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RESEARCH ARTICLES

Design and Evaluation of an Automated System for *In Vitro* Dissolution Testing Utilizing a High-Pressure Liquid Chromatographic Multiport Switching Valve

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Abstract □ An automated system for the simultaneous dissolution testing of six samples was developed consisting of four basic units: dissolution vessels and stirring unit, a peristaltic pump, a rotary stream multiport switching valve and programmer, and a UV spectrophotometer with recorder. Among the major advantages of such a system are: (*a*) paddle or basket stirring with variable speed is used, (*b*) the tablet or capsule (wire coil required) locates reproducibly at the bottom of a round-bottom reaction flask when utilizing paddle-type stirring, (*c*) a USP basket for tablet or capsule dissolution testing can be used, (*d*) continuous or intermittent sampling is possible, (*e*) the flow system readily adapts to UV–visible detector or fluorescence spectroscopy, (*f*) the system readily adapts to automated determination of the intrinsic dissolution of a material, and (*g*) the cost is low because of the multiport switching valve and inexpensive UV monitor required. Studies were performed using this apparatus to demonstrate the response characteristics of the system, its reproducibility, potential problems, and precautions required. This dissolution system was used to determine the dissolution characteristics of a new steroid tablet formulation, including a formulation and lot demonstrated to be bioavailable.

Keyphrases □ Dissolution testing—six samples simultaneously, automated system designed and evaluated □ Automated systems—dissolution testing of six samples simultaneously, system designed and evaluated

Dissolution rate testing is an important aspect (1, 2) of dosage form development. It can provide a means for the prediction of drug bioavailability. It is an important test during the optimization of a tablet or capsule formulation as well as a control test on the final product. Numerous dissolution rate testing methods have been employed, all having the following essential features: a dissolution container, a device for agitating the dissolution fluid, a method for sampling or transporting the dissolution fluid, and an analytical technique for measuring the dissolved drug.

To make the procedure more efficient, multiple dissolution systems with automated sampling and analysis have been designed and tested (3–13). The systems differ in the type of dissolution vessel and stirring used but generally employ one of two sampling designs. Most systems (3–5, 8–13) use a pumping arrangement that causes flow from the dissolution vessel to a spectrometer and back to the dissolution vessel. With multiple dissolution vessels, the spectrometer must be capable of switching cells at preprogrammed intervals to accommodate the multiple samples. Alternatively, the switching of cells at the spectrometer can be replaced by a stream switching valve. One commercially available system (7) utilizes this technique, and another application of this configuration was reported recently (6).

The objective of this research was to determine if a satisfactory and economical dissolution system could be constructed using a standard dissolution vessel and stirring apparatus in conjunction with a peristaltic pump, high-pressure liquid chromatographic (HPLC) multiport stream switching valve, and UV spectrometer. This report discusses the construction and testing of such a system and its application to tablet and capsule dissolution testing; the advantages and disadvantages are described.

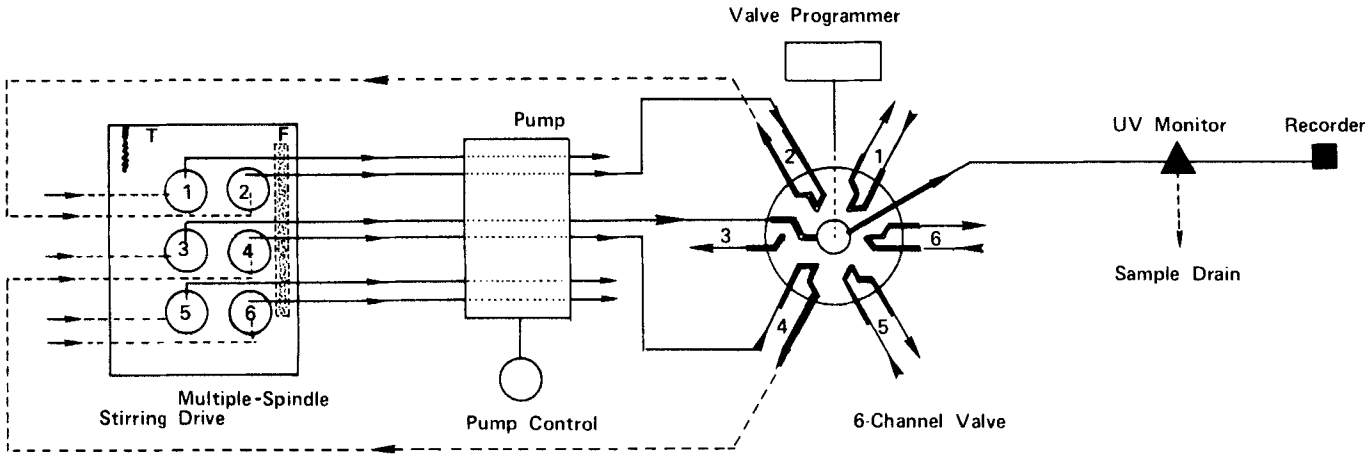

Figure 1—*Schematic diagram of automated dissolution apparatus. Key: T, thermostat; and F, sintered-glass or Millipore filter.*

EXPERIMENTAL

Automated Dissolution System—The automated dissolution system is shown in Fig. 1, and the instruments used are described as follows.

