
WATER- INSOLUBLE DRUG FORMULATION

EXPENSIVE ITEM

This item must be returned
by recorded delivery

Dong Liu

Invitation to Authors



Interpharm Press publishes books focused upon applied technology and regulatory affairs impacting healthcare manufacturers worldwide. If you are considering writing or contributing to a book applicable to the pharmaceutical, biotechnology, medical device, diagnostic, cosmetic, or veterinary medicine manufacturing industries, please contact our director of publications.

Library of Congress Cataloging-in-Publication Data

Water-insoluble drug formation / Rong Liu, editor.

p. cm.

Includes bibliographical references.

1. Solutions (Pharmacy) 2. Drugs—Solubility. I. Liu, Jung.

RS201.S6 W38 2000
615'.42—dc21

00-033450

10 9 8 7 6 5 4 3 2 1

ISBN: 1-57491-105-8

Copyright © 2000 by Interpharm Press. All rights reserved.

All rights reserved. This book is protected by copyright. No part of it may be reproduced, stored in a retrieval system, or transmitted in any form or by any means, electronic, mechanical, photocopying, recording, or otherwise, without written permission from the publisher. Printed in the United States of America.

Where a product trademark, registration mark, or other protected mark is made in the text, ownership of the mark remains with the lawful owner of the mark. No claim, intentional or otherwise, is made by reference to any such marks in this book.

While every effort has been made by Interpharm Press to ensure the accuracy of the information contained in this book, this organization accepts no responsibility for errors or omissions.

Interpharm Press
15 Inverness Way E
Englewood, CO 80112-5776

Phone: +1-303-662-9101
Fax: +1-303-754-3953
Orders/on-line catalog: www.interpharm.com

17

Soft Gelatin Capsules Development

S. Esmail Tabibi
Shanker L. Gupta
*Pharmaceutical Resources Branch
National Cancer Institute, NIH
Bethesda, Maryland*

A pharmaceutical scientist will eventually face the task of formulating an oily or an oil-soluble medicament in liquid formulation as a solid dosage form using the soft gelatin capsule, sometimes referred to as *softgel* or *liquigel*[™]. In the formulation of common oral dosage forms, the formulator has access to excipients and processing technologies, thus enabling him to conduct a systematic formulation and process-development research and produce an elegant and stable dosage form. On the other hand, due to its nature, the softgel technology has become specialized processing in which the formulator will rely on the others to produce the shell formulation and conducts the shell-content compatibility studies. A suitable formulated medicament is finally encapsulated as the content into a compatible soft gelatin shell.

Because of the highly cost-intensive operation of softgel capsule production, it is not possible for formulation scientists to conduct research on all phases of the formulation and process development of soft gelatin capsules. However, based on the unique advantages and special properties of this type of dosage form, the formulators should familiarize themselves with the overall technology and processes involved both in the composition development and manufacturing aspects.

Softgel capsules have gained popularity and use in the pharmaceutical industry for human and veterinary applications as an oral dosage form; as suppositories for

rectal and vaginal administration; single-use applicators for ophthalmic, otic, and topical formulations; and rectal ointments. Their use in cosmetic industry is beyond the scope of this manuscript.

Softgel capsules come in a variety of shapes, sizes, and colors that may be specific to the manufacturer. In Figure 17.1, some representative shapes and sizes are presented. This chapter, provides an overview of the manufacturing methods, formulation of the content medicament, the composition of the shell, quality control procedures, stability, and shelf-life testing. We also discuss in some detail examples of the products formulated in softgel dosage form.

MANUFACTURING METHODS

Processing Equipment

An exhaustive discussion on the advantages and disadvantages of different types of machinery used in the production of soft gelatin capsules is beyond the scope of this chapter. An excellent review by Stanley (1986) described the manufacturing process and formulation aspects of the softgel technology. A brief description of the various processing technologies follows.

