLUNTEERS TAKING SINGLE ORAL DOSES OF THE DRUG ON AN EMPTY STOMACH

Subject	Form *	k_a (h^{-1})	k_e (h^{-1})	Cl_{tot} ($ml \cdot h^{-1} \cdot kg^{-1}$)	V_d ($l \cdot kg^{-1}$)	$C_{max\text{-}calc}$ ($\mu mol \cdot l^{-1}$)	$C_{max\text{-}obs}$ ($\mu mol \cdot l^{-1}$)	$t_{max\text{-}calc}$ (h)	$t_{max\text{-}obs}$ (h)	$AUC_{0\text{-}\infty}$ ($\mu mol \cdot h \cdot l^{-1}$)
WP	A	1.240	0.014	18.1	1.29	7.34	7.96	3.66	2	394.56
	D	1.925	0.011	13.1	1.21	7.99	8.25	2.70	5	489.75
HM	A	0.731	0.017	31.8	1.87	6.37	6.69	5.27	6	334.74
	D	1.287	0.021	40.0	1.90	6.41	6.31	3.25	8	292.54
AR	A	0.341	0.011	16.7	1.51	7.70	7.19	10.41	8	496.91
	D	1.611	0.013	22.8	1.75	7.16	7.62	3.02	2	422.80
KL	A	0.960	0.014	32.5	2.32	4.51	4.61	4.47	8	267.41
	D	1.053	0.014	39.9	2.85	3.69	3.89	4.16	12	191.46
MA	A	1.430	0.026	32.4	1.24	8.57	9.23	2.86	1	324.91
	D	2.591	0.026	32.4	1.25	8.74	10.16	1.79	2	388.43
AL	A	- **	- **	- **	- **	- **	3.13	- **	12	150.11
	D	- **	- **	- **	- **	- **	6.31	- **	8	396.65
OE	A	1.545	0.023	30.8	1.34	8.47	8.72	2.77	3	351.66
	D	1.291	0.020	22.0	1.10	10.30	11.85	3.28	3	484.38
MJ	A	0.538	0.016	19.7	1.23	9.66	12.02	6.74	3	533.39
	D	2.405	0.014	16.1	1.15	11.17	12.78	2.15	3	611.02
Mean	A	0.969	0.017	26.0	1.54	7.52	7.44	5.17	5.4	356.71
		(0.451)	(0.005)	(7.4)	(0.41)	(1.68)	(2.76)	(2.70)	(3.8)	(122.17)
(±S.D.)	D	1.738	0.017	26.6	1.60	7.92	8.40	2.91	5.4	410.38
		(0.591)	(0.005)	(10.9)	(0.63)	(2.51)	(3.02)	(0.79)	(3.6)	(126.54)

* A = anhydrous form; D = dihydrate.

