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Effects of Selected Drugs on an Auditory or Thalamic Conditioned Stimulus Eliciting Recruitment in the Cat

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Abstract □ Minimally effective oral doses of chlorpromazine, imipramine, and pentobarbital necessary to block a discrete trial (bar-press) conditioned avoidance response were compared in cats chronically implanted with electrodes over the cerebral cortex and in the nucleus centralis medialis of the thalamus. Three conditioned stimulus contingencies consisting of tone and low or high voltage thalamic stimulation were presented. Minimal conditioned response blocking doses of these agents produced only slight qualitative changes in cortically recorded recruitment. Drug treatment affected the conditioned stimulus contingencies differentially, and the rank order in terms of ease of disruption of the conditioned avoidance response was high voltage thalamic conditioned stimulus > low voltage thalamic conditioned stimulus > auditory conditioned stimulus. The differential effect of these drugs might have been due to the additive inhibition of these agents and the thalamic conditioned stimulus on performance. With the exception of chlorpromazine, the behavioral effects of these drugs and their effects on recruitment were dissociated.

Keyphrases □ Chlorpromazine—effects on conditioned avoidance response, conscious cat □ Imipramine—effects on conditioned avoidance response, conscious cat □ Pentobarbital—effects on conditioned avoidance response, conscious cat □ Thalamic recruitment—effects of chlorpromazine, imipramine, and pentobarbital, conditioned avoidance response, conscious cat

Electrical stimulation of midline thalamic nuclei and other subcortical sites evokes potentials which, when recorded cortically, resemble spontaneous spindle bursts. Since these potentials increase in amplitude with time, apparently through the recruitment of additional responsive neurons, the recorded event has come to be known as the recruiting response. Several studies (1–3) defined these properties and examined the sites of origin of the recruiting response. Since these classic studies, many investigators have studied the behavioral effects of electrical stimulation of regions of the brain from which cortical recruitment may be elicited.

Midline thalamic stimulation has been shown to act as a conditioned stimulus for the formation of a conditioned avoidance response in cats (4–6), dogs (7), and squirrel monkeys (8). Changes in the amplitude of recruitment during learning and performance have been variously interpreted as reflecting behavioral facilitatory or inhibitory processes (6). However, Pecci-Saavedra *et al.* (8) attributed these changes to alterations in the level of arousal associated with learning.

The effects of psychotropic drugs which modify learned behavior on the recruiting system have been extensively tested; however, the relationship between the effects of these agents on recruitment and their effects on behavior is unknown since all studies have been done in paralyzed or anesthetized preparations (9–14). The present study was designed to bridge the gap between these studies and, thus, to examine the mutual alterations in behavior induced by stimulation of the recruiting system and the action of psychotropic drugs. The effects of selected drugs on avoidance behavior conditioned by either tone or midline thalamic stimulation were studied to compare directly the behavioral effects of these agents to their effects on recruitment.

EXPERIMENTAL

Adult female cats, 2.5–3.5 kg, were chronically implanted with cortical and subcortical electrodes under aseptic conditions. Stainless steel rivets (3-mm diameter heads) insulated with epoxy varnish (except at their tips) were positioned on the dura through burr holes in the skull, and an uninsulated rivet was cemented in the bone overlying the frontal sinus as a connection to ground. A bipolar concentric electrode, consisting of an outer 23-gauge stainless steel cannula and an inner insulated stainless steel wire [0.01 cm (0.005 in.) diameter], was placed in the region of the nucleus centralis medialis of the thalamus according to reported stereotaxic coordinates (anterior, 9.5 mm; lateral, 0.0 mm; horizontal, 1.0 mm) (15). The electrode was insulated with epoxy varnish, and the tips were bared 0.5 mm and separated by 1.0 mm.

The position of this electrode was considered satisfactory if, during surgery, recruiting potentials could be recorded from the cortical leads upon stimulation of the medial thalamus. The parameters of stimulation[1] are given under *Results*. The electrodes were wired to a connector[2], and the assembly was secured to the skull with dental acrylate.

