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DISSOLUTION RATE TESTING WITH THE COLUMN METHOD: METHODOLOGY AND RESULTS

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ABSTRACT

A detailed description of a column (flow-through) type dissolution apparatus is given, including features of automated sampling, assay, and computerized data processing. Standardized testing parameters are presented which permit reproducible performance in different laboratories, under conditions close to those of physiological dissolution and absorption. Without major modifications the same apparatus can be used for various dosage forms such as powders, granules, tablets, coated tablets, and capsules. Examples are given which demonstrate reproducibility as well as correlation with *in-vivo* data. It is suggested that this methodological approach be regarded as a promising alternative to the present official methods.

INTRODUCTION

Dissolution rate testing has become a research tool as well as a pre-requisite for registration and quality control of oral dosage forms. At present, the United States Pharmacopeia requires

a dissolution rate test for a dozen official products using the *rotating-basket* method (1). The U. S. National Formulary has similar requirements but allows the use of the *disintegration tester* for this purpose (2), in addition to the *rotating bottle* for timed-release tablets and capsules (3). The British Pharmacopeia adopted a dissolution rate test for digoxin tablets, also requiring the rotating basket. To our knowledge the *beaker method* according to Levy was favoured at some time for the European Pharmacopeia. Registration authorities in several countries (e.g. USA, Australia, Canada, New Zealand, Scandinavian countries) tend to request dissolution data not only for slow- or controlled-release products but also for new 'normal' formulations. As a milestone in the history of dissolution testing, the USP Revision Committee in early 1976 adopted a policy statement (4) which 'favors the inclusion, during the 1975-1980 revision period, of a *Dissolution* test in the monographs for all official oral solid dosage forms except where such inclusion is judged inappropriate'.

The *column method*, although in some reviews (5, 6) judged as 'the superior test method for the future', has thus far not found much support in quality control laboratories and official agencies*. In our company it is in permanent use for ten years: much experience has been accumulated, automation has been achieved, and many examples of correlation with *in-vivo* data have been found. It is the purpose of this paper to present a detailed description of the column method and to communicate some of our results as a contribution to the present discussion on dissolution rate tests.

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* Only recently we discovered some documents which indicate that about 20 years ago the column method was favoured by the FDA and also considered by USP, for the release from timed-release preparations: a letter dated Aug. 23, 1957, from E.B. Vliet to the members of a Subcommittee on Tablets and a paper by D. J. Campbell and J. G. Theivagt in Drug Standards, 26, 73 (1958).

METHODOLOGY

The column method has been described by various authors since about 1967, sometimes under synonyms such as *flow-cell, flow-through,* or *continuous-flow* (7 to 26). Its fundamental characteristics are summarized in Fig. 1. Typically, the test specimen is positioned within a vertical cylindrical cell of small dimension and hold-up volume V_h, but conical cells are used as a meaningful alternative (12, 23, 24, 25). The specimen is exposed to a permanent flow Q of solvent. Because of the small volume and the relatively large flow rate, residence time $t_h = V_h/Q$ of the liquid in the cell is short, usually in the order of magnitude of one minute. Since the linear flow velocity as defined from the ratio (flow rate / cross section) is assumed to present a realistic model of the agitation *in vivo*, no additional source of agitation is employed in the typical design. The addition of a stirrer in the cell, as in (24), certainly increases method flexibility but also the complexity of the design by adding another moving part which requires constant control. Usually fresh solvent is passed through the cell, hence the concentration c_e in the cell or in the eluate represents the *differential amount* dissolved per time unit, from which the *cumulative amount* is obtained by integration over time t.

On the other hand the stirred-vessel design is characterized as follows: large volume of the dissolution vessel; minimum liquid exchange (only for assay purposes); almost infinitely large residence time; agitation by means of stirrers, rotating baskets, spinning filters, or other rocking or shaking devices; finally direct correspondence between concentration c_e and cumulative amount dissolved, $m(t)$.

Designs intermediate between column and stirred vessel are used by some authors. On the one hand the column may be modified

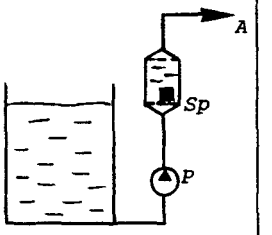
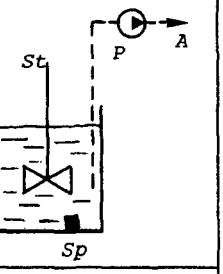
	COLUMN	STIRRED VESSEL
A to assay *P* pump *Sp* specimen *St* stirrer		
Vessel holdup volume, V_h	10...30 ml	300...1000 ml
Flow rate, Q	10...100 ml/min	0...1 ml/min
Residence time, V_h/Q	approx. 1 min	100...oo min
Solvent amount	unlimited	250...1000 ml
Agitation	linear velocity determined by flow (5...20 cm/min)	determined by stirrer or other rotating or shaking device
Sink limitations	dynamically by flow rate	statically by total volume
Time profile of solute concentration, $c_e(t)$	differential $c_e(t) = (dm/dt)/Q$	cumulative $c_e(t) = m/V_h$

FIGURE 1

Schematic Comparison of Column and Stirred-Vessel Dissolution Systems.
Values given are typical but can vary in different set-ups; intermediate designs are possible.

to have a larger volume approaching a stirred vessel in size (12). On the other hand any stirred vessel can be modified in such a way that its content is continuously replaced in order to approach sink conditions (27, 28, 29). These intermediates however, suffer from complex hydrodynamics; also the concentration time profile represents neither the differential nor the cumulative dissolution

kinetics, and cumbersome corrections are required to arrive at the desired dissolution curve (18, 29).