** Not calculated because of unsuccessful curve fitting.

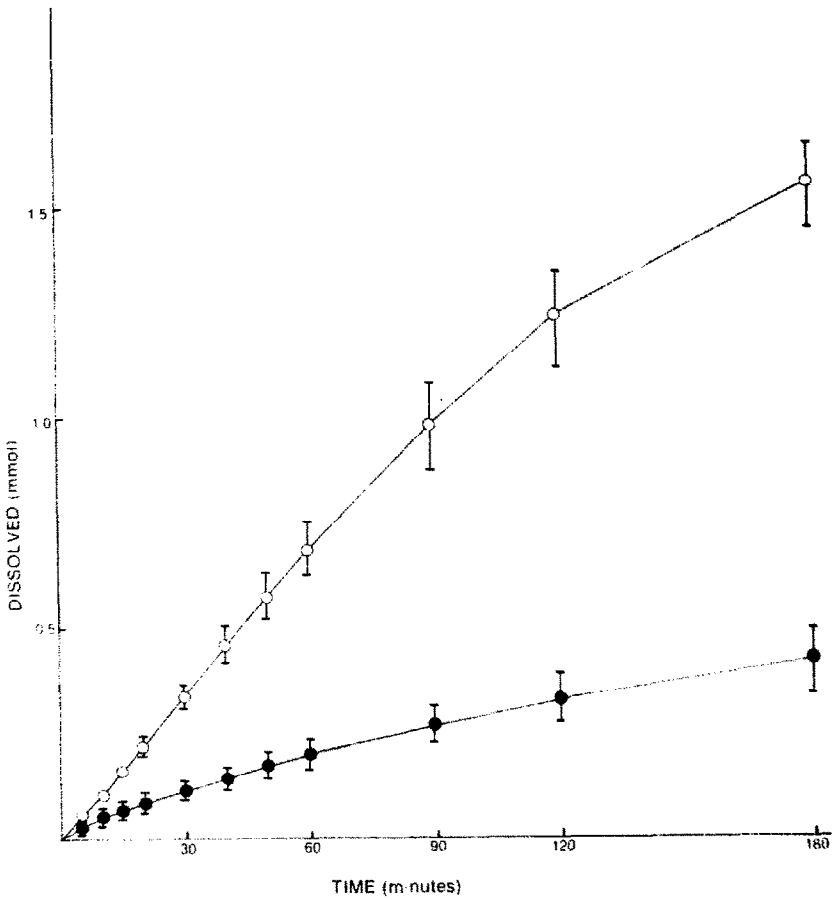

Fig. 2. Dissolution behaviour of carbamazepine anhydrate (———) and dihydrate (- - - - -) in 0.1 M hydrochloric acid.

ics of the anhydrous and dihydrate forms of carbamazepine were almost identical. The differences in serum levels, C_{max}, t_{max}, $AUC_{0-\infty}$, k_e, V_d and Cl_{tot} were not significant. Only the absorption of the dihydrate was faster than that of anhydrous form, the difference in absorption rate constants being significant at the 5% level when evaluated statistically.

The dissolution rate data found, when using 0.01 M hydrochloric acid as the medium, support the observation of slower absorption of anhydrous carbamazepine. The dihydrate clearly dissolved faster than the anhydrate (Fig. 2). However, when a wetting agent was added to the medium, the dissolution patterns change. In this situation the initial dissolution rate of the anhydrous form was faster than that of the dihydrate and only from about 1 h onwards was the case reversed (Fig. 3). Due to the relatively low surface tension of stomach fluid it might be supported that a dissolution medium containing surface-active agents would give better in vitro–in vivo correlation than a water-based medium without any surfactant. Present dissolution results with carbamazepine do, however, not allow any conclusions in this respect.