Experiments were initiated no sooner than 2 weeks following

[1] Grass model S-4 stimulator and SIU-4 isolation unit were used.
[2] Amphenol No. 57-40140.

Table I—Thalamic Conditioned Stimulus (CS) Parameters

Cat	Low Voltage CS, v	High Voltage CS, v	Duration, msec	Frequency, Hz
P-102	4.0	4.5	0.2	10
C-103	4.0	4.5	0.5	8
M-104	5.0	6.4	1.0	8

electrode placement. Cats were trained and tested in a chamber (55.8 × 58.4 × 58.4 cm internal dimensions) which was electrically shielded and grounded. A discrete-trial conditional avoidance–escape schedule with variable intertrial intervals was automatically programmed by conventional timers and relays. One trial consisted of presentation of the conditioned stimulus for 12 sec. If a bar-press response was not made during this time, the conditioned stimulus was terminated and 3 mamp of randomly scrambled foot shock was delivered through a grid floor. After animals had learned to avoid shock by responding during delivery of tone (auditory conditioned stimulus), they were subsequently trained to bar press during presentation of thalamic stimulation which elicited recruitment (thalamic conditioned stimulus).

In drug studies, an experimental session consisted of 10 discrete trials of each of three randomly presented conditioned stimulus contingencies: the auditory conditioned stimulus and two differential voltage levels of the thalamic conditioned stimulus. Selection of these voltages of stimulation is described under *Results*.

The effects of chlorpromazine hydrochloride[3], imipramine hydrochloride[4], and pentobarbital sodium at selected oral doses, administered in gelatin capsules, on these contingencies were studied. The animals were tested 1 hr following drug administration on the day following a control run (lactose); thus, each cat served as its own control for a given experiment. Drugs were given no more frequently than once weekly to avoid dose interaction, and one replicate of each dose was obtained. The cats were observed remotely with the aid of a closed-circuit television system[5], and the effects of these drugs on recruitment and on the spontaneous electrocorticogram (ECoG) were recorded by means of an electroencephalograph[6].

Difference between the conditioned response rate under control and drug conditions was the measure used in an analysis of variance, and differences between means for drug days and preceding control sessions were determined by a paired t-test. Since the subjects were trained to at least a 90% avoidance rate under each contingency, it was expected that drug effects would be unidirectional, and a one-tailed test of statistical significance ($p < 0.05$) was used. Individual animal performance was considered changed if the response rate differed by more than 2 *SD* of the mean response of all previous control days. Mean performance in control sessions under each contingency was compared using the Student t test (two tailed).

RESULTS

The subjects of this experiment learned to avoid shock in 98.5 ± 1.2% of control trials (historical value for 18 sessions) when tone was used. The performance rates in control sessions were 95.6 ± 1.8 and 91.3 ± 2.6% using the low and high voltage thalamic conditioned stimulus, respectively. Compared to tone, the performance rate for either the low ($p < 0.4$) or the high ($p < 0.1$) voltage thalamic conditioned stimulus trials was not significantly less. The parameters of stimulation used in each animal are shown in Table I.

The intensity of the low voltage thalamic conditioned stimulus was selected to be threshold for eliciting recruitment waves that waxed and waned, and the amplitudes of these evoked waves were as high as 500 μv. In preliminary experiments, pairing of the thalamic stimulation with the auditory conditioned stimulus was chosen to be subthreshold for behavioral inhibition. It caused recruiting wave amplitudes as high as 500 μv to be more consistently recorded.

Although no attempt was made to determine the voltage threshold for blockade of performance in each subject, recruitment could be elicited without concurrent conditioned avoidance response disruption by reducing the stimulating voltage to the levels shown in Table I. Thus, stimulation of the thalamus affected performance in a voltage-dependent manner.