As a useful extension of the column method a *fixed volume of fluid* can be re-cycled through the cell rather than fresh solvent from an 'infinite' reservoir (9, 10, 12, 14, 17, 21). This closed-system mode may be preferred either to increase analytical sensitivity or to save solvent in long test runs. It will not affect the dissolution kinetics as long as sink conditions prevail throughout the test. Note that in this mode the column method is kinetically equivalent to a stirred-vessel system with a peculiar type of 'stirrer'.

Dissolution Apparatus DISOTEST

The column apparatus as used in our laboratories[1] is shown in Fig. 2. It consists of a constant-temperature bath of approx. five liters content, equipped with electronic temperature control, circulation pump, and up to six dissolution units assembled next to each other on top of the bath. The units can be operated individually. Figure 3 illustrates the design of each unit.

The pumped liquid enters through a stainless-steel coil submerged in the bath, *8*, where it is pre-heated to the desired temperature. The standard *dissolution cell*, *2*, is made from acryl glass and consists of a conical bottom and an upper cylindrical body. Filling-up the cone with 1-mm-diam. glass beads provides a cylindrical chamber with defined geometry and equally distributed flow entrance throughout the cross section. When omitting the glass beads the design offers an empty cone with small entrance bore, with more turbulent conditions of flow. As a third alternative a thin metal wire hook is attached to the filter head, which extends into the center of the cell lumen.

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[1] DISOTEST, Sotax AG, 4008 Basel, Switzerland

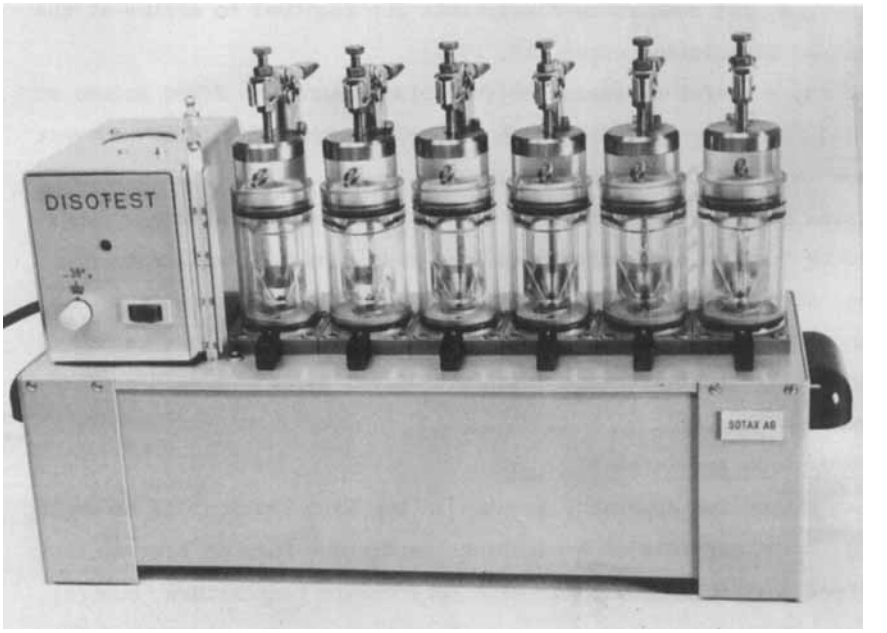


FIGURE 2

Photograph of the Six-Channel Dissolution Apparatus DISOTEST, with Water Bath and Temperature Control

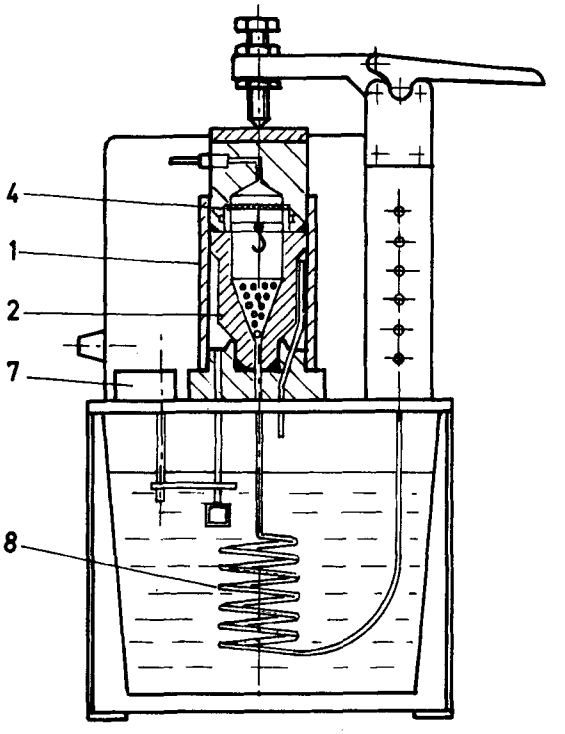
The *filter head, 4,* for the continuous eluate filtration is a standard multilayer assembly with the following components (in the direction of flow):

- coarse stainless steel wire gauze with 0.4 mm free opening
- fine stainless steel wire gauze with 0.07 mm free opening
- filtering aid, e.g. loosely stuffed asbestos[2]
- one or two disk membrane filters, e.g.[3]

