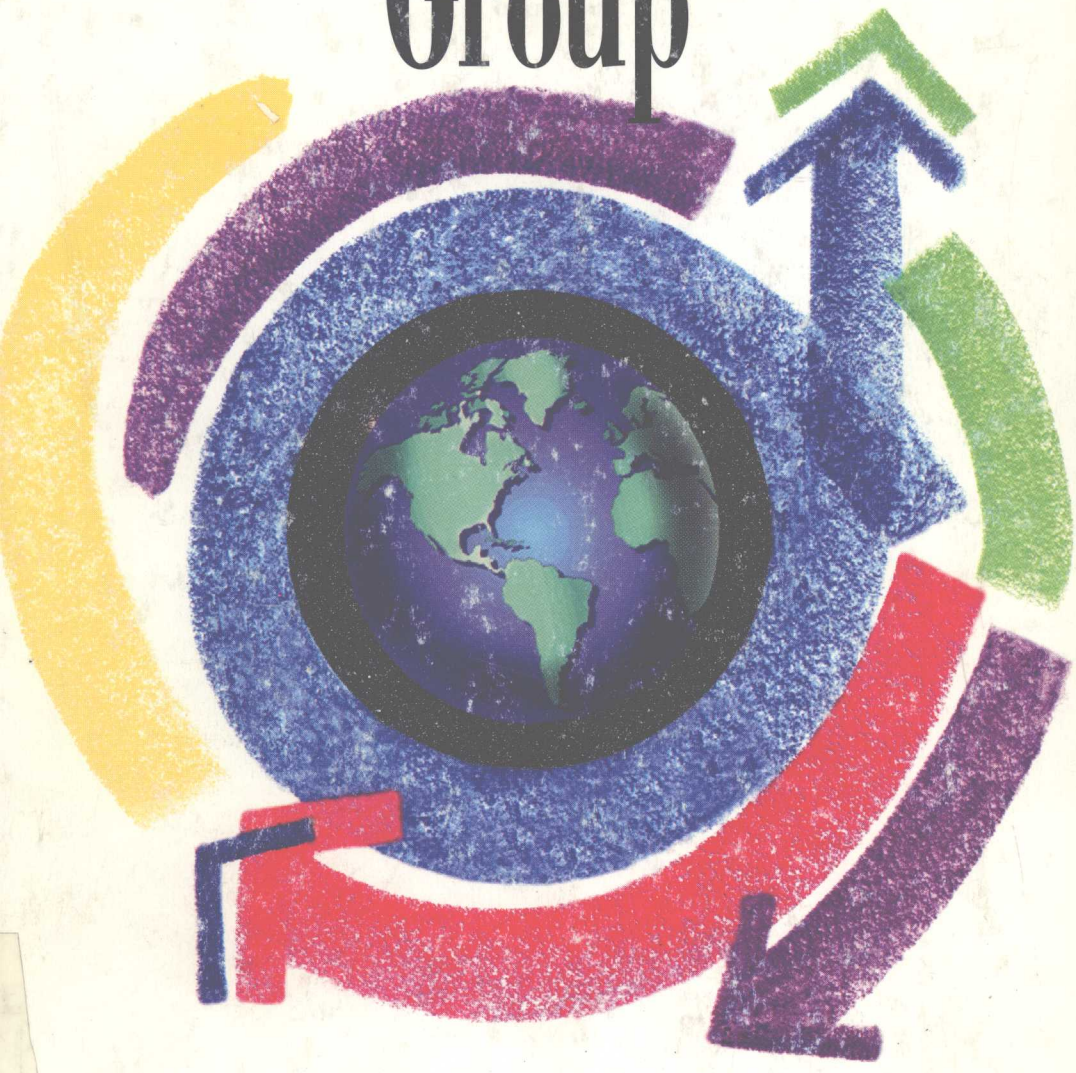
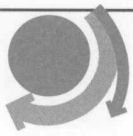
Dissolution Discussion Group®



Volume 1

A User's Perspective on Dissolution



Dissolution Discussion Group®

Volume 1

A User's Perspective on Dissolution

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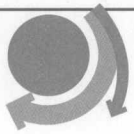
Published by:

VanKel



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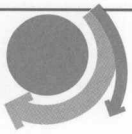
All proceeds from this book support the Dissolution Discussion Group Web site, development and meetings.

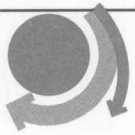


Preface

In January 1998, VanKel founded the Dissolution Discussion Group (DDG) on the World Wide Web in support of dissolution scientists everywhere. DDG provides an independent forum to openly and conveniently discuss practical issues challenging the pharmaceutical industry. To make DDG available to the greatest number of users possible, membership is free and access is available around the globe via the Internet at www.dissolution.com. With over 1,000 members joining in the first year, DDG is already a successful and valuable source for technical support for scientists developing, validating, and performing dissolution tests and the related chemical analyses.