The effects of chlorpromazine, imipramine, and pentobarbital on each conditioned stimulus continency are shown in Tables II–IV. Drug effects on duplicate tests at each of three dose levels in three subjects were compared by an analysis of variance. In spite of the variability of the subjects in their sensitivity to the drugs ($F = 6.2$, $df = 2/52$, $p < 0.05$), a highly significant dose–response relationship was obtained ($F = 42.2$, $df = 2/52$, $p < 0.01$). Drug treatment affected the three contingencies differentially ($F = 11.9$, $df = 2/52$, $p < 0.01$), and the rank order in terms of ease of response disruption was high voltage thalamic conditioned stimulus > low voltage thalamic conditioned stimulus > tone.

The lowest dose of chlorpromazine that produced a significant attenuation of performance for the group ($n = 3$) compared to control sessions was 1 mg/kg for either the low ($p < 0.05$) or high ($p < 0.01$) voltage thalamic conditioned stimulus, and it was 2 mg/kg ($p < 0.05$) for the auditory conditioned stimulus (Table II). Ataxia and motor incoordination in these subjects were slight or moderate following doses of 1 and 2 mg/kg, respectively. A dose as low as 1 mg/kg altered the spontaneous ECoG in all animals, but presentation of tone abolished high voltage slow wave activity.

The ECoG representing recruitment evoked by thalamic stimulation in Cat P-102 is shown in Fig. 1. This subject and Cat M-104 terminated the thalamic conditioned stimulus in control trials and in chlorpromazine (0.5 mg/kg) trials following a secondary increase in the negativity of the recruiting response. Chlorpromazine generally increased recruitment amplitude, but the administration of 1 and 2 mg/kg to two animals (P-102 and M-104) prevented the secondary increase in recruitment negativity subsequent to the initial burst in trials in which the avoidance response was disrupted (Fig. 1).

Compared to control sessions, the lowest dose of imipramine studied (2 mg/kg) interfered with the action of the high-voltage thalamic conditioned stimulus ($p < 0.05$); however, performance conditioned to either tone or low voltage thalamic stimulation was not altered significantly in the group ($n = 3$) following 2, 4, or 8 mg/kg (Table III). However, based upon comparison with performance on 18 control days, three out of three subjects in tone trials were affected by the 8-mg/kg dose. Performance was affected in as many as two out of three subjects following 4 mg/kg in low voltage trials. ECoG synchrony was observed following all doses, and presentation of tone usually activated the record. Drug treatment increased the negativity of recruitment elicited by the thalamic conditioned stimuli and increased the tendency for recruitment amplitude to wax and wane during stimulus presentation. In Cat P-102 (Fig. 2), the recruiting response change from control trials was less following 2 mg/kg than following either 4 or 8 mg/kg.

The lowest dose of pentobarbital that produced significant attenuation of performance for the group ($n = 3$) compared to control sessions (Table IV) was 10 mg/kg for tone ($p < 0.01$) and either the low ($p < 0.01$) or high ($p < 0.05$) voltage thalamic conditioned stimulus. Moderate motor incoordination was produced by each dose, and the subjects appeared to doze intermittently following the 10-mg/kg dose. High voltage slow waves and occasional spindle burst activity were recorded in all subjects following 5 mg/kg, and higher doses (7.5 and 10 mg/kg) increased the occurrence of spindle activity that was incompletely blocked by presentation of tone. Recruitment amplitudes were slightly increased; but as shown in Figs. 2 and 3, imipramine and pentobarbital produced essentially similar changes. The general appearance of the recruiting response seemed to be similar following doses of pentobarbital which either did or did not disrupt performance.

The results reported were obtained from subjects in which placement of the electrode within the nucleus centralis medialis of the thalamus was histologically confirmed.

DISCUSSION

Sufficient evidence has been accumulated from several studies (16, 17) to confirm the observation that recruitment occurs in parallel to behavioral inhibition. However, elicitation of the recruiting

[3] Supplied by Smith Kline and French, Philadelphia, Pa.
[4] Supplied by Geigy, Ardsley, N.Y.
[5] Motorola, Inc.
[6] Model D, Medcraft.