Multiple-Spindle Stirring Drive with Variable Speed Drive Control[1]—This unit has the capacity for six dissolution vessels. The stirring can be accomplished by paddles or L-shaped stirrers (14) or the USP basket. This assortment allows the versatility for performing tablet or capsule dissolution testing as well as intrinsic dissolution rate determination.

Dissolution Vessel—A closeup of the dissolution vessel, a 1-liter round-bottom reaction kettle[2], is shown in Fig. 2. This particular stirring propeller[3] is polyethylene. Figure 3 pictures the two types of sampling devices used. The filter device consists of an 18-gauge needle[4] (i) joined to a connector[4] (ii), which is connected to a filter holder[5] (iii). The remaining adaptor[4] (iv) connects the filter to the tubing.

The second type of sampling device (Fig. 3*b*) was a modified sintered-glass filter. The cup of a sintered-glass filter[6] was cut off at the glass frit. The stem was then replaced with a capillary tube (0.8 mm i.d. × 4.1 mm o.d.; 14-cm length), with 1.5 cm of the end ground to a smaller diameter (approximately 3.0 mm) to accept the silicone rubber tubing. The filter holder sampling device requires filter replacement after each use, and the sintered-glass filter requires cleaning between samples. Under these conditions, no filter clogging was observed with the formulations and products tested.

The sintered-glass filter has been acceptable for tablets and capsules other than the cloprednol tablets and capsules tested, including certain commercially available prednisone and prednisolone tablets and capsules and tablets of three new nonhormonal anti-inflammatory drugs. The acceptability of either filter depends on the tablet or capsule formulation undergoing dissolution testing.

Pump—A peristaltic tubing pump[7] with six pump heads was used. The tubing between the dissolution vessel and the valve was silicone rubber (0.8 mm i.d.; 4.13 mm o.d.). The connection of this tubing to the switching valve was accomplished as indicated in Fig. 4.

Two sizes of polytef tubing were used to make the connector. The one[8] that formed the sleeve was 1.5 mm i.d. × 3.0 mm o.d.; the other[8] was 0.8 mm i.d. × 1.5 mm o.d. The return tubing from the valve to the dissolution vessel was also polytef[9], 0.8 mm i.d. × 1.5 mm o.d., as was the tubing connection between the switching valve and the UV flowcell.

Six-Channel Stream Selection Valve for HPLC and Sequential Valve Programmer—The stream selection valve[10] is designed for the selection of one stream to send to the analyzer (UV monitor in this case) and for the continuous return of all other streams. The valve is of rotary design and advances *via* an air solenoid. The valve is controlled by a special programmer[10] that allows the switching between streams to occur at a preset time interval. The available intervals are 0–99 sec and 0–9.9 and 0–99 min.

UV Monitor and Recorder—The UV monitor[8] monitors the effluent from the HPLC column. The unit allows multiple-frequency monitoring by use of interchangeable filters. The absorbance ranges from 0.05 to 2.0 absorbance units full scale. The instrument utilizes a 1-cm 100-μl bubble-free flowcell. Other cells with shorter path lengths also are available.

The absorbance readings were recorded on a 25.4-cm laboratory chart recorder[11].

Volume in Tubing System and Lag Time—The tubing sections of the dissolution systems were designed to contain a small volume. This volume allows the utilization of the small bore switching valve and prevents a large dissolution fluid loss after it passes through the detector. This procedure generally does not require concentration corrections for the small volume loss from the dissolution vessel. The pump speed of 50 rpm delivers 2.4 ml/min, which is 80% of the theoretical rate for that size pump head. The difference can be assigned to the flow resistances in the system.

With a total volume in the system from the vessel to the detector (filter stick configuration design) of only 0.90 ml, there is a lag time of approximately 0.375 min between the vessel and the detector. The observed lag time from the switching valve to the detector is 0.09 min, which compares favorably with that calculated for a volume of 0.2 ml and a flow rate of 2.4 ml/min. Additional time is required for the true absorbance level to be reached because of the mixing that occurs as the fluid flows through the tubing and flowcell. The minimum switching interval that can then be used is 1 min. The time values reported here are not corrected for the instrument lag time.