The DDG Web site has been very active in its inaugural year with numerous questions posted and hundreds of responses offered. This activity should not be unexpected since the field of dissolution is ever changing. Dissolution testing evolves at a dynamic pace to keep up with novel dosage forms and delivery systems developed by researchers and formulators. In the past, scientists relied on a few succinct paragraphs in a compendia, the interpretation of a local regulatory agent, an out of date text, or a fellow employee whose knowledge was limited by his or her own experience. Now, the DDG is available to scientists around the world and it is revolutionizing the way they approach their work. DDG provides a vehicle to make decades of combined experience available in all facets of dissolution.

Members have succeeded in making the DDG Web site a worldwide association that is as current as the last moment a question or comment was posted. There are some of us, however, who still take comfort in reaching for a book on the nearest shelf. Others may require the convenience of a written text or may not have access to the information highway and it is for these reasons we publish this reference. The questions and comments in this book have been edited for clarity, however, care was taken to assure the information presented is a true representation of the content of the Web site. For this reason, the accuracy of claims posted by any of the members of DDG is open for

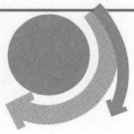


question or debate. It is this interaction that furthers the growth of DDG by provoking thought, challenging the mind, and encouraging communication to benefit those who have dedicated their careers to the science of dissolution. Your response to any question or comment printed in this reference is welcome online at www.dissolution.com or you can mail your comments to VanKel Technology Group, Dept. DDG, 13000 Weston Parkway, Cary, NC, USA, 27513-2228. We are happy to post mailed comments and questions on the DDG Web site and return online responses to you via mail if you do not have Internet access.

This book offers broadly based information on many related dissolution topics such as calibration tips and personal opinions on varying dissolution issues. One such topic includes a number of suggestions related to deaeration techniques for the preparation of media for calibration. Other topics covered are more specific to the field, such as pellicle formation with gelatin capsules. Within the DDG Web site, members often cite current literature and network with other scientists. To assist you in using this text effectively and efficiently, a detailed glossary is provided with definitions specific to the field of dissolution.

VanKel extends its appreciation to those who encouraged us to undertake the development of the DDG. We are grateful to the members that made the first postings on DDG, thereby inspiring others to follow. Thanks also to those who attended our first meetings in Cary, North Carolina; Madison, New Jersey; and Brussels, Belgium. Their confidence and willingness to promote this new organization was crucial to the DDG's success in its inaugural year. Special gratitude is extended to Charles Collins, Ph.D. for his scientific input and support in compiling this text.

Cary, North Carolina — James E. Swon



About This Book

SECTION 16.4: MEDIA SELECTION

I am looking at the release of a drug suspended in an ointment base. The drug is very soluble in water, slightly soluble in methanol (enough for sink conditions), and insoluble in most non-polar organic solvents. I am having a tremendously difficult time developing an IVRT method for this. I have been through various combinations of the following agents: Water, Buffered Water, Hydro Alcoholic solutions, DMSO, Acetonitrile, MeOH, IPA, and Hexane Chloroform.

One Combination of two of the above works, but I do not believe I am seeing release rate so much as a slow extraction of the drug form the base.

If any of you have any shareable info/opinions, it would be much appreciated.
Later.
3/24/98

Member Comment
Check out a reply to message listed above (topic: solubility). It says:

Re: Solubility Discussion Group

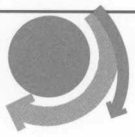
Organic media are usually a "no-no" unless you have shown an in-vivo/in-vitro relationship. Anyone heard of "emulphor" as a surfactant?

Editor's Note
See Solubility, Chapter 23.1 for a definition of emulphor.

The bold portions that start each section typically represent a member's question or statement. This begins a "thread" on the DDG bulletin board. The date at the end of the bold portion shows the origination of the thread.

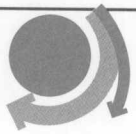
This section represents a response which may come in the form of an answer or a comment made to the original bulletin board posting. All postings were made in 1998. Occasionally a comment may require clarification or enhancement to better define or resolve an issue. In those cases there will be an Editor's note below the member comment.

In addition to clarifying or enhancing a comment, an editor's note may include references or direct the reader to another part of the book for more information.



Our knowledge is the amassed thought and experience of innumerable minds.

–Ralph Waldo Emerson



Contents

Apparatus

SECTION 1.1: USP APPARATUS 4

I have been using USP Apparatus 4 and would like to know what the guidelines are for routine calibration.
Regards,
4/15/98

Member Comment

As far as I know there is no official calibration method for Apparatus 4. What kind of products are you performing dissolution tests on?

Member Comment

In reply to your query, I have been involved in the development of a USP Apparatus 4 test for a two component tablet formulation in which the components have markedly differing solubility properties. It was found that when using the USP Apparatus 2 for this particular product one component caused a reduction in sink conditions and slow release of the other component. By using the USP Apparatus 4 the "interfering" component was removed from the cell using a medium in which the affected component is insoluble, after a specified time the medium is switched and dissolution of the affected component allowed to occur.