Table II—Effects of Chlorpromazine on Three Conditioned Stimulus (CS) Contingencies

Dose, mg/kg po	Cat	Percent Conditioned Avoidance: Auditory CS, Tone Control	Auditory CS, Tone Treatment	n/N[a]	Thalamic CS: Low Voltage Control	Low Voltage Treatment	n/N[a]	High Voltage Control	High Voltage Treatment	n/N[a]
0.5	P-102	95	90		90	85		100	85	
	C-103	100	95		90	80		100	35	
	M-104	100	95		100	75		90	0	
Mean ± *SEM*		98.3 ± 1.7	93.3 ± 1.7	1/3	93.3 ± 3.3	80.0 ± 2.9	3/3	96.7 ± 3.3	40.0 ± 24.7	2/3
1.0	P-102	95	65		100	70		95	35	
	C-103	100	15		95	10		100	5	
	M-104	100	80		100	40		80	5	
Mean ± *SEM*		98.3 ± 1.7	53.3 ± 19.6	3/3	98.3 ± 1.7	40.0 ± 17.3[b]	3/3	91.7 ± 6.0	15.0 ± 10.0[c]	3/3
2.0	P-102	95	25		90	15		95	0	
	C-103	95	5		90	0		85	0	
	M-104	100	15		100	0		75	0	
Mean ± *SEM*		96.7 ± 1.7	15.0 ± 5.8[c]	3/3	93.3 ± 3.3	5.0 ± 5.0[c]	3/3	85.0 ± 5.8	0.0 ± 0.0[c]	3/3

[a] Number of cats showing a significant change on drug day in percent conditioned avoidance/response number of cats in group; based upon comparison with performance on 18 control days. [b] $p < 0.05$ (Student t test, one tailed). [c] $p < 0.01$ (Student t test, one tailed).

Table III—Effects of Imipramine on Three Conditioned Stimulus (CS) Contingencies

Dose, mg/kg po	Cat	Percent Conditioned Avoidance: Auditory CS, Tone Control	Auditory CS, Tone Treatment	n/N[a]	Thalamic CS: Low Voltage Control	Low Voltage Treatment	n/N[a]	High Voltage Control	High Voltage Treatment	n/N[a]
2.0	P-102	90	90		85	90		100	75	
	C-103	100	100		100	50		85	30	
	M-104	100	100		100	100		95	15	
Mean ± *SEM*		96.7 ± 3.3	96.7 ± 3.3	1/3	95.0 ± 5.0	80.0 ± 15.3	1/3	93.3 ± 4.4	40.0 ± 18.0[b]	3/3
4.0	P-102	95	60		85	55		90	10	
	C-103	100	95		95	15		95	0	
	M-104	100	95		95	100		100	5	
Mean ± *SEM*		98.3 ± 1.7'	83.3 ± 11.7	1/3	91.7 ± 3.3	56.7 ± 24.6	2/3	95.0 ± 2.9	5.0 ± 2.9[c]	3/3
8.0	P-102	100	75		100	70		70	0	
	C-103	100	0		100	0		95	0	
	M-104	100	90		95	90		90	0	
Mean ± *SEM*		100.0 ± 0.0	55.0 ± 27.8	3/3	98.3 ± 1.7	53.3 ± 27.3	2/3	85.0 ± 7.6	0.0 ± 0.0[c]	3/3

[a] Number of cats showing a significant change on drug day in percent conditioned avoidance response/number of cats in group; based upon comparison with performance on 18 control days. [b] $p < 0.05$ (Student t test, one tailed). [c] $p < 0.01$ (Student t test, one tailed).

Table IV—Effects of Pentobarbital on Three Conditioned Stimulus (CS) Contingencies