Intrinsic Dissolution Studies—The intrinsic dissolution studies were performed using a static disk, a variation of that described previously (15, 16). The die was constructed of stainless steel (diameter 3.81 cm, thickness 0.953 cm, and diameter of hole 1.27 cm). Cloprednol[12] (6-chloro-11β,17α,21-trihydroxypregna-1,4,6-triene-3,20-dione) was compressed in the die using a hydraulic press[13] at 1134 kg. The pure steroid tablet was positioned at the die surface, and the unit was placed at the bottom of the dissolution vessel. The polyethylene propeller was positioned 2.5 cm above the bottom of the vessel and revolved at 100 rpm; 0.5 liter of deaerated, distilled water was used.

Tablet Dissolution Studies—Tablet dissolution studies were performed using deaerated, distilled water. The polyethylene propeller was used as described previously, or the USP basket (40 mesh) was located 2.5 cm from the bottom of the dissolution flask. With the propeller stirrer, the tablet was added to the dissolution vessel and then descended to the bottom of the vessel.

The polyethylene propeller stirrer was used because: (*a*) it provided equivalent or better mixing characteristics than other commercially

[1] Model 72R115, Hanson Research Corp., Northridge, CA 91324.
[2] Kimax 33700-S1, Owens-Illinois, Toledo, OH 43666.
[3] No. S-76680, Sargent-Welch, Anaheim, CA 92803.
[4] Needle 1293 (T462 LNR), connector 3114 (MLL/MLL), and adaptor 3084 (L 1609), Becton-Dickinson & Co., Rutherford, NJ 07070.
[5] Swinnex (13 mm), Millipore Corp., Bedford, MA 01730.
[6] Kimble 28400, Scientific Products, Menlo Park, CA 94025.
[7] Variable speed Masterflex 7545-13 with pump heads No. 7013 and tubing 6411-41, Cole-Parmer, Chicago, IL 60648.
[8] Sleeve tubing No. 200-32, inner tubing No. 200-31, and Biochemical UV monitor model 150, Altex Scientific, Inc., Berkeley, CA 94710.
[9] No. 3114-030, Glenco Scientific Inc., Houston, TX 77007.
[10] Valve ASF-6-HPa-HC and programmer VSP-216R, Valco Instruments Co., Houston, TX 77024.
[11] Model 261, Linear Instruments Corp., Irvine, CA 92705.
[12] Syntex Corp., Palo Alto, CA 94304.
[13] Fred S. Carver Co., Summit, N.J.

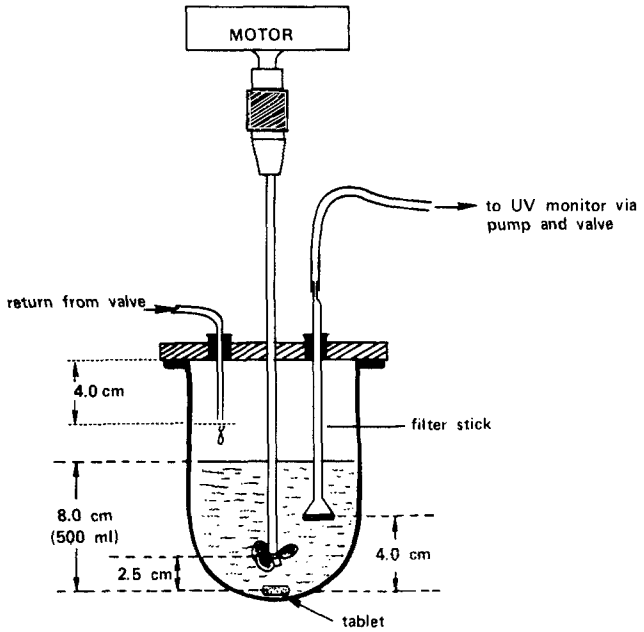

Figure 2—*Dissolution vessel as set for tablet dissolution.*

available stirrers, (*b*) it was in a fixed position on the shaft so it was not subject to a shift in position, (*c*) it was essentially unbreakable, and (*d*) it was readily available commercially.

RESULTS AND DISCUSSION

Intrinsic Dissolution as a Test for System Reproducibility—A measure of the reproducibility of the dissolution system was determined by comparing the intrinsic dissolution rate of cloprednol. Three of the six dissolution vessels were randomly chosen to be representative of the dissolution system; the results from these determinations are given in Table I. To determine if the dissolution rate (slope) of each run was equivalent, the Student *t* test (17) was performed on each pair of results. From the calculated values (Table I), the dissolution rates were equivalent at the 95% level of significance.