The disk filter is put into the filter head just against the supporting plate, *4*. The PTFE basket with the wire gauzes is

[2] Article no. 1560, D. Merck, Darmstadt, West Germany

[3] Glass-fibre membrane filter, type 13400, Sartorius GmbH, Göttingen, West Germany



Disotest

Size: 500 mm wide
× 160 mm deep
× 300 mm high

Weight: approx. 10 kg

Cell

Diameter: 22.6 mm

Cyl. height: 30 mm

Inlet bore: 0.8 mm

Cone angle: 40°

FIGURE 3

Cross-Sectional Side View of the Dissolution Unit, Drawn to Scale. For explanation and numbering see text.

stuffed with asbestos and pressed into the head. The prepared cell (with specimen and -if required- glass beads) and the filter head are then assembled into the jacket tube, *1*, and clamped together. Sealing is achieved by O-rings. The jacket is connected to the water bath by means of the switch, *7*. Since cell and jacket are transparent, observation of disintegration and dissolution is always possible.

A heavy-duty *volumetric piston pump*[4] is used to maintain the pre-set flow rate independent of the flow resistance in the cell

[4] Model HK, Lewa, 725 Leonberg, West Germany. Pumping heads are manufactured by Sotax AG, 4008 Basel, Switzerland

and the filter. Up to six pump heads are flanged onto the common drive unit. The resulting flow pulsates with a profile typical for a rocker-arm plunger pump. The average flow rate is defined from the number of strokes (in our case 130 per minute) and the stroke amplitude which can be varied between zero and 15 mm. Connecting tubes between pump and dissolution unit are from PTFE with 0.12" inner diameter, with standard 1/4"-28 flange tube-end fittings[5]. Connections are short and sufficiently stiff so that the original pulsation of the pump is not attenuated.

Experimental Conditions

Positioning of the Specimen - Usually one single specimen is tested per cell to obtain a maximum of information on the release uniformity. More than one are taken if needed for increased assay sensitivity or more representative sampling. However, one cannot compare directly results obtained with differing number of units. Typically, a *tablet* is placed on top of the bed of glass beads which just fill the entrance cone *(laminar conditions)*. In certain cases it was found more appropriate to omit the glass beads and to place the specimen directly into the jet of fluid entering the empty cone *(turbulent conditions)*. In special cases such as inlay tablets or those with non-dissolving coating it is desired that the specimen is exposed to the fluid from all sides: it is then suspended on the hook attached to the filter head, just in the center of the cylindrical cell.

Capsules first tend to float under the filter and then drop after complete wetting, opening, and escape of the enclosed air. Reproducibility is improved if the capsule is loosely stuffed into the glass beads in an upright position. Even in this way it first will float to the top but is more uniformly wetted by the ascending liquid. A special technique is required for *drug powders*. To achieve complete wetting and reproducible results the material is

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[5] System CHEMINERT, Chromatronix Inc., Berkeley, Calif., USA

first thoroughly mixed with lactose and then with asbestos; the mixture is then stuffed loosely into the cell between two layers of glass beads.

Test Fluids - The test is usually performed at 37°C with simulated gastric or intestinal fluid of pH 1.3 and 7.5, respectively. Enzymes are omitted for reasons of analytical ease, but sodium laurylsulfate or polysorbate 20 are added sometimes in concentrations of 0.1 to 0.2 percent, in order to model the lowered surface tension in the physiological environment. Unbuffered water is avoided because of the resulting undefined pH conditions. Mixed organic-aqueous media are not used because of their unphysiologic character. Normally the test is started with simulated gastric fluid and, if the dissolution is not essentially completed after 1 to 2 hours, the medium is changed from gastric to intestinal pH. This change is routinely done for slow-release or enteric-coated forms.

Flow Conditions - The pump design enables the flow rate to be set continuously from 0 to 100 ml/min. We use 16 and 50 ml/min as standard test conditions. The flow is pulsating with 130 strokes per minute. In the *open-system mode* which is used most frequently, fresh solvent is pumped from a large reservoir through the cell and the eluate is discarded after assay. In the *closed-system mode* pump inlet and cell outlet are connected to a stirred flask which contains the fixed volume ranging from 250 to 1000 ml.

Assay and Data Processing

Whenever possible the eluate concentration, c_e, of dissolved drug is determined by direct UV/VIS assay in order to keep the expenditure at a reasonable level. Depending on the assay method and previous knowledge of the time profile of dissolution the eluate is analyzed either *off line*, i.e. after completion of the test, or *on line* during collection of the next fraction.

In *off-line mode* the eluate or an aliquote fraction is continuously collected into a *fraction collector*[6]. Sampling intervals are usually in a progressive series such as 1, 2, 3, 6, 9, 12, 18, 24, and 30 minutes or a multiple thereof. This is to gain maximum information from the limited number of sampling points. For routine control purposes special schedules can be programmed, e.g. 1, 2, 3, 5, and 7 hours with pH change after the first hour (for slow-release forms).

The experimental set-up for the *on-line mode* of sampling, assay, and data processing is similar to the 'computerized automated system' described recently by Cioffi *et al.* (28). Although primarily conceived for UV/VIS assay it is capable of dealing with all other automated procedures which can be handled by Auto Analyzer systems. The following description and the flow diagram in Fig. 4 applies to a six-channel unit.