Dose, mg/kg po	Cat	Percent Conditioned Avoidance: Auditory CS, Tone Control	Auditory CS, Tone Treatment	n/N[a]	Thalamic CS: Low Voltage Control	Low Voltage Treatment	n/N[a]	High Voltage Control	High Voltage Treatment	n/N[a]
5.0	P-102	100	75		90	95		75	55	
	C-103	100	100		100	100		100	100	
	M-104	100	100		100	100		95	80	
Mean ± *SEM*		100.0 ± 0.0	91.7 ± 8.3	1/3	96.7 ± 3.3	98.3 ± 1.7	0/3	90.0 ± 7.6	78.3 ± 13.0	2/3
7.5	P-102	100	45		95	35		90	10	
	C-103	100	90		95	25		100	5	
	M-104	100	80		95	95		100	100	
Mean ± *SEM*		100.0 ± 0.0	71.7 ± 13.6	3/3	95.0 ± 0.0	51.7 ± 21.8	2/3	96.7 ± 3.3	38.3 ± 30.9	2/3
10.0	P-102	95	0		95	0		65	0	
	C-103	100	0		100	0		100	0	
	M-104	100	15		100	10		100	25	
Mean ± *SEM*		98.3 ± 1.7	5.0 ± 5.0[b]	3/3	98.3 ± 1.7	3.3 ± 3.3[b]	3/3	88.3 ± 11.7	8.3 ± 8.3[c]	3/3

[a] Number of cats showing a significant change on drug day in percent conditioned avoidance response/number of cats in group; based upon comparison with performance on 18 control days. [b] $p < 0.05$ (Student t test, one tailed). [c] $p < 0.01$ (Student t test, one tailed).

response by thalamic stimulation was not exclusively associated with behavioral inhibition and, as shown in the present investigation and as reported by others (4, 5, 7, 8), it was possible to establish avoidance behavior conditioned to thalamic stimulation eliciting recruitment.

Even though the avoidance rate in control trials using the auditory conditioned stimulus was not significantly different from rates obtained using either voltage of the thalamic conditioned stimulus, higher intensities of thalamic stimulation presented concurrent to tone prevented ongoing performance in these subjects in

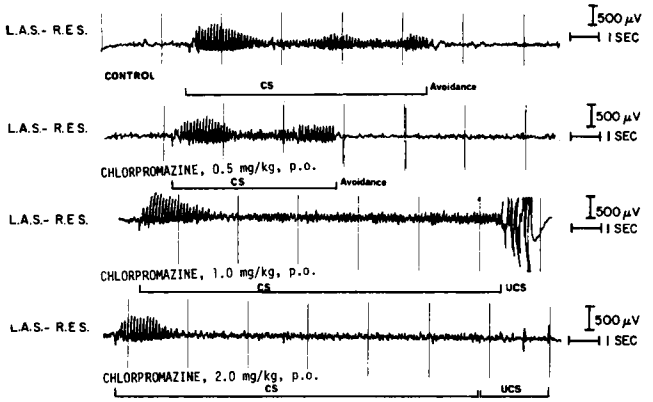

Figure 1—*Effects of chlorpromazine hydrochloride on the ECoG of the recruiting response evoked by the high-voltage thalamic conditioned stimulus (CS) in the cat (P-102). The duration of the conditioned stimulus (CS) (4.5 v, 10 Hz, 0.2-msec stimulation of the nucleus centralis medialis) is shown by the bracketed area beneath each trace here and in Figs. 2 and 3. The unconditioned stimulus (UCS) was an escapable 3-mamp shock applied through a grid floor; the abbreviation L.A.S.-R.E.S. represents a bipolar lead between the left anterior sigmoid gyrus and right ectosylvian gyrus.*

preliminary experiments. Similar cessation of lever pressing in cats by low frequency stimulation of nonspecific thalamic nuclei was previously reported for negatively reinforced behavior (4) and positively reinforced behavior (16). The results of the present investigation suggest that the nonspecific inhibitory effect is voltage dependent; *i.e.*, higher voltages of stimulation produce greater inhibition of behavior.

Conditioned responses are abolished by doses of chlorpromazine that do not seriously affect motor abilities (18); however, much higher doses of imipramine are required to suppress the conditioned avoidance response (19). The barbiturates block conditioned responding only at doses that produce motor incoordination. While similar results were obtained in this study, it was shown that a lower dose of chlorpromazine or imipramine was required to disrupt significantly responses conditioned to thalamic stimulation than to tone. The differential effects of these agents might be explained by the summation of their inhibitory effects on conditioned performance and their facilitation of the diffuse thalamic system (12), which would increase the nonspecific inhibitory effect and decrease response probability to a greater degree than expected.