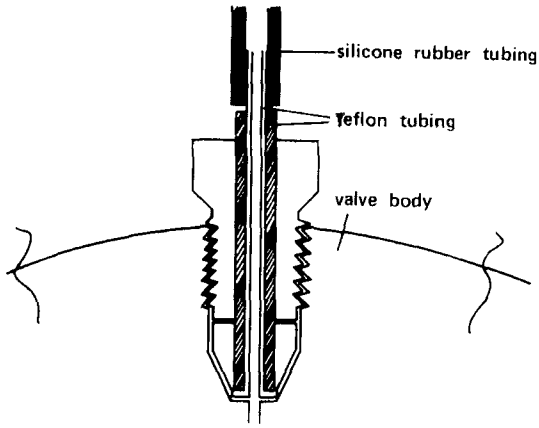

Figure 4—*Diagram of silicone tubing connection to inlet of switching valve.*

Effect of Stirring Rate on Cloprednol Tablet Dissolution—The described tablet dissolution apparatus was used employing a polyethylene stirrer and sintered-glass filter. The effect of stirring on cloprednol tablet dissolution is demonstrated in Fig. 5. The tablet batch was representative of those produced during the later stages of development. The results indicated an increase in dissolution rate with an increase in stirring, as expected. Although an increased stirring rate may be used to produce an increased dissolution rate, the risk exists that important differences in dissolution of tablets of different lots and/or formulation composition may be masked. A slow stirring rate, however, may produce a tablet dissolution condition that is too sensitive; *i.e.*, differences in the dissolution

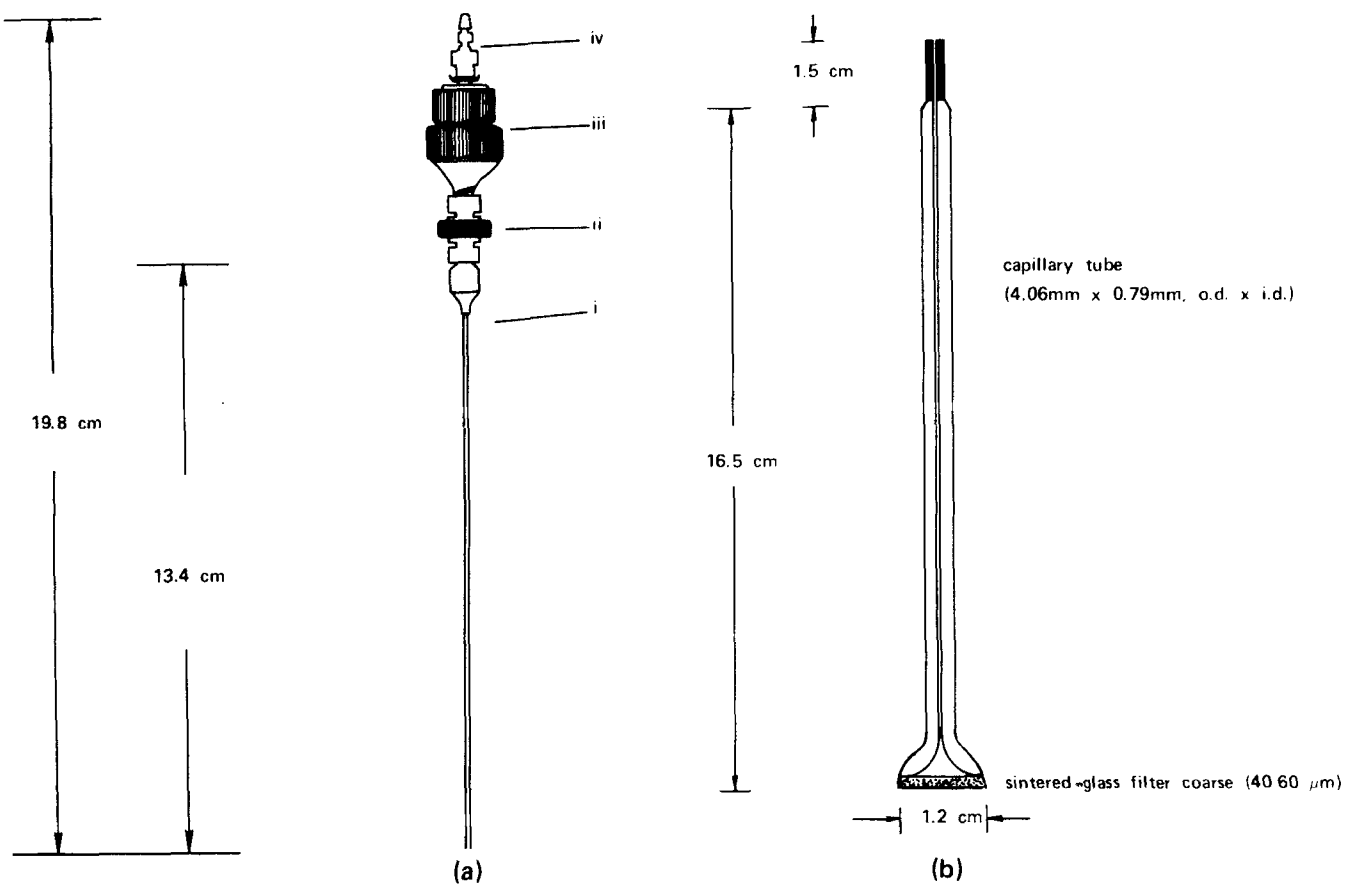

Figure 3—*Dissolution sampling devices. Key: a, filter device; and b, filter stick.*