Feed of Solvent - The fluids (gastric, intestinal, or special buffers) are prepared in large plastic containers of approx. 60 liters content. As required, they are manually transferred into 20-liter glass flasks, *1*, by vacuum suction and through sinter-glass filters which retain any solid impurities and de-gas the liquid. The flasks are connected to the pump, *4*, by pneumatical *3-way valves*[6], *2*, which allow programmed pH changes during the test. Air accidentally entrapped in the tubing is removed through *air escapes, 3,* in order to ensure good performance of the pump and to avoid wetting problems of the specimen. Two groups of three channels each can be operated simultaneously with different media.

On-Line Sampling - The eluate of the dissolution cells is continuously collected into a battery of six *collecting vessels, 8,* with a capacity of approx. 50 ml. The *by-pass, 6,* together with the 25-channel peristaltic *proportioning pump*[7], *7,* allows sampling

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[6] Designed in this laboratory and available from Sotax AG, Basel, Switzerland

[7] Model MP-25-GJ4, Ismatec SA, Zürich, Switzerland

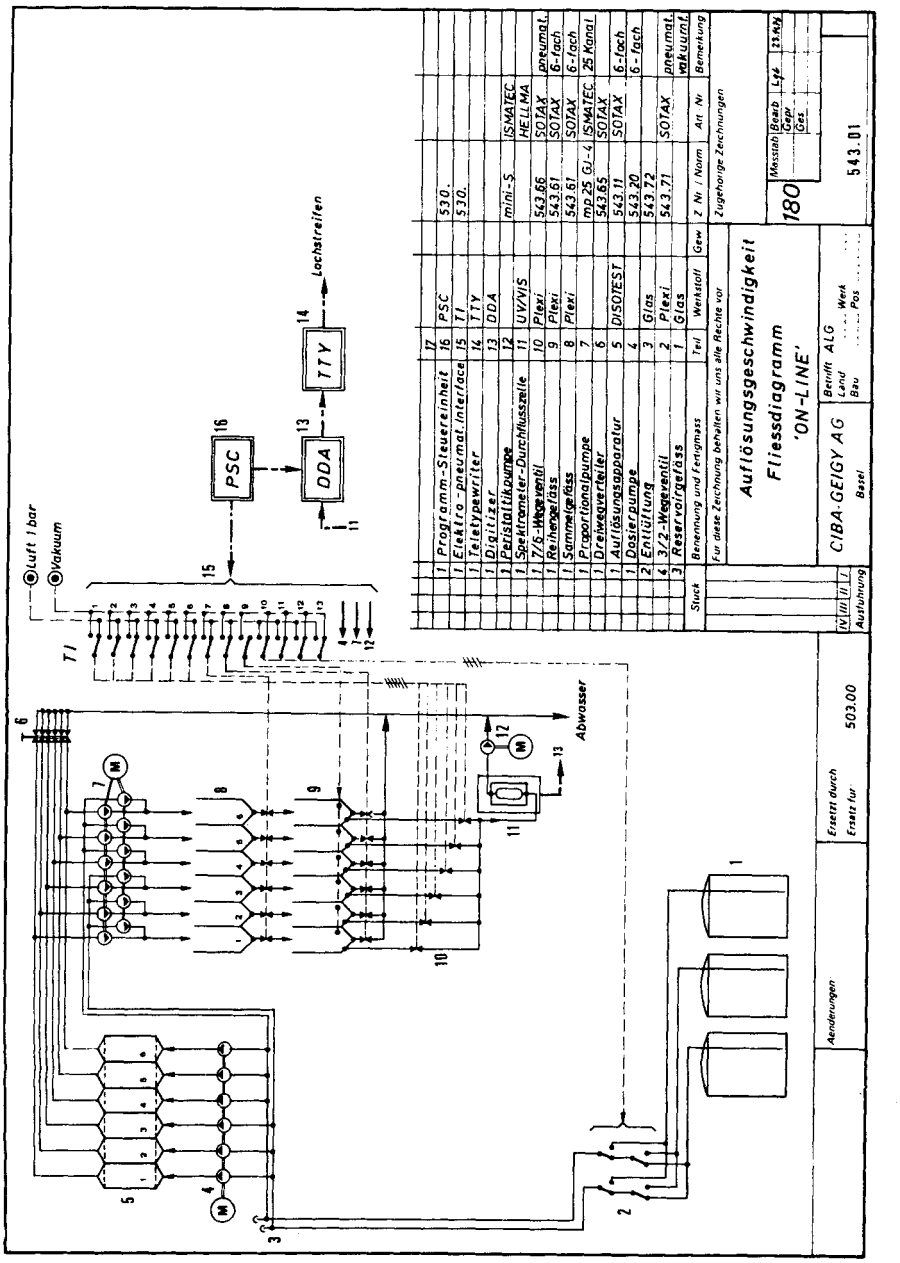

FIGURE 4 - Flow Diagram of the Automated On-line Set-up for Direct UV Assay.

of any aliquote and/or proportional addition of diluent or reagent. At each sampling time a subroutine cycle is started with up to eight steps of equal length (usually 20 seconds):

- During *step I* the content of all collecting vessels is allowed to flow into six corresponding *serial vessels*[6], *9*. Air is bubbled through the serial vessels to ensure complete mixing.

- In *steps II - VII* the outlet of the collecting vessels is shut and each of the serial vessels is sequentially connected with the single micro flow cell[8], *11*, of the spectrophotometer[9]. Switching is done by a pneumatically actuated *7/6-way valve*[6], *10*, with small hold-up volume. The *sampling pump*[10], *12*, is located after the flow cell; connections between the serial vessels and the spectrophotometer are as short as possible and made from small-size (0.023" i.d.) PTFE tubing with CHEMINERT fittings; reading is done just in the moment of switching from one channel to the next. By these measures complete replacement of the liquid in the common line is achieved within the shortest time possible.