The fact that pentobarbital did not differentially affect any contingency is in agreement with the results of Rutledge and Doty (20), who compared drug effects on behavior in cats conditioned to either tone or high frequency (50 Hz) cortical stimulation. While the frequencies and sites of brain stimulation in the two studies

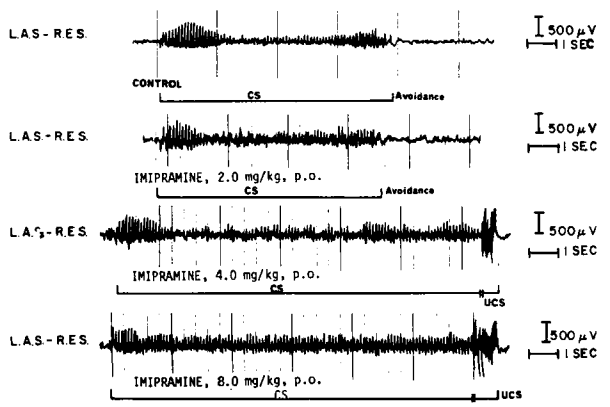

Figure 2—*Effects of imipramine hydrochloride on the ECoG of the recruiting response evoked by the high-voltage thalamic conditioned stimulus (CS) in the cat (P-102).*

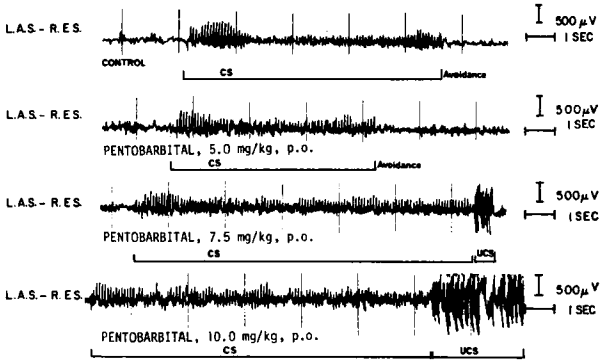

Figure 3—*Effects of pentobarbital sodium on the ECoG of the recruiting response evoked by the high-voltage thalamic conditioned stimulus (CS) in the cat (P-102).*

differed, lower doses of chlorpromazine were required to block responses conditioned to tone than to cortical stimulation. The finding in the present study that chlorpromazine produced reverse differential effects on behavior conditioned to either tone or thalamic stimulation suggests that, compared to cortical stimulation, the motivational effect of thalamic stimulation might be inferior and might provide additional evidence of drug-induced enhancement of a nonspecific inhibitory effect at the thalamic level.

The subjects of this study never bar pressed during the initial recruitment envelope in either control or drug trials, a finding that supports the conclusion of Angyan *et al.* (4) that recruitment is associated with behavioral inhibition. However, in the present experiment, thalamic stimulation was presented for 12 sec rather than for 5 sec as in the former study, allowing an avoidance response to be made following the initial interval of inhibition. The secondary increase of recruiting response negativity observed prior to an avoidance response may be analogous to surface-negative potentials described by Skinner (21) as associated with expectancy or attention or both. Since these increases in recruitment negativity did not appear in trials where chlorpromazine blocked the behavioral response, this type of recruitment change following chlorpromazine may represent the effect of the drug on either expectancy or attention rather than on the recruitment mechanism itself. Chlorpromazine slightly increased recruitment amplitude elicited by the thalamic conditioned stimulus, perhaps through a direct or indirect facilitation of the diffuse thalamic system. There is evidence that chlorpromazine suppresses the cortex and the brain stem reticular formation but stimulates the diffuse thalamic system (12).

