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Royal Hansc

Dissolution To

Disclaimer

The laboratory procedures described herein may involve hazardous material. The authors, speaking for themselves, expressly disclaim any liability to users of these lab procedures and apparatus for consequential damages of any kind arising out of or connected with their use. Items of apparatus and test methodology described in this handbook are intended to illustrate proper techniques to obtain a quality analysis and are not to be considered official and/or required. Official compendia and regulatory requirements are to be considered the only authoritative source for such matters.

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This, the Third Edition of the *Handb*
dedicated to the memory of William A
Hanson Research Corporation. Dr. Hans
and longtime leader in the field of dissol

Prior to his death at the end of 1994
contributor to the evolution of test appar
nificant experiments in the field led to h
in Engineering with a dissertation on the
maceutical dissolution testing.

Dr. Hanson supplemented his technica
book of Dissolution Testing in 1982, foll
1991. As the field of dissolution testing c
are proud to follow in Dr. Hanson's gia
Third Edition of his important book.

Cons

Over the last several decades, the d
a pioneering prototype into a standardiz
age quality assurance. Considering indu
drug R&D, formulations, and clinical t
been proven to provide a simple, cost-e
test for drug release characteristics. For
of consideration by developing countri
ceutical community.

The second edition of this Handbook
was written when the methods, techniq
tion testing had been established using
paratus 2 (Paddle) as the techniques o
remain the dominant methods to analyz
lease dosage forms. The USP has now
cating Cylinder), Apparatus 4 (Flow-Th
dle Over Disk), Apparatus 6 (Cylinder)
ing Holder) (1) and the EP has added
cating cylinder and paddle over disk tr
these apparatus are described in detail

As this Third Edition goes to press, a
USP General Chapters Dissolution <7
with the European Pharmacopeia and Ja
completion. This effort, led by the Int
monization (ICH), will include coordi

tions, equipment modifications, and use of validated sinkers and automated equipment are included (see Chapter 7 for more details).

Why Dissolution Testing?

Besides accommodating the obvious need for meeting the legal requirements for compendial drugs, dissolution testing is increasingly used to test special oral dosage forms now listed in the compendia. Those dosage forms include vitamins, herbals, veterinary drugs, chewable tablets, suppositories, suspensions, soft gelatin capsules, creams, ointments, gels, transdermal systems, and the vast ever-increasing number of extended-release preparations. In addition, there are new product types and dosage forms under development, such as chewing gums, powders, granules, dispersions, microparticles, stents, liposomes, nanospheres and implants, which may require dissolution testing. The pharmaceutical industry will continue to use dissolution testing as a laudable quality control measure for their production operations. They also are acutely aware that the worldwide sociological trend is toward extension of regulation. In the pharmaceutical business, as in any other, it pays to anticipate future developments.

Dissolution testing, of course, is a regular quality control procedure in good manufacturing practices (GMP). Whether or not its numbers have been correlated with biological effectiveness, the standard dissolution test is a simple and inexpensive indicator of a product's physical consistency. If one batch differs widely from others in its dissolution characteristics, or if the dissolution times of production batches show a consistent trend upwards or downwards, it sounds a sure warning that some factor in the raw material, formulation, or process is out of control.

Dissolution data are also useful in the early stages of drug development and formulation. In the early stages of development, researchers may take steps to optimize drug and dosage-form characteristics that will influence subsequent bioavailability data.

Disintegration Tests

More than fifty years ago, it was recognized that unless an oral dosage form disintegrated into small aggregates, the body could not absorb it efficiently. A unique apparatus was devised to establish a standard for disintegration. Its description is still published in USP, but now the

testing. Disintegration testing was origin
establish minimum standards.

In the early stages of pharmaceutical
"elegant" tablet: a tablet of beauty tha
change color. Of course, the harder the
chip or fracture during packaging or shi

Hardness can be increased by increasi
pression forces. Unfortunately, hardness
where the tablet will not disintegrate in
the only release of drug will arise from t
of the outside of the dosage form. In 19
Ralph Shangraw, et al. (3) showed tha
taining folic acid were not meeting the
an hour. This has important implications
vivo. Even today, physicians have obse
in patients' stools.