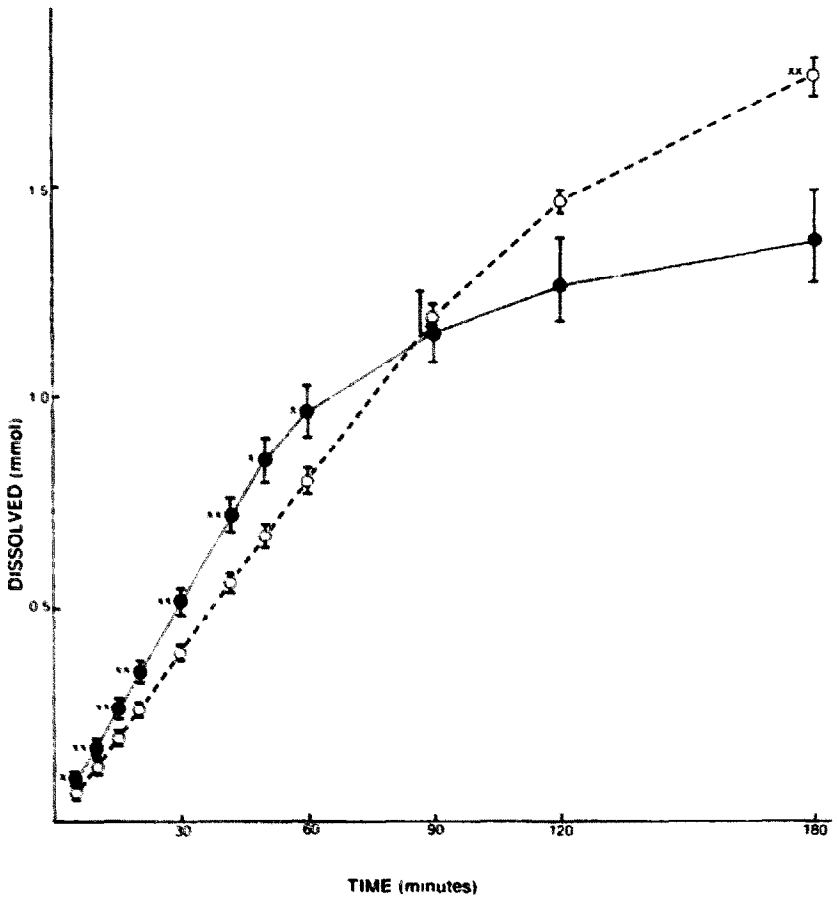

Fig. 3. Dissolution behaviour of carbamazepine anhydrate (———) and dihydrate (- - - - - -) in 0.1 M hydrochloric acid with 0.01% polysorbate 80. Significance of the differences * $P < 0.05$; ** $P < 0.001$.

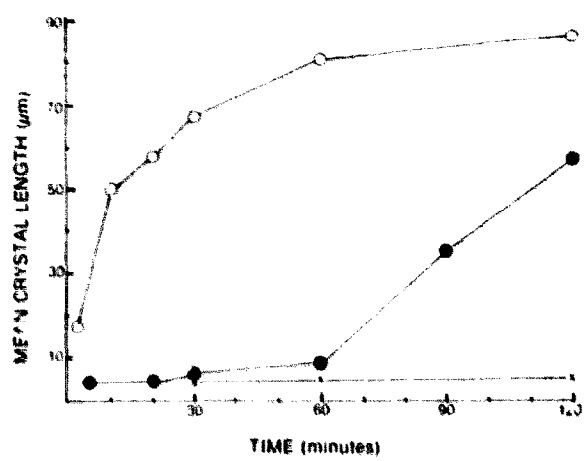

Fig. 4. Crystal length of different forms of carbamazepine versus time. O———O, carbamazepine anhydrate in 0.1 M HCl; ●———●, anhydrous carbamazepine in 0.1 M HCl with 0.05% of polysorbate; ×——— ×, dihydrate in 0.1 M HCL or in 0.1 M HCl polysorbate 80 (the curves were identical in these two media).

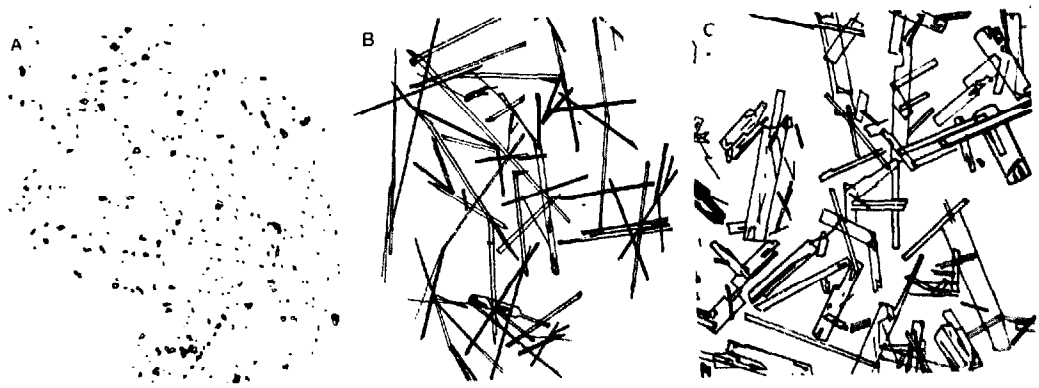

Fig. 5. Crystals of carbamazepine drawn from photomicrographs. A: crystal of anhydrous carbamazepine before crystal growth tests (enlargement 10×40). B: carbamazepine crystals after 2 h in 0.1 M hydrochloric acid (enlargement 10×10). C: carbamazepine crystals after 2 h in 0.01 M hydrochloric acid with 0.05% of polysorbate 80 (enlargement 10×10).