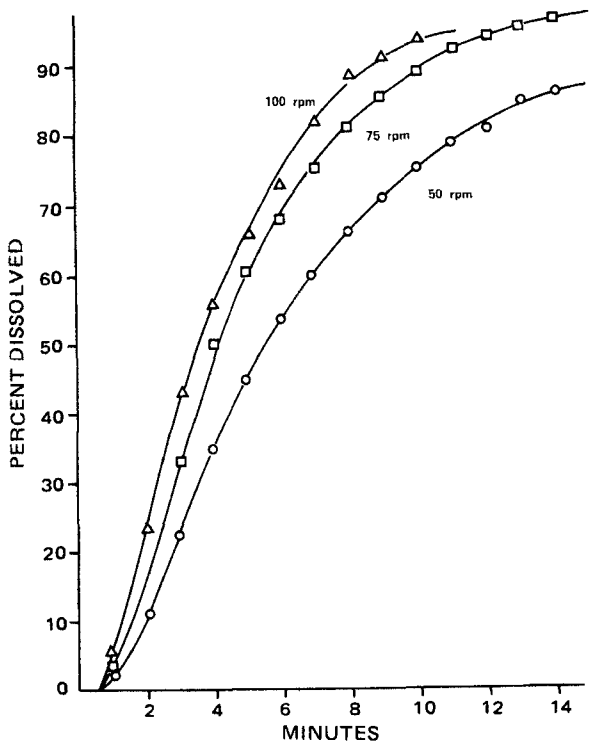

Figure 5—*Effect of stirring rate on the dissolution rate of 2.5-mg cloprednol tablets at a pump speed of 50 rpm and 37°.*

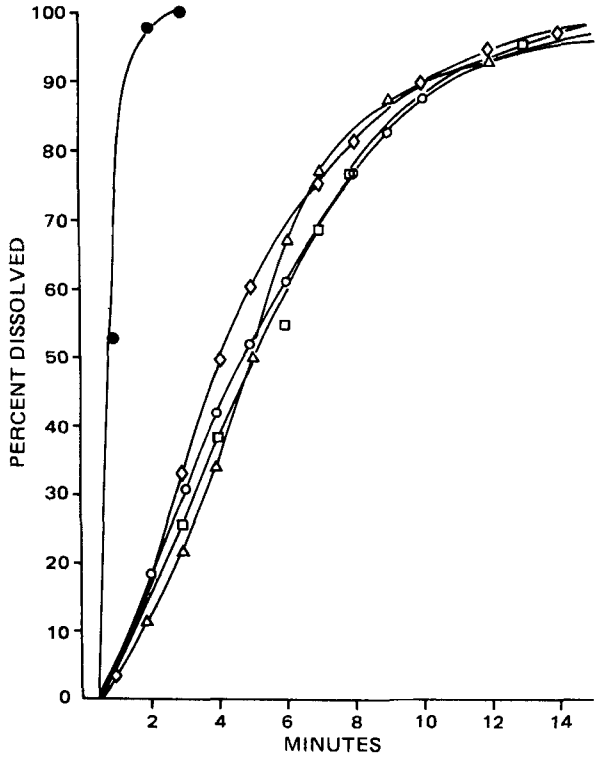

Figure 6—In vitro *dissolution of four representative 2.5-mg cloprednol tablet batches [Lots S (○), U (△), T (□), and W (◇)] and one experimental batch [Lot Z (●)]. The pump speed was 50 rpm, the propeller speed was 75 rpm, and the temperature was 37°. The automated dissolution apparatus with a coarse sintered-glass filter was used.*

rate of tablet lots and/or formulations may be observed that have no relevance to *in vivo* bioavailability or absorption rate.

Ideally, a stirring rate should be chosen to correlate with bioavailability. The choice of stirring rate was discussed previously (1); short of having a bioavailability correlation, the stirring rate should distinguish formulation differences and correspond to that reported in the pertinent literature. The stirring rate of 75 rpm in the studies on cloprednol tablet dissolution was chosen in that manner.