- The final *step VIII* immediately follows the last sampling step (no. VII in case of six channels). In this step the contents of all serial vessels are discarded simultaneously by gravity discharge. In addition, this step may be used to re-adjust the spectrometer or to run a standard solution.

Sequence Control - The entire sampling program for on-line and off-line operation is controlled by a specially designed *Programmable Sequence Control (PSC)* unit developed in this laboratory. The unit consists of logical circuits in TTL technique, with basic time derived from a 1 Hz digital clock. The actual number of channels (1 through 6), the sampling time module, the total number

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8 Flow cell with either 2 or 10 mm optical path and approx. 0.4 and 1 ml hold-up volume; Hellma, 7840 Müllheim, West Germany

9 UV/VIS spectrophotometer, mod. 139, Perkin-Elmer, Norwalk, Con., USA

10 Peristaltic pump, mod. mini-S, Ismatec SA, Zürich, Switzerland

of fractions to be sampled, and the time module for assay subroutines (I through VIII) is selected by multiswitches on the front pannel. Three groups each with 30 binary switches are available for programming the sampling sequence together with changes of the test fluids for two independent groups (1...3 and 4...6). The PSC unit also allows for correcting of the time delay of approx. one minute between the start of pumping or fluid change and the point when the eluate reaches the collecting vessel.

The progress of the program is displayed by diode pilot lamps and 7-segment displays indicating the time elapsed. Output signals for the various automated units are transmitted by periphery drivers and reed relais to a separate *technological interface (TI)* which contains all electro-pneumatical valves for operating the membrane valves in the liquid line, either by vacuum (open) or 1-bar pressurized air (closed). This unit also contains the remote-control switches for actuation of the various pumps. Another direct line connects the PSC unit with the DDA unit, for transmission of the printing commands (either elapsed time or absorbance readings) together with the formating instruction.

Data Processing - Absorbance readings are digitized by a *digital data acquisition (DDA)* module[11] and punched onto paper tape *via* teletypewriter *(TTY)*[12], together with the manually entered headline information and testing parameters. After completion of the test run the raw data are spooled to the central computer system *via* another teletype terminal[13]. The computerized calculations involve the following steps[14]:

First, the absorbance readings are converted to eluate concentrations, c_e, by means of standard absorptivities and adjust-

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11 Modified model CRS-30, Infotronics Ltd., Shannon, Ireland

12 Teletype model ASR 33, Teletype Corp., Skokie, Ill., USA

13 System OS/370-168, IBM; with time sharing option TSO

14 Fortran program FPDISSOL, developed in this laboratory

ment for any dilution. The concentration of the i-th fraction is converted to the differential amount dissolved during that time, by multiplying it with the corresponding fraction volume, V_i, or the product of flow rate Q and time interval Δt_i:

$$dm_i = c_{e,i} \cdot V_i = c_{e,i} \cdot Q \cdot \Delta t_i$$

with convenient units, e.g.

$$(mg) = (mg/ml) \cdot (ml) = (mg/ml) \cdot (ml/min) \cdot (min)$$

The cumulative amount dissolved at time t_i is obtained by successive summation

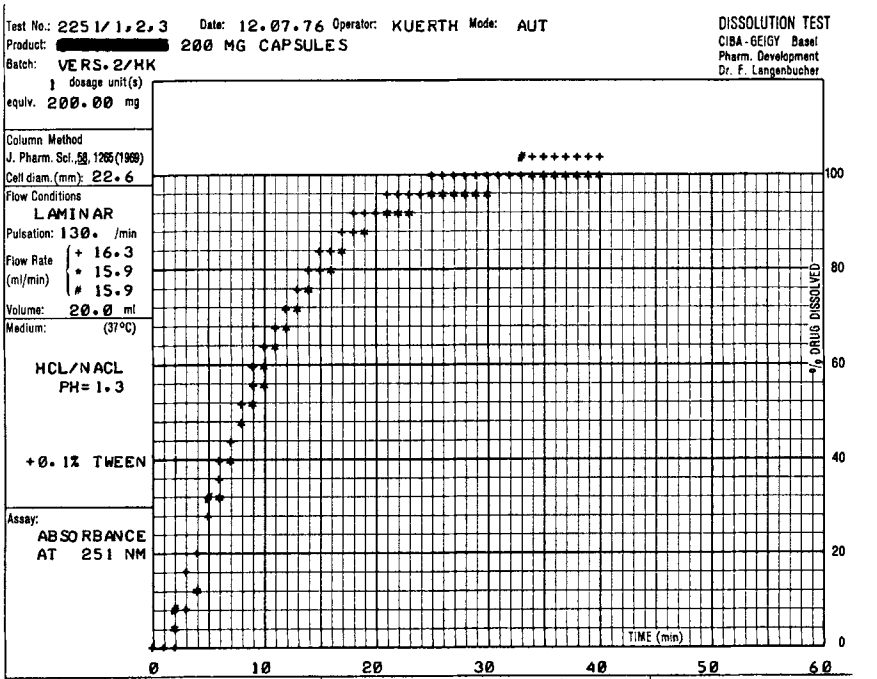
$$m_i = m_{i-1} + dm_i$$

Finally, all m_i are converted to fractions of the nominal dose by calculating $F_i = m_i/m_o$, the time profile of which represents the desired cumulative dissolution curve $F(t)$.