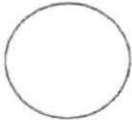
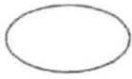



Plate Process

Historically, the soft gelatin capsules were manufactured by the *plate method*, in which elasticized sheets of the formulated gelatin shell were placed on the die plate that contained a number of capsule-shaped cavities. By applying a vacuum, the gelatin was drawn into the cavities to form capsule wells. The capsule wells were then filled with drug formulation and covered by another sheet of the elasticized gelatin or the gelatin sheet was folded back over the filled wells. The upper plate was then placed on the top of the upper sheet and was pressed to form and cut the capsules. These capsules, generally, had one flat side. The major problems with this type of processing were the lack of dosage uniformity, high manufacturing losses, and that it was labor/cost intensive. This equipment is no longer available.

Rotary Die Process

According to Ebert (1977), Robert P. Scherer, in 1933, invented and perfected the *rotary die process* that almost eliminated all of the problems associated with the plate process and produced softgel dosage forms with improved uniformity and high standards of accuracy. This is the first continuous process in which the outer faces of two counterrotating rollers contain precisely machined and aligned die cavities. The die rollers rotate in opposite directions, and the matching die cavities from each die roller create the capsule pocket. Figure 17.2 presents a schematic view of the rotary die

Figure 17.1 The shapes and sizes of commonly used soft-gelatin capsules.

Nomination	Rounds		Ovals		Oblongs		Tubes		Supp
Shape									
	Capsule Size	Optimum Fill Volume (minim)*	Capsule Size	Optimum Fill Volume (minim)	Capsule Size	Optimum Fill Volume (minim)	Capsule Size	Optimum Fill Volume (minim)	Capsule Size
			2	2.3					
	3	3.0	3	3.0					
	4	4.0	4	4.0	3	3.0	3	3.0	
	5	5.0	5	5.0	4	4.0	4	4.0	
	6	6.0	6	6.0	5	5.0	5	5.0	
	7	7.0	7 ^{1/2}	7.5	6	6.0	6	6.0	10
	9	9.0	10	10.0	8	8.0	8	8.0	17
	15	15.0	12	12.0	9 ^{1/2}	9.5	17 ^{1/2}	17.5	40
	20	20.0	16	16.0	11	11.0	30	32.0	80
	40	40.0	20	20.0	12	12.0	45	45.0	
	50	50.0	30	30.0	14	14.0	65	65.0	
	80	65.0	40	40.0	16	16.0	90	90.0	
	90	80.0	60	60.0	20	20.0	120	120.0	
			80	80.0					
			85	85.0					

*A minim is equal to 0.0616 mL.

Explore Litigation Insights

Docket Alarm provides insights to develop a more informed litigation strategy and the peace of mind of knowing you're on top of things.

Real-Time Litigation Alerts



Keep your litigation team up-to-date with **real-time alerts** and advanced team management tools built for the enterprise, all while greatly reducing PACER spend.

Our comprehensive service means we can handle Federal, State, and Administrative courts across the country.

Advanced Docket Research



With over 230 million records, Docket Alarm's cloud-native docket research platform finds what other services can't. Coverage includes Federal, State, plus PTAB, TTAB, ITC and NLRB decisions, all in one place.

Identify arguments that have been successful in the past with full text, pinpoint searching. Link to case law cited within any court document via Fastcase.

Analytics At Your Fingertips



Learn what happened the last time a particular judge, opposing counsel or company faced cases similar to yours.

Advanced out-of-the-box PTAB and TTAB analytics are always at your fingertips.

API

Docket Alarm offers a powerful API (application programming interface) to developers that want to integrate case filings into their apps.

LAW FIRMS

Build custom dashboards for your attorneys and clients with live data direct from the court.

Automate many repetitive legal tasks like conflict checks, document management, and marketing.

FINANCIAL INSTITUTIONS

Litigation and bankruptcy checks for companies and debtors.

E-DISCOVERY AND LEGAL VENDORS

Sync your system to PACER to automate legal marketing.