Table II—Mean Individual Plasma Concentration Parameters for Methaqualone and Analysis of Variance for Each Indicated Parameter

Hours	Plasma Concentration, μg/ml (Mean ± SD)[a] Tablet A	Tablet B	Statistical Significance[b] Treatment Effect	Period Effect	Subject Effect
0.5	1.27 ± 1.27	1.35 ± 0.936	NS	NS	NS
1.0	3.10 ± 1.05	3.30 ± 1.09	NS	NS	NS
2.0	3.52 ± 0.863	3.29 ± 0.552	NS	NS	NS
3.0	2.93 ± 0.647	2.78 ± 0.572	NS	NS	NS
4.0	2.36 ± 0.575	2.30 ± 0.480	NS	NS	0.05
6.0	1.64 ± 0.366	1.59 ± 0.369	NS	NS	0.01
8.0	1.39 ± 0.287	1.43 ± 0.378	NS	NS	0.05
12.0	1.14 ± 0.265	1.17 ± 0.354	NS	NS	0.05
16.0	1.04 ± 0.279	1.02 ± 0.289	NS	0.05	0.05
24.0	0.848 ± 0.214	0.815 ± 0.253	NS	NS	NS
Peak concentration[c]	3.97 ± 0.718	3.70 ± 0.664	NS	NS	NS
Peak time, hr	1.82 ± 0.750	1.36 ± 0.664	NS	NS	NS
AUC[cd], (μg hr)/ml	34.6 ± 6.17	34.2 ± 8.00	NS	NS	0.05

[a] Average of 11 subjects. [b] A statistical package (10) was used to detect the significance of the factors at the 0.05 level. [c] A difference of 25% in overall means can be detected with $\alpha = 0.05$ and $\beta = 0.05$. [d] Area under plasma concentration–time curve from 0 to 24 hr.

The two methaqualone tablets tested in this study were bioequivalent. Thus, the currently used dissolution test did not accurately reflect the *in vivo* performance of methaqualone tablets. Since a dissolution test serves no useful purpose unless it reflects the potential safety or efficacy of a drug product, this study indicates that a new testing procedure is required.

Both tablets did not meet the existing NF dissolution rate standard (Table I). However, Tablet A could readily be considered an appropriate reference standard since the product met all NDA specifications. Furthermore, the data clearly show that changes of more than 50% in the *in vitro* dissolution rate of a tablet dosage form produced no apparent significant effect *in vivo*. Additionally, Chemburkar *et al.* (8) indicated that the dissolution rate test that most closely correlated with *in vivo* bioavailability was an extremely slow 2-rpm procedure. Based on their report plus the findings in this paper, serious considerations should be given toward revision of the current NF dissolution rate standards for methaqualone tablets.

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Binding of Drugs to Ion-Exchange Resins in Simulated Gastric Fluid

V. KHOUW, H. G. GILES ˣ, and E. M. SELLERS

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Abstract □ The binding of 13 frequently abused drugs to two ion-exchange resins was studied in simulated gastric fluid. The results were compared with those previously obtained with activated charcoal as the adsorbent. The ion-exchange resins adsorbed the drugs more slowly than activated charcoal, and the binding capacities of the resins were inferior. These ion-exchange resins are unlikely to be very useful in removing drugs from the stomach.

Keyphrases □ Binding—various drugs to two ion-exchange resins in simulated gastric fluid, compared to previous results with charcoal □ Ion-exchange resins—binding of various drugs in simulated gastric fluid, compared to previous results with charcoal □ Adsorption—various drugs to two ion-exchange resins in simulated gastric fluid, compared to previous results with charcoal

The effective removal of drugs from the blood of animals and humans by hemoperfusion is well established (1). In the early work, use was made of the irreversible binding of drugs to activated charcoal by nonspecific surface adsorption. Charcoal hemoperfusion is not currently employed, however, since Hagstram *et al.* (2) documented platelet adsorption and the release of particles of charcoal into blood. More recently, coated activated charcoal (3)