RESULTS AND DISCUSSION

The examples given below are taken from test results accumulated over the last years in our laboratory. In general, the data have been obtained from experimental forms differing either in their formula or manufacturing procedure so that any inference to existing or marketed products from CIBA-GEIGY would be unjustified. The selection has been made with the objective to present a realistic picture of the test performance.

Figure 5 shows a typical test report as printed by the computer on a standard form. Up to three replicates are given on a single page; note that as soon as data points coincide in the printplot, only one symbol is printed in that particular field. Product identification and testing conditions are listed on the top and on the left margin. For comprehensive characterization of the curves, the printout gives the typical dissolution times $t(20\%)$, $t(50\%)$, and $t(80\%)$ as well as the fitted RRSBW parameters t_ϕ, F_∞, t_d, β, and the corresponding residual standard deviation,



Parameters	N	t(20%)	t(50%)	t(80%)	t_0	F_∞	τ_d	β	s
1 (+)	54	3.8	7.6	14.2	0.7	103.1	9.8	1.27	1.1
2 (•)	54	4.3	8.2	15.2	0.6	100.5	10.3	1.31	1.3
3 (#)	54	3.5	7.7	14.5	1.0	103.1	9.5	1.19	0.7
	Mean:	3.9	7.8	14.6	0.8	102.2	9.8	1.26	1.0

Observed Points (t[min], F[%]):

t(min)												
	0.0	0.8	1.5	2.3	3.0	3.8	4.5	5.3	6.0	6.8	7.5	8.3
F %	+ 0.1	0.1	1.5	6.3	14.1	21.9	28.2	34.8	40.6	45.8	51.1	55.6
	• 0.1	0.3	3.5	8.0	13.1	19.3	26.8	33.6	38.7	44.0	49.0	53.7
	# 0.1	0.6	6.7	14.9	21.9	27.8	33.4	38.9	44.0	48.7	53.2	57.1
	9.0	9.8	10.5	11.3	12.0	12.8	13.5	14.3	15.0	15.8	16.5	17.3
	59.5	63.4	66.8	70.1	73.1	76.0	78.6	81.2	83.4	85.4	87.3	89.0
	57.6	61.4	65.0	68.3	71.3	74.0	76.5	78.9	80.9	82.9	84.7	86.2
	60.7	64.1	67.4	70.7	73.7	76.4	79.1	81.5	83.7	85.8	87.6	89.1
	18.0	18.8	19.5	20.3	21.0	21.8	22.5	23.3	24.0	24.8	25.5	26.3
	90.5	91.9	93.1	94.2	95.0	95.9	96.6	97.3	98.0	98.5	99.0	99.5
	87.7	89.1	90.4	91.3	92.1	92.9	93.6	94.3	94.9	95.5	96.0	96.4
	90.7	92.0	93.3	94.3	95.2	96.1	96.9	97.6	98.2	98.7	99.3	99.7
	27.0	27.8	28.5	29.3	30.0	30.8	31.5	32.3	33.0	33.8	34.5	35.3
	99.8	100.2	100.5	100.8	101.0	101.3	101.5	101.7	101.9	102.0	102.1	102.3
	96.8	97.2	97.5	97.8	98.1	98.3	98.5	98.7	98.9	99.1	99.2	99.4
	100.1	100.4	100.7	101.1	101.3	101.6	101.8	102.0	102.2	102.3	102.5	102.6
	36.0	36.8	37.5	38.3	39.0	39.8						
	102.3	102.5	102.6	102.7	102.7	102.8						
	99.5	99.6	99.7	99.8	99.9	99.9						
	102.8	102.9	103.0	103.1	103.2	103.2						

FIGURE 5

Typical Dissolution Test Report, Obtained as Computer Printplot on Standard Form.

s. The practical information contained in these parameters is discussed elsewhere (30); it should only be mentioned that the dissolution time t_d is the most informative parameter for the overall *rate* of dissolution whereas the end plateau F_∞ is a reliable check of all *quantitative* aspects such as content, amount released, flow rate, and absorptivity.

Adequate pumping and filtration is a pre-requisite for the *column* method since relatively large volumes have to be processed continuously. Flow rate and profile have to stay very close to the pre-set values since they essentially determine the degree of agitation in the system and, hence, the kinetics of disintegration and dissolution. The volumetric flow, in addition, defines the actual volume of each collected fraction which enters the calculation of the amount dissolved: unless this parameter is known accurately, each fraction has to be checked individually and aliquote sampling is almost impossible. The *filtering assembly* as described is of universal applicability, low in cost and easy to handle. This applies even to high flow rates (several liters per hour) and is also true for forms which are known for filtration problems (e.g. gelatine capsules). A pressure build-up of 2 to 3 bar in the system must be tolerated and the *pump* must be chosen such as to maintain the specified flow in spite of the varying pressure. Peristaltic or centrifugal pumps are inappropriate and a heavy-duty volumetric design is required: the one used at present is satisfactory in general, but suffers from corrosion problems[15].

At any instant the specimen is exposed to only a small *liquid volume*, within the cell. However the drug solution is continuously replaced by fresh solvent and the 'sink condition' is maintained without need for mixed organic media, absorbents, or dialysis systems. This *in-vitro* solute removal sufficiently models the *in-*

[15] An improved design is currently under construction which solves this problem, is more reliable, less expensive, and offers a standardized sinusoidal drive. It will be manufactured by Sotax AG, Basel, under the designation of DISOPUMP.

vivo removal by absorption. The solvent consumption of, e.g., one liter per hour is not unrealistic if one considers the quantity of physiological daily G.I. secretion and water re-absorption (31). The closed-system mode offers an alternative whenever assay sensitivity is low or the liquid consumption in long test runs is considered too high; it is important, however, that sink conditions are warranted also in this mode.