Dissolution Profiles of Representative Cloprednol Tablet Batches—The dissolution profiles of four representative batches (S, U, T, and W) of cloprednol tablets were determined (Fig. 6). The dissolution procedure was described previously. The tablet hardness values of these batches (Table II) were within the hardness specification for cloprednol tablets. As shown in Fig. 7, the dissolution profiles and the percent dissolved at 10 min were very similar.

Preliminary Examination of Effect of Cloprednol Particle Size on Tablet Dissolution—The dissolution results presented thus far have been for tablets prepared by a wet granulation process. The particle size of cloprednol for Batches S, U, T, and W was monitored, and most particles prior to granulation were 100–250 μm. The dissolution from tablets made with cloprednol of this particle size was rapid and complete, as discussed previously. It was judged important to determine whether a reduction in particle size of the cloprednol would further improve its dissolution from tablets.

Accordingly, micronized cloprednol (particle size ≤ 10 μm) was incorporated into a direct compression tablet formulation. The dissolution profile of this lot (Z) indicated improved dissolution characteristics (Fig. 6). Some improvement, besides greater surface area due to micronization, may result from: (*a*) softer tablets (Table II) or (*b*) the difference between the direct compression and granulation formulations. These possibilities are currently being explored. The importance of the increased tablet dissolution rate with the micronized material may be considered limited after study of the following results on bioavailability and dissolution.

***In Vitro* Dissolution Results from a Tablet Lot and Two Capsule Lots Used in a Bioavailability Study**—The *in vitro* dissolution of tablets may become a meaningful test upon establishing its relationship with bioavailability. During cloprednol tablet development, many dissolution profiles were obtained on formulation modifications, tablet hardness, *etc.*, some of which have been presented here. To provide a tablet lot for *in vivo* bioavailability testing, the following rationale was used.

The tablet formulation had certain ranges for the levels of excipients used, which allowed formula changes (within the designated range) during scale-up development. If the "poorest" formula was chosen, that being the one with excipients adjusted within their ranges to provide a tablet with a reduced dissolution rate, a base level could be established for a dissolution test, provided it exhibited satisfactory bioavailability. A tablet (C) such as this was manufactured and used in a bioavailability study. Also included were two capsule lots previously used in clinical studies and an oral solution.

The results of this study were reported previously (18) and indicated that the two capsules and tablet were equivalently bioavailable. The *in vitro* dissolution data obtained for these solid oral dosage forms are presented in Fig. 7. The difference between the two capsule formulations

Table I—Cloprednol Intrinsic Dissolution Results as a Measure of the Reproducibility of the Dissolution System

Minutes	Absorbance of Run[a]		
	a	*b*	*c*
14	0.033	0.032	0.034
26	0.062	0.059	0.062
38	0.086	0.082	0.084
50	0.110	0.104	0.106
62	0.132	0.126	0.128
74	0.148	0.144	0.144
Least-squares calculation for slope, absorbance unit/min	0.00192	0.00186	0.00183

[a] Calculated t values: *a versus b* = 0.505, *b versus c* = 0.313, and *a versus c* = 0.679; $t_{0.95}$ (df = 8) = 1.86.

Table II—Cloprednol Tablet Hardness and *In Vitro* Dissolution Data

Tablet Batch	Hardness (Strong–Cobb) ± *SD*	Percent Dissolved in 10 min ± *SD*
Z	6.22 ± 0.50	100.00 ± 0.00
S	7.57 ± 0.83	87.95 ± 8.90
U	9.11 ± 0.48	89.08 ± 4.30
T	9.09 ± 0.49	89.28 ± 4.07
W	9.62 ± 0.68	89.48 ± 5.09

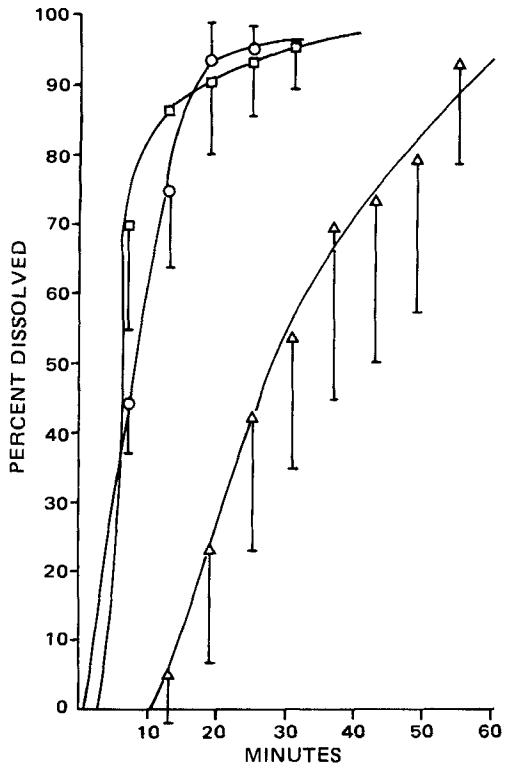

Figure 7—In vitro *dissolution of two 1.25-mg capsule lots [A (□) and B (△)] and one 2.50-mg tablet lot [C (○)], all shown to be bioequivalent and bioavailable. The pump speed was 50 rpm, the propeller speed was 75 rpm, and the temperature was 37°. The automated dissolution apparatus with a coarse sintered-glass filter was used.*