The disintegration test was introduced
apparatus consists of six vertical tubes, e
diameter, arranged in a rack with a 10-me
surface. The tubes are moved 5.5 cm up a
submerged in water or simulated intestina
°C). To help the process along, a compl
the tablet during the up-and-down mover

The disintegration test has been offic
it had enjoyed international acceptanc
been introduced, one incorporating a 10
tubes to keep capsules from floating ou
cated apparatus that registers the time fo
plots results on a digital printer. The tab
no palpable mass remains on the 10-me
time, typically 30 minutes for ordinary
teric-coated tablets.

The test had been mandatory for ora
40 years, but its elimination and replac
lution standard was encouraged in Pha
probably because the disintegration test
correlation with bioavailability (5). In
recognized that the ultimate solution of
tors: the disintegration of the tablet and
ticles in the tablet. That process is ou

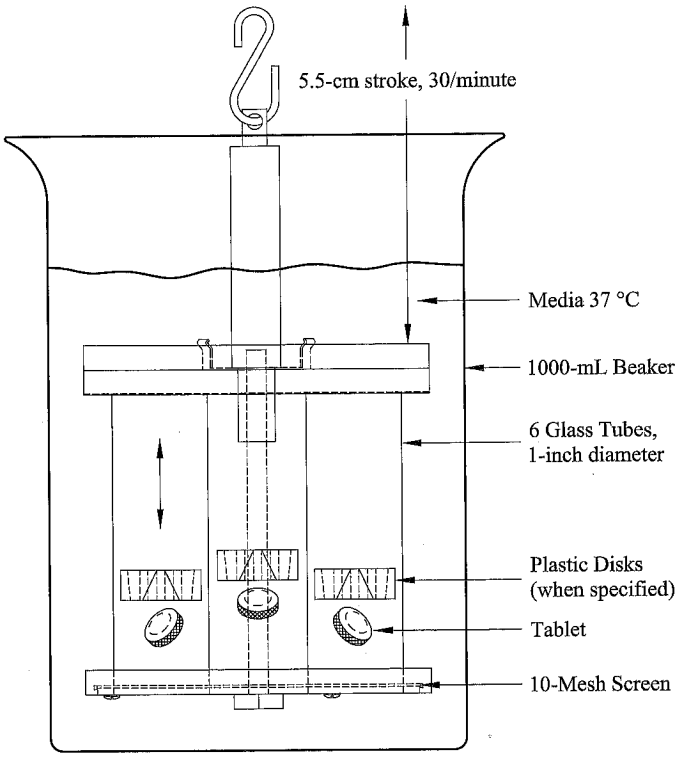

Figure 1-1 USP disintegration testing apparatus. (See USP <701> Disintegration.)

From the pattern shown in the diagram it is apparent that the dissolution rate includes the time factor resulting from the disintegration process. It also becomes obvious that dissolution testing includes disintegration time and, therefore, that if dissolution data become mandatory, then disintegration information becomes superfluous.

During the period 1990–1995, many USP disintegration tests were replaced with dissolution tests, and the disks were removed from <701> Disintegration USP General chapter. Disks may still be called for in individual USP monographs.

Early Dissolution Test Development

In the early 1960s, problems regarding the bioavailability of drugs

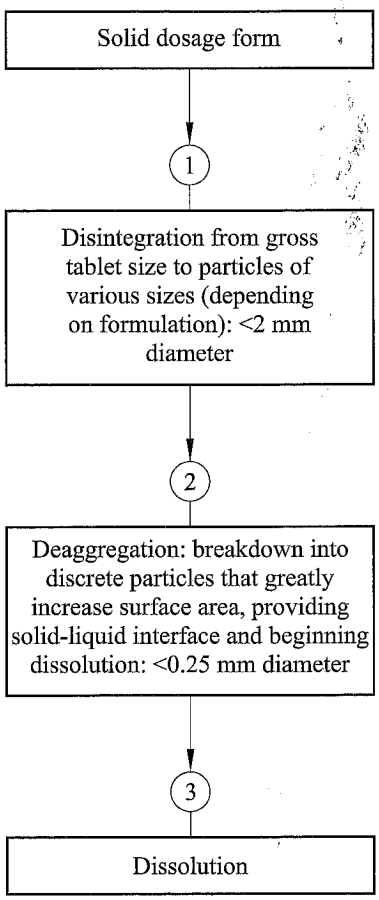

Figure 1-2 The three stages in the diss

cies, and compendial standards groups. manufacturer forcibly brought the matt vestigation of identical competitive pro dicated a substantial difference in the p which were otherwise pharmaceutically existing tests for physical properties.

The matter was brought to the attenti and a study of various dissolution test

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