The increase in recruitment amplitude produced by imipramine, especially following the 8-mg/kg dose, is in accord with the results of Monnier and Krupp (12), who reported an increased recruiting response in the rabbit cortex by a similar dose. However, Sigg (13) found that imipramine (5–10 mg/kg) did not alter the threshold voltage required to induce recruitment in the cat cortex, and others (14) reported that imipramine decreased both its surface-positive and surface-negative components. Nevertheless, the present results show that imipramine blocks performance conditioned to thalamic stimulation independent of its effects on recruitment.

Domino (9) suggested that the enhancement of recruitment by low doses of pentobarbital was a release phenomenon due to depression of the midbrain reticular formation rather than to direct stimulation of the diffuse projection system; this would account for the small increase in its amplitude observed in the present study. Like imipramine, the effects of pentobarbital on recruitment appear to be independent of its effects on conditioned behavior, and, as noted previously, the barbiturate generally slightly enhanced recruitment following doses that either did or did not prevent responding conditioned to thalamic stimulation. These results suggest that, with the exception of chlorpromazine, the effects of these behavior-modifying drugs upon the characteristics of the cortically recorded recruiting response are not related to their effects on learned behavior.

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Nonsink Dissolution Rate Equations

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Abstract □ In spite of the fact that film theory is based on severe assumptions, it is shown to be a good working model. The Niebergall–Goyan equation, the Short–Sharkey–Rhodes equation, and the Pothisiri–Carstensen equation—all based on simple film theory—are shown to hold through 80–90% of the dissolution process for *p*-hydroxybenzoic acid and sodium chloride, both at values below and above the amount necessary to saturate the dissolution medium. Deviations are attributed to experimental difficulties and to improper definition of monodisperseness rather than to the assumptions made in the theory.

Keyphrases □ Nonsink dissolution of monodisperse powders—various rate equations examined □ Dissolution of monodisperse powders—various rate equations examined □ Powders, monodisperse—various nonsink dissolution rate equations examined

Dissolution of monodisperse powders has been studied and reported by several investigators. The intents of this study are to consolidate a variety of equations, to point out their shortcomings and strengths, and to show that film theory is a good working model.

BACKGROUND

The dissolution rate equations dealt with here are based on the Noyes–Whitney equation (1):

$$-dW/dt = kO(S - C) \qquad \text{(Eq. 1)}$$

where W is the weight remaining, k is the intrinsic dissolution rate constant, O is the surface area, S is the saturation concentration, and C is the concentration at time t.

The assumptions made are: *(a)* a film [the so-called Nernst–Brunner layer (2–4)] surrounds each particle; *(b)* the film need not be hydrodynamically stagnant but behaves so that there is a linear concentration gradient in it; and *(c)* the concentration gradient imparts a concentration, C, at the boundary between the film and the bulk solution. The thickness of this boundary is assumed not to change during dissolution; *i.e.*, it is assumed to be independent of particle size. Niebergall *et al.* (5) studied this point, but it will not be discussed in this report.

Another assumption is that the particles are isotropic and isometric, although Carstensen and Patel (6) showed that this condition need not be a prerequisite. The Ostwald–Freundlich effect (7, 8), where a smaller particle is more soluble than a larger particle, is also neglected.

A dissolution rate equation for monodisperse powders was first suggested by Wilhelm *et al.* (9); they employed graphical integration to solve exact dissolution rate equations. Hixson and Crowell (10) arrived at the cube root law for dissolution of monodisperse powders under sink conditions (*i.e.*, when $C \ll S$):

$$W_o^{1/3} - W^{1/3} = \frac{W_o^{1/3} 2kS}{\rho d} t \qquad \text{(Eq. 2)}$$

where d is the diameter of the particle (assumed spherical), and ρ is the particle density. For Fick's law (11) to apply to film theory, it is required that:

$$k = D/h \qquad \text{(Eq. 3)}$$

where D is the diffusion coefficient of the solute in solution, and h is the thickness of the Nernst–Brunner layer. Since D can be determined experimentally or obtained by the Stokes–Einstein equation (12) or the Wilke equation (13), an estimate of h can be made from dissolution rate studies.

Niebergall and Goyan (14) extended the Hixson–Crowell equation to the situation where the amount studied (W_o) equals exactly