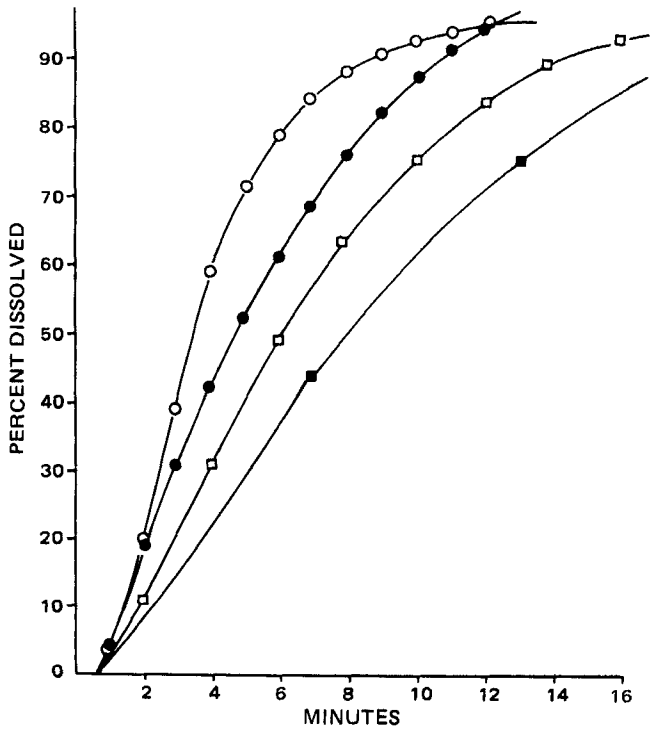

Figure 8—In vitro *dissolution of two formulations of cloprednol tablets comparing the USP basket and propeller method. Key: ○, Lot S, USP basket method, 50 rpm; ●, Lot S, propeller method, 75 rpm; □, Lot C, USP basket method, 50 rpm; and ■, Lot C, propeller method, 75 rpm. The pump speed was 50 rpm, and the temperature was 37°. The automated dissolution apparatus with a coarse sintered-glass filter was used.*

was that Tablet B, with the slower dissolution, contained lubricant (magnesium stearate) and Tablet A did not. These differences in dissolution were observed as a twofold difference in plasma levels at 0.25 hr in the bioavailability study (18). These differences were not significant and disappeared at 0.5 hr.

Therefore, for all subsequent tablet batches to be considered completely bioavailable, their *in vitro* dissolution rate must be comparable to or better than the *in vitro* dissolution rate of the tablets demonstrated to be bioavailable. The major risk of such a requirement is that the *in vitro* dissolution test may be too rigorous, since an *in vitro* dissolution profile has not been established for a cloprednol tablet that was poorly bioavailable.

Comparison to USP Basket Dissolution Procedure—One further measure of the discriminatory nature of this *in vitro* dissolution test is to compare it to the USP basket dissolution procedure. The USP requires dissolution testing of prednisolone and prednisone tablets, both steroids similar in their physical properties to cloprednol. The USP test for these two steroids designates a basket rotation of 100 rpm and 60% dissolution in 20 min.

With a rotation of 100 rpm, the cloprednol tablets dissolved extremely rapidly; therefore, the results reported (Fig. 8) are at 50 rpm. Even at this rate, the dissolution rates with the USP basket are faster than those observed with the propeller method. The cloprednol tablet dissolution results under these conditions were more than adequate to pass the USP requirements for the steroid tablets of prednisone and prednisolone, indicating that the propeller dissolution method has greater sensitivity than the USP basket dissolution test for prednisone and prednisolone tablets. As discussed previously, this result may indicate that the propeller dissolution method for cloprednol tablets can distinguish differences in tablet batches or formulation changes that are not distinguished *in vivo*.

This finding points to a particular difficulty in choosing an *in vitro* dissolution procedure that will show dissolution differences corresponding to differences *in vivo*. It is expected that the *in vitro* procedure will detect some dissolution differences not detected *in vivo*, as was adequately shown by Sullivan *et al.* (19). Obviously, a highly sensitive dissolution procedure provides a safety margin during the early product life of a new drug entity. The dissolution procedure may then be refined as more data become available.