Member Comment

Sotax developed a calibration method for their Apparatus 4.

Member Comment

Can we get a copy to post on the Web site? There is lots of interest in this method. (The Moderator)

Member Comment

Actually, no calibration test for USP Apparatus 4 is available. FIP Working Group 4 performed two collaborative studies concerning the suitability of USP prednisone and salicylic acid calibrators to "calibrate" the flow-through cell apparatus. Results were presented and are being published by FIP Working Group 4 very soon.

Member Comment

Has anyone undertaken an experimental design approach to robustness of USP Apparatus 4 methods?

SECTION 1.2: PADDLE ROTATION

The USP states to drop tablets and allow them to fall to the bottom BEFORE starting the paddles rotating. At our DDG meeting (April 98) we found that the majority of attendees do not follow this practice. What do others do? Does anyone have current data showing a difference one way or another? DDG Attendees
4/16/98

Member Comment

I have started following this practice of dropping the tablets in the vessels prior to starting the paddles. Also, I have only performed dissolution analysis by sampling manually this way. Unfortunately, I do not have any data for the differences. I am working on an immediate release dosage form, if the tablet was to hit the paddle while it is rotating, this could affect the dissolution rate considerably.

Member Comment

I have always carried out manual testing by having the paddles rotating prior to the test. This particular issue does not seem to have been seen as a problem.

With automated testing (Zymark MultiDose) the paddles are stopped prior to addition of the dosage form to the vessels.

Member Comment

There is a concern where a dosage form COULD have

an undesired mechanical interaction with the paddle as the unit goes to the bottom of the vessel. For instance, the paddle could hit and break the tablet which would drastically change the dissolution results. To avoid the possibility, the paddles are stopped while the unit is introduced.

Member Comment

Rotating the paddle for long periods of time (in excess of 30 minutes) can possibly deaerate non-deaerated medium and vice a versa. I can't think of a really good reason to rotate the paddles before testing. Does it really decrease vessel medium equilibration time?

Member Comment

The original question was posed at the Dissolution Discussion Group in reference to the USP requirement that the dosage form be allowed to sink to the bottom of the vessel before rotation begins.

And yes, stirring does speed up the temperature equilibration process. For the same reason that the bath heater is actually a heater/ circulator - heating by convection alone is a relatively slow process.

Does this stirring change the amount of air dissolved in the medium? Probably, but who cares! There are only two monographs in the USP that require deaeration and, of course, the calibrators. That's not a large effect considering there are nearly 800 monographs.

Member Comment

The USP specifies <711> Apparatus 2 that "the dosage

unit is allowed to sink to the bottom of the vessel before rotation of the blade is started." The system (Zymark) was designed to meet the USP specifications.

SECTION 1.3: BASKET CLEARANCE

When attaching a basket to a shaft for Apparatus 1, does anyone know how much, if any, clearance is allowed between the basket and the shaft? In other words, when looking at the basket turning on the shaft, I can see a very small gap between the basket and shaft at one point where the two meet. Any suggestions?
5/5/98

Member Comment

If you are seeing "gaps," your basket may be bent. If it is bent you will get excess wobble which will affect your results. Check the wobble at the bottom rim of the basket at the speed you run the product (i.e. 50 or 100 rpm). The USP states limits on the wobble. If you are within limits, then the gap probably does not affect the dissolution.

SECTION 1.4: DEPOT FORMULATIONS

I am looking for a (USP) method for a dissolution test of depot formulations. Does anybody have any suggestions or experience with such formulation? Is USP Apparatus 4 the most logical choice? Thanks. 5/19/98

Editor's Note

Member's comments are always welcome on-line at www.dissolution.com or fax to: DDG Moderator (USA) 919-677-1138.

SECTION 1.5: USP APPARATUS 3

Has anyone had any experience using USP Apparatus 3? What applications does it have? What vendors make Apparatus 3 systems? Ease of operation? Benefits over paddles or baskets? Any personal experience will be appreciated.
6/16/98

Member Comment

A lot of companies manufacture USP Apparatus 3 (VanKel, Hanson, Caleva etc.). This apparatus is mainly used for multiparticulates dosage forms like pellets.

Member Comment

You can call VanKel to get a listing of papers on Apparatus 3. They were involved with Schering who helped develop the USP calibration method. In addition, to being a good method for extended release products (due to the ability to do pH profiling and automated sampling over 12 or more hours), I have seen where Apparatus 3 has been used to replace rotating bottles.

Member Comment

When you want to compare in-vitro data to in-vivo results of extended release products, the USP Apparatus 3 (Bio-Dis) gives much better results than the paddle/ basket apparatus. Thanks to its stronger agitation and its ability to run pH gradients it can mimic the in-vivo conditions much better. However, it can only be