The *parallel-to-series conversion* achieved by means of the collecting and serial vessels in connection with the 7/6-way valve makes it possible to use only one single spectrophotometer flow cell without the need for any 'multiple cell positioning attachments'. Readings for all six channels are synchronized for one common starting time, and no delayed start is required as, e.g., in (28). Furthermore the averaged content of the serial vessels represents exactly the drug amount dissolved during that sampling interval; momentary random fluctuations which are typical for small-volume flow systems are automatically leveled, and repetitive readings are unnecessary.

Method *reproducibility* may be seen from the oxprenolol data shown in Table 1. Three replicates are given for each of eight batches, obtained in two laboratories A and B with different test units and different operators. From the ranges within the replicates, a joint standard deviation of approx. 3 percent is estimated for the single F values[16], independent of sampling time and laboratory. Differences between the two laboratories are random and not larger than expected from the variability between replicates. Where the final plateau, F_∞, was determined, its value is consistent with the average content found independently from a

[16] In an earlier comparative study (32), the coefficient of variation for the column method was reported as between 15 and 20 percent. This larger variability may be assigned to the larger material inhomogeneity. Unfortunately enough, no real standard substance is known for method assessment.

TABLE 1

Dissolution Rate Data from Eight Different Batches of Experimental Oxprenolol Slow-Release Tablets; Percent Dissolved at 60, 120, 240, and 480 minutes, as Obtained in Laboratories A and B

Test no.(A)	*F(60)* A	B	*F(120)* A	B	*F(240)* A	B	*F(480)* A	B	F_∞ A	Content B
1957/4	27.0	29	43.2	44	63.3	65	89.2	89	103.7	102.6
/5	32.3	28	49.3	43	70.8	62	95.7	86	106.2	
/6	28.6	29	45.5	45	67.1	65	92.4	90	104.9	
1965/4	28.6	29	45.6	45	66.5	69	91.7	89	103.9	102.0
/5	28.8	28	45.5	45	67.3	65	92.5	89	103.0	
/6	32.0	30	48.7	45	71.1	63	94.9	87	103.4	
1974/1	24.8	32	40.1	48	58.6	68	82.3	91	96.0	102.0
/2	30.9	33	48.7	50	68.8	67	92.3	93	103.2	
/3	31.5	32	49.3	48	70.9	70	94.4	88	105.1	
1974/4	29.5	30	46.9	45	68.0	65	91.3	87	103.0	102.1
/5	29.7	27	46.7	42	67.1	68	90.8	84	103.0	
/6	34.5	32	53.0	48	75.8	61	99.1	90	107.9	
1977/1	34.9	37	52.1	52	74.5	76	94.9	94	102.7	101.8
/2	31.9	31	49.8	47	71.5	69	93.0	93	102.9	
/3	32.8	36	50.6	53	72.3	74	95.1	96	104.8	
1977/4	29.8	32	47.9	49	69.0	70	92.0	91	102.1	102.9
/5	30.3	32	48.3	49	69.7	70	92.1	93	-	
/6	31.6	31	50.6	47	72.7	67	95.1	89	104.9	
1985/1	32.4	33	48.1	50	70.8	73	93.2	91	106.1	101.8
/2	33.2	27	49.6	45	72.0	64	94.5	93	-	
/3	32.2	32	48.6	49	71.2	71	93.8	89	-	
1985/4	31.3	32	47.7	47	69.3	67	92.9	90	104.2	102.6
/5	24.7	30	40.0	45	60.1	70	85.7	92	-	
/6	32.3	34	48.3	52	69.5	66	92.4	90	-	

Flow rate: laminar at 16 ml/min
Solvent: pH 1.3 for 60 min, thereafter pH 7.5 buffer
Mode: off-line without recycling
In A, residual cell content after 480 min was determined separately and added to *F(480)* to give F_∞; this is compared to the actual content from a sample of 20 tablets.

pooled sample of 20 tablets. Note however, that the estimated variability is not an absolute value since it is highly dependent on the test material and also includes the inhomogeneity of the submitted batches.

The ultimate criterion for dissolution rate testing as such and for any method in particular is its ability to reflect (and predict) *in-vivo* behavior during the invasion period of a drug, after oral application of the drug form (33). Figure 6 compiles a few examples of qualitative correlations observed between dissolution *in vitro* and plasma concentrations *in vivo*. Each point in the graphs represents a separate experimental formulation which is characterized by the dissolution time, t_d, and the observed parameters of the plasma concentration maximum, t_{max} and c_{max} resp. t_d is the average value of three single determinations; t_{max} and c_{max} are the mean values of, in general, six healthy human subjects.

Aside from the two outlying data points in the clomipramine and the oxprenolol graph (which were caused by an atypically long absorption period and a long concentration plateau value, resp.), the results demonstrate a direct relationship between t_d and t_{max} and an inverse relationship between t_d and c_{max}. This is as to be expected in view of the laws governing simple pharmacokinetic models. A quantitative correlation would have to comprise a thorough discussion of the particular drug kinetics (solubility in the gastro-intestinal pH range, water-lipid partition, absorbability throughout the G.I. tract, etc.). Such a discussion is beyond the scope of this communication and will be reported later.