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Iodipamide Kinetics: Capacity-Limited Biliary Excretion with Simultaneous Pseudo-First-Order Renal Excretion

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Abstract □ Iodipamide was infused into three dogs with bile fistulas to achieve various steady-state blood levels. When using ultracentrifugation techniques, iodipamide was found to be highly bound to plasma protein. The total blood clearance was low relative to hepatic blood flow. For either the whole blood concentration or the unbound concentration of iodipamide, the biliary excretion was shown to be capacity limited with a transport maximum, T_m, of approximately 1.0 μmole/kg/min. The steady-state renal excretion rate, plotted against the whole blood concentration of iodipamide, resulted in a concave ascending curve, which could lead to the false conclusion that iodipamide was undergoing active renal tubular reabsorption. However, when corrected for plasma protein binding, a linear relationship was obtained, suggesting that the renal excretion of iodipamide is a pseudo-first-order process. The Michaelis–Menten parameters for the extrarenal elimination, when calculated using the whole blood concentration of iodipamide, led to a similar discrepancy compared to the parameter estimates obtained from biliary excretion rate data. This discrepancy can be eliminated when one uses the unbound concentration of iodipamide in the parameter estimates.

Keyphrases □ Iodipamide—capacity-limited excretion kinetics, dogs □ Excretion kinetics, capacity limited—iodipamide in dogs □ Pharmacokinetics—excretion of iodipamide in dogs □ Radiopaque media—iodipamide, capacity-limited excretion kinetics, dogs

Iodipamide, 3,3′-(adipoyldiimino)bis[2,4,6-triiodobenzoic acid], is the most commonly used intravenous cholangiographic agent in the United States. Clinically, a dose of 166 or 233 mg/kg is recommended for intravenous administration over 3–10 min or the same dose is administered by a slow infusion over 2 hr (1). Nausea, vomiting, hypotension, and occasional kidney damage have been reported with these administration methods. Conflicting opinions exist concerning the appropriate dose and administration route of iodipamide to produce maximal radiological opacification of the biliary tree (1–3) with negligible side effects.

Following intravenous administration, iodipamide is taken up by the liver and excreted unchanged into the bile. Biliary excretion was demonstrated to be capacity limited with a transport maximum, T_m (4, 5). Therefore, plasma levels in excess of those necessary to saturate the biliary excretion offer little or no advantages in opacification of the biliary tree. Increased doses lead to increased drug concentrations in other body organs and add stress on the kidney excretory process. Iodipamide exists in the blood as the unchanged drug and is excreted unchanged in the urine. The percentage of the dose excreted in the urine increases with an increasing dose (6). Therefore, iodipamide offers a good opportunity to investigate the capacity-limited hepatic uptake or biliary excretion in the presence of renal excretion.

A steady-state approach was utilized in the pharmacokinetic studies of iodipamide in dogs to gain a better understanding of the capacity-limited hepatic elimination with simultaneous renal excretion. It is hoped that through this understanding, an optimal dosage and route of administration can be developed to provide maximal visualization of the biliary tree and the least toxic effects.

THEORETICAL

When a drug is infused into the animal for a sufficiently long time to establish steady-state blood concentration, the elimination rate by all routes should equal the infusion rate. For a drug such as iodipamide, which is eliminated by the kidney and other organs, the elimination rate from the blood is the sum of renal excretion and extrarenal elimination. Therefore, if the renal excretion rate at steady state is determined, the difference between the infusion rate and the steady-state renal excretion should equal the extrarenal elimination rate; *i.e.*:

$$R' = R^0 - \frac{dAu}{dt} \qquad \text{(Eq. 1)}$$

where R^0 is the zero-order infusion rate, R' is the steady-state extrarenal elimination rate, and dAu/dt is the steady-state renal excretion rate.

If one assumes that the extrarenal elimination is capacity limited, it can be described by the Michaelis–Menten equation:

$$R' = \frac{V_m C_{ss}}{K_m + C_{ss}} \qquad \text{(Eq. 2)}$$

where V_m is the maximal rate of extrarenal elimination and K_m is the apparent Michaelis–Menten constant. For a drug that has high blood clearance, C_{ss} will be the whole blood concentration at a steady state; for a drug with low clearance, C_{ss} should be referred to the unbound concentration. If the unbound drug concentration shows a constant proportionality to the whole blood concentration, the use of the steady-state whole blood concentration should theoretically yield the same value of V_m and an apparent value of K_m as when the unbound concentration is used. However, this is not the case with iodipamide, which has a relatively low clearance, probably because the unbound fraction varies with concentration.

The term V_m is used to denote the maximal rate of capacity-limited extrarenal elimination, as defined in Eq. 2, and T_m is used to denote the maximal rate of capacity-limited biliary excretion since it is not known whether these two referred to the same or different capacity-limited