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Table I—Kinetic Studies

Drug	Resin 1 Initial $t_{1/2}$, min	Resin 1 Linear Interval, min	Resin 1 Correlation Coefficient	Resin 1 % Free at End of Linear Interval	Resin 1 % Free Final	Resin 1 Time of Finish, min	Resin 2 Initial $t_{1/2}$, min	Resin 2 Linear Interval, min	Resin 2 Correlation Coefficient	Resin 2 % Free at End of Linear Interval	Resin 2 % Free Final	Resin 2 Time of Finish, min
Amitriptyline	15.4	30	0.993	20.2	1.2	120	9.7	60	0.998	1.2	1.2	60
Aspirin (acetylsalicylic acid)	23.5	20	0.999	49.6	1.6	240	18.0	90	0.999	2.7	2.7	90
Chlordiazepoxide	36.7	45	0.968	40.3	19.1	240	20.3	60	0.999	11.6	2.3	240
Secobarbital	11.5	15	0.997	40.0	2.0	150	11.7	30	0.996	16.0	0.8	90

and two ion-exchange resins (4) were employed in hemoperfusion to circumvent the deleterious properties of plain, activated charcoal. The ion-exchange resins[1] are hard, insoluble spheres of porous polystyrene. They are hydrophobic and have large surface areas.

Although effective in hemoperfusion, the ion-exchange resins have not been tested for the removal of drugs from the stomach. If the resins are effective in this regard, they may be useful in the management of drug overdose. The binding of drugs *in vitro* to two ion-exchange resins was examined and compared to results previously obtained with activated charcoal (5).

EXPERIMENTAL

The studies were carried out by dissolving 0–10 mg of the drugs in 25 ml of simulated gastric fluid (5) at pH 1.3. Resin 1 or 2 was added to the solution, the solutions were incubated with shaking at 37° in a metabolic shaker, and the resin was allowed to settle. Free drug concentrations in the supernate were determined spectrophotometrically by comparison with standard curves.

RESULTS AND DISCUSSION

In general, the log drug concentration *versus* time profiles (Fig. 1) for the drugs showed two-mode relationships (least-squares analysis). From these relationships, the half-life of disappearance of each drug may be estimated (Table I). Without exception, the drug adsorption rate onto Resin 2 was faster than onto Resin 1, reflecting the larger surface area of Resin 2 (1). In comparison, however, drug adsorption onto activated charcoal under identical circumstances is so fast that the drug concentration in the supernate after 2 min of incubation is below the lower limit of the spectrophotometric assay.

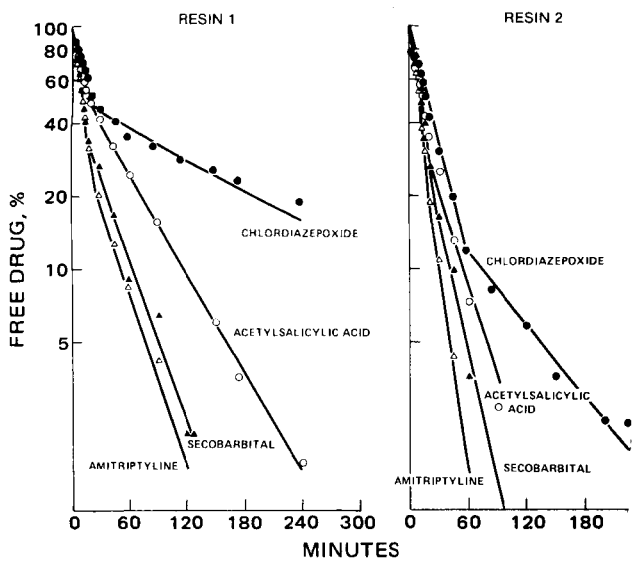

Figure 1—*Binding of drugs to ion-exchange resins in simulated gastric fluid.*

[1] Resin 1 was Amberlite XAD-2, 330 m^2/g; and Resin 2 was Amberlite XAD-4, 750 m^2/g. They were obtained from BDH Chemicals, Toronto, Ontario, Canada, and manufactured by Rohm and Haas, Philadelphia, Pa.

Table II—Comparison of Binding Capacities

Drug	Binding Capacity, mg/g: Resin 2	Binding Capacity, mg/g: Activated Charcoal
Amitriptyline	35	133
Amobarbital	43	51
Aspirin (acetylsalicylic acid)	54	262
Chlordiazepoxide	47	157
Chlorpromazine	40	—
Diazepam	50	136
Glutethimide	43	252
Methaqualone	39	179
Pentobarbital	55	103
Phenobarbital	49	70
Propoxyphene hydrochloride	26	127
Propoxyphene napsylate	28	137
Secobarbital	55	124

By employing the Langmuir equation, the binding capacities of Resin 2 were determined (5) (Table II). Comparison with previously obtained data with activated charcoal as the adsorbent (5) indicates that activated charcoal has a far higher binding capacity for the drugs studied.

These ion-exchange resins offer neither the advantage of rate nor extent of the drug adsorption shown by activated charcoal and are unlikely to be very useful in reducing the adsorption of drugs from the stomach.

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