The results of the crystal growth studies show that the size of anhydrous carbamazepine particles increased in aqueous milieu but that of the dihydrate did not (Fig. 4). From the results it is also evident that polysorbate 80 delayed the onset of the growth of particle size for a while whereas in 0.1 M hydrochloric acid without surfactant the increase in particle size started immediately the crystals came into contact with the medium. The presence of the surface-active agent also influenced the shape of the crystals (Fig. 5).

Discussion

Thermodynamically, anhydrous forms of drugs are more active than hydrates. Consequently, as shown by Shefter and Higuchi (1963), the anhydrous forms dissolve more rapidly than the hydrated forms. Thus, the absorption of poorly water-soluble drugs should be faster when anhydrous forms instead of hydrates are administered. The absorption of carbamazepine and its dissolution in 0.01 M hydrochloric acid seem not to be in accordance with these statements.

The contrast is, however, only apparent. The wettability of the solid phase and particle–particle interactions are important factors affecting dissolution rate. This has been shown earlier, e.g. by Allen et al. (1978) who found that in phosphate buffer (pH 7.5) at 37°C erythromycin dihydrate dissolves faster than the less hydrated or anhydrous forms. In the present study when polysorbate 80, which ensures a proper wetting of carbamazepine particles, was used in the medium, the initial rate of dissolution of the anhydrous form was faster than that of the dihydrate. The initial rates, calculated by the method of least-squares as slopes of the straight parts of the lines depicted in Fig. 3 are 0.017 and 0.013 μmol/min, for the anhydrate and dihydrate, respectively. This phase, that is to say the dissolution with apparent zero-order kinetics, lasts about 50 min for the anhydrous form and about 90 min for carbamazepine dihydrate.

The dissolution of carbamazepine in different media, however, does not depend only on the wettability of the particles. It is self-evident that as the solid phase dissolves, the effective surface area decreases and so the dissolution rate in systems like the flow-through cell should decrease after a certain initial phase which has apparent zero-order kinetics. This is what happens when carbamazepine dihydrate dissolves. However, the effective surface area of anhydrous carbamazepine decreases not only due to dissolution but also due to the increase in the size on the remaining crystals.

The crystal growth of anhydrous carbamazepine in 0.1 M hydrochloric acid is rapid and begins immediately upon contact with the medium. In fact, the observed change in the dissolution of the anhydrous form is probably not only a question of the growth of anhydrous crystals but is complicated by transformation of this form to the dihydrate, which is the only stable form in aqueous milieu. This kind of crystal transformation associated with particle growth has been reported previously by Carless et al. (1968a and b), Ebian et al. (1975) and Moustafa et al. (1975).

The wetting agent, polysorbate 80, when used as a component in the dissolution medium, hinders—though only temporarily—the growth of the crystals of anhydrous carbamazepine. This is analogous to the results of Moustafa et al. (1975) who made the same observation with succinylsulfathiazole. Thus the main reason for the delayed particle growth in 0.1 M hydrochloric acid with polysorbate 80 is, most probably, a retarding effect of the wetting agent on the rate of transformation of anhydrous form to dihydrate.

Therefore, when all the factors are considered there is no discrepancy between the present results of absorption and dissolution studies with carbamazepine and the general rule of faster dissolution of anhydrous forms of drugs as compared with hydrates. When the rapid crystal growth of anhydrous carbamazepine is hindered by the retarding effect of polysorbate 80 on the transformation of this thermodynamically more active form to the water-stable dihydrate, the dissolution of the anhydrous crystals is faster than that of the hydrated form. When the wetting agent is not present, the transformation and crystal growth are rapid and the dissolution of (initially) anhydrous form is slow. All this is all the more obvious when it is borne in mind that true sink conditions do not necessarily prevail in the flow-through cell (Posti and Speiser, 1980).

To summarize, the somewhat slower absorption of anhydrous carbamazepine when compared with that of the dihydrate may be due, in part, to the poor wettability of the anhydrous form. Because of the relatively low surface tension in the gastrointestinal tract this is, however, unlikely to be the only explanation. According to the present in vitro data, crystal transformation and growth may more than fully compensate for the greater thermodynamic activity of the anhydrous carbamazepine and may also contribute to the observed difference in the absorption rates of the two crystal forms studied.

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