The development of an acceptable in vitro test to help establish the bioequivalency of critical life sustaining drugs has been studied since the middle 1950s.\textsuperscript{1}

In the late 1960s the USP and NF organized a task force to pursue this project. A series of collaborative studies was used to compare various methods. Wm. E. Mader, Director of the (then) Drug Standards Laboratories provided general direction for the project.

There was an agonizing comparison of proposed methods and finally the rotating basket method suggested by Pernarowski\textsuperscript{2} was officially accepted and dissolution tests became a part of the monographs of four critical drugs in NF and six in the USP XVIII(1970).

There followed a hectic ten years of growing pains in dissolution technology. The basket method soon proved poorly adaptable to some dosage forms and the paddle procedure suggested by Poole\textsuperscript{3} was also adopted as an optional method.

Independent variables involved in these physical tests were studied and classified by many investigators. These variables included vibration, alignment, flask geometry, shaft wobble, sorption, dissolved gas, centering, sampling position and a host of others. As a result of these variables the dissolution rate might increase or decrease as much as 20%. Consistent repeatable dissolution test results from laboratory to laboratory were difficult to obtain.

The FDA focused on these problems with a program of studies under the direction of Bill Furman and Don Cox. These studies were published as dissolution GLP in an article that is still a classic\textsuperscript{4}.

The recognition of variables led to the development of calibration standard tablets by the USP to provide technicians with a validation tool for their equipment. The general use of these calibrating standards has calmed the turbulent waters of dissolution arguments. At least for the basket and paddle methods a universal qualification of equipment is now available. Such calibration standards are needed and will no doubt be forthcoming for all types of dissolution apparatus.

As different drugs were studied other problems in dissolution techniques arose. For example some drugs have such low solubility that the individual dose reaches saturation in the 900 mL medium specified. This led, particularly in Europe, to a general use of the flow through cell method pioneered by Langenbacher of Ciba Geigy\textsuperscript{5}.

### USP Apparatus 1
**Rotating Basket**

**Standard**
- 40 Mesh Stainless
- 900mL

**Modifications**
- 10-100 Mesh
- 100-4000mL Volume
- Basket Dimensions
- Suppository (3.2mm Slits)
- pH Change During Test

**Useful For**
- Solids
- Beads
- Floatera
- Modified Release
- Surfactants in Media

### USP Apparatus 2
**Paddle**

**Standard**
- Teflon or Stainless
- 900mL
- Wire Sinker for Floaters

**Modifications**
- 100-4000mL Volume
- Surfactants in Media
- Basket Dimensions
- Media pH Change
- Apparatus 5

**Useful For**
- Modified Release
- Transdermal Patch
- As Apparatus 5 (Paddle Over Disk)
By the early 1990s dissolution requirements had expanded to over 480 monographs. A general policy statement was issued that no known bio-inequivalence problems exist with a dosage form in which 75% dissolves in water in 45 minutes (USP XXII). This, in effect, means that all oral dosage forms must either meet this general standard, or detailed dissolution requirements of their specific monographs.

As dissolution has been applied to different dosage forms such as modified release, polymeric beads, pH sensitive, and transdermal patches new dissolution techniques have been developed. These newer methods may have some advantages with some of these dosage forms. As a result there are seven official dissolution apparatus methods now described in the 5th Supplement of the USPXXII/NFXVII effective Nov. 15, 1991. (These are briefly outlined throughout this article.)

In addition to these seven procedures the use of percutaneous absorption methods are likely to become official where data concerning the kinetics of transfer of substances across membranes is being studied. This is useful in establishing uniformity in topical ointments.

Originally there was a concept that in order to be useful, methods of dissolution in some way must substantially reflect bioabsorption processes. This concept occasionally reoccurs today. However it has long been held invalid and dissolution results held significant in the bioabsorption process only if shown to be rate limiting, e.g. successful in discriminating between acceptable and unacceptable bioavailability. Dissolution data however is useful as a distinct physical characteristic of a compound associated with batch to batch uniformity. As such it can and is used in comparing the characteristics, including bioavailability, of two separate formulations.

Exciting innovations are on the horizon for those of us interested in dissolution testing. Dissolution characteristics certainly will be a part of any and all new drug and new dosage forms. As well dissolution characteristics will be demanded for current materials and dosage forms not yet covered. This includes dietary supplements.

The development of self regulating drug delivery systems utilizing (continued on page eleven)
Dissolution — 25 Years

(continued from page seven)

Iontophoresis and modification of membrane transfer kinetics will demand new and innovative dissolution tests.

BIBLIOGRAPHY

USP APPARATUS 5
PADDLE OVER DISC

STANDARD PADDLE USED
TYPICAL VOLUME 900ml

MODIFICATIONS
- DISC DESIGN
- VOLUME

USEFUL FOR
- TRANSDERMAL PATCH
- OINTMENTS
- FLOATERS
- EMULSIONS
- BOLUS

DOSAGE FORM COVERED BY SCREEN

USP APPARATUS 6
ROTATING CYLINDER

SPECIAL CYLINDER USED
TYPICAL VOLUME 900ml

USEFUL FOR
- TRANSDERMAL PATCH

DOSAGE FORM

USP APPARATUS 7
RECIPIROCATING DISK

RECIPIROCATING DISK SAMPLE HOLDER

SEQUENTIAL MEDIA TUBES TYPICAL VOLUMES 50-400ml

USEFUL FOR
- TRANSDERMAL PATCHES
- SOLID DOSAGE FORMS
- pH PROFILE
- SMALL VOLUME

MODIFICATIONS
- VOLUME 20-200ml
- DOSAGE FORM HOLDER

PERCUTANEOUS ABSORPTION
HANSON VERTICAL CELL TECHNIQUE

USEFUL FOR
- PATCH STUDIES
- TOPICALS TO BE ABSORBED THROUGH SKIN
- MAY BE PROLONGED TEST

VARIATIONS
- VOLUME
- MEMBRANE AREA
- MEDIA COMPOSITION
- MAY BE AUTOMATED

TOP PLATE SAMPLING PORT

DOSE DONOR AREA
MEMBRANE

RECEPTOR WATER JACKET

MAGNETIC STIRRER TYPICAL ORIFICE 15mm VOLUME 7ml

MEDIA REPLACE TUBE (OPTIONAL)