CONCLUDING REMARKS

The realm of this paper is not strictly scientific because we have not communicated new findings in the field of dissolution-rate research, nor were we able to demonstrate that 'our method shows good correlation with every product' (33). Nevertheless we

would like to comment on a few merits of our methodological approach, from the point of view of a suitable test for drug development and quality control.

Firstly, the column or flow-through system meets the primary requirement that it 'be experimentally sound (i.e. that it does not involve any avoidable and controllable variables) and that it yield reproducible results' (34). We feel that the *hardware* of this method, i.e. the cell geometry and the flow profile, can be easily standardized between different laboratories. Consequently, good reproducibility is expected *a priori* and has been verified in our experience over many years. On the other hand, a set of parameters is available (cell diameter, flow rate, flow profile) which allow for individual adjustment whenever required.

Secondly, we wanted to emphasize that the method principle is of almost universal *applicability*. The same basic equipment is suitable for experimental dosage form evaluation as well as for quality control purposes, and that for all kinds of forms (granules, tablets, coated tablets, capsules, special forms). By choosing between open or closed system it is possible to find optimum conditions with respect to sink requirement, solvent consumption, analytical accuracy, etc.. In any case, artificial extraction techniques or mixed organic solvents can be avoided.

Thirdly, we intended to show that the column method is capable of reliable *experimental performance*. Suitable equipment was designed and is now commercially available: a sixfold thermostated dissolution unit, a corresponding volumetric pump, a filtration system, and additional components for automated and computerized multichannel sampling off line or on line. Although initial investment costs seem high at first glance, they are justified when ease of handling (including cleaning and service), compactness, and automation facilities are taken into account.

Finally, we may stress that with our method *correlations* with *in vivo* have been obtained at least to the same degree as reported

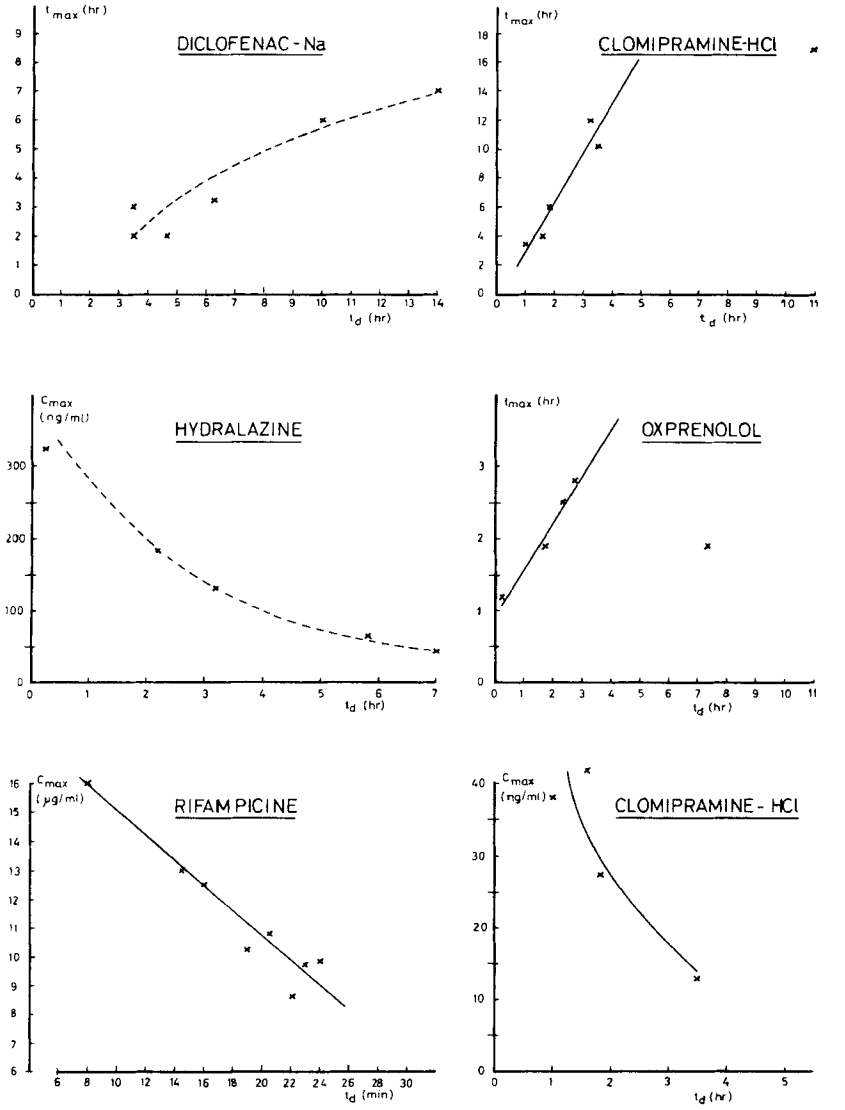


FIGURE 6

Correlation of *In-vitro* Dissolution Time, t_d, with *In-vivo* Plasma Concentration Parameters, t_{max} and c_{max}, respectively. Each Data Pair Shown Represents a Distinct Experimental Formulation of the Indicated Compound

for other methods, and that these correlations have been successfully applied in subsequent formulation work.

In concluding we suggest that the column method which was known for quite some time and whose merits have been discussed in many papers, be regarded as a promising alternative to the methods which are now under consideration for industrial and official purposes.

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