Pharmaceutics

The science of dosage form design

Edited by M E Aulton

Churchill Livingstone

CHURCHILL LIVINGSTONE
Medical Division of Longman Group UK Limited
Distributed in the United States of America by
Churchill Livingstone Inc., 650 Avenue of the Americas,
New York, 10011, and associated companies, branches
and representatives throughout the world.

First published 1988
Reprinted 1989
Reprinted 1990
Reprinted 1991
Reprinted 1992

ISBN 0-443-03643-8

British Library Cataloguing in Publication Data
Pharmaceutics: the science of dosage form
design.
1. Pharmaceutics
I. Aulton, Michael E.
615'.19 RS403

Library of Congress Cataloging in Publication Data
Pharmaceutics: the science of dosage form design.
Replaces: Cooper and Gunn's tutorial pharmacy.
6th ed. 1972.
Includes bibliographies and index.
1. Drugs — Design of delivery systems. 2. Drugs
— Dosage forms. 3. Biopharmaceutics.
4. Pharmaceutical technology. 5. Chemistry,
Pharmaceutical. 6. Microbiology, Pharmaceutical.
I. Aulton, Michael E.
[DNLM: 1. Biopharmaceutics. 2. Chemistry,
Pharmaceutical. 3. Dosage Forms. 4. Technology,
Pharmaceutical. 5. Microbiology, Pharmaceutical.
QV 785 P5366]
RS420.P48 1987 615.5'8 86–25888

Printed in Hong Kong
CPP/05

Contents

Parenteral products

THE BIOPHARMACY OF INJECTIONS

Routes of administration
- *Intracutaneous or intradermal route*
- *Subcutaneous or hypodermic route*
- *Intramuscular route*
- *Intravascular routes*
- *Intracardiac route*
- *Intraspinal routes*
- *Intra-articular and intrabursal routes*
- *Ophthalmic routes*

Bioavailability of drugs from injections

FORMULATION OF INJECTIONS

Volume of the injection

The vehicle
- *Water and pyrogens*
- *Water-miscible vehicles*
- *Water-immiscible vehicles*

Osmotic pressure
- *Intravascular injections*
- *Intrathecal injections*
- *Intramuscular injections*
- *Intracutaneous injections*
- *Subcutaneous injections*

Hydrogen ion concentration (pH)
- *To increase the stability of the injection*
- *To minimize pain, irritation and necrosis on injection*
- *To provide unsatisfactory conditions for growth of micro-organisms*
- *To enhance physiological activity*
- *Buffers*

Specific gravity of injections

Suspensions for injection
- *Wettability*
- *Sedimentation rate*
- *Claying*
- *Size and shape of particles*
- *Thixotropy*
- *Preparation of aqueous suspension injections*
- *Suspensions in oily vehicles*
  - ***Addition of a gelling agent***
  - ***Particle size***

Emulsions for injection
- *Intravenous therapy and emulsions*

Colloidal dispersions and solubilized products

QUALITY ASSURANCE OF INJECTIONS

Microbiological preservation
- *The use of bactericides in single-dose injections*
- *The use of bactericides in multiple-dose injections*
- *Bactericides suitable for aqueous injections*
- *Bactericides suitable for oily injections*
- *Limitations in the use of bactericides*
- *Incompatibilities of common bactericides*

Chemical stability of the medicament
- *Adjustment of pH*
- *Addition of a reducing agent or antioxidant*
- *Replacement of air by an inert gas*
- *Use of a sequestering agents*
- *Inclusion of specific stabilizers*
  - ***Calcium Gluconate Injection BP***
  - ***Sodium Bicarbonate Injection BP***
  - ***Mersalyl Injection BP***
- *Limitations in the use of additives*

Particulate contamination

PACKAGING OF INJECTIONS

Containers for injections
- *Ideal properties*
- *Types of container*
- *Single-dose versus multiple-dose containers*

Materials for injection containers
- *Glass*
  - ***Types of glass***

Associated problems for parenterals

Plastics

Types of plastics

Associated problems for parenterals

Closures

Types and properties of closure materials

Associated problems for parenterals

STERILIZATION OF INJECTIONS

Injections are sterile products intended for administration into the bodily tissues. Their formulation involves careful consideration of all the following inter-relating factors:

1 the proposed route of administration,
2 the volume of the injection,
3 the vehicle in which the medicament is to be dissolved or suspended,
4 the osmotic pressure of the solution,
5 the use of preservative,
6 the pH of the solution,
7 the stability of the medicament and methods of sterilization,
8 the specific gravity of the injection,
9 the properties of suspensions for injection,
10 the properties of emulsions for injection,
11 containers or closures for injections,
12 particulate contamination,
13 biopharmacy of injections.

THE BIOPHARMACY OF INJECTIONS

Injections are administered into the body by many routes. The route of administration affects the formulation and biopharmaceutics of the preparation. There now follows a description of routes of administration to clarify nomenclature used throughout the rest of the chapter. Fig. 21.1 shows the sites of injection.

Routes of administration

The most important routes are as follows.

Intracutaneous or intradermal route

Injections are made into the skin between the inner layer (dermis) and the outer layer (epidermis). The volume that can be injected intradermally is small, usually 0.1–0.2 ml, due to the poor vascularity of the site which gives poor dispersion of the drug, and leaves blisters or weals at the site of the injection. The route is used mainly for diagnostic tests.

Subcutaneous or hypodermic route

Injections are made under the skin into the subcutaneous tissue. The volume injected is usually 1 ml or less. This route is not used for aqueous suspensions or oily suspensions and fluids since these would cause pain and irritation at the injection site.

Intramuscular route

Injections are made by passing the needle into the muscle tissue via the skin, subcutaneous tissue and membrane enclosing the muscle. The volume is usually no greater than 2 ml and should not exceed 4 ml. This route is used for aqueous and oily suspensions and oily solutions, since if they were injected intravenously blockage of small blood vessels might occur leading to poor vascular supply of local tissues possibly resulting in gangrene.

Intravascular routes

These are either intra-arterial (into arteries) or intravenous (into veins). The intra-arterial route is used for an immediate effect in a peripheral organ, e.g. to improve circulation to the extremities when arterial flow is restricted by arterial spasm or early gangrene. Tolazoline hydrochloride, a peripheral vasodilator, is sometimes administered by this route.

Substances are introduced directly into the blood stream by the intravenous route. The most common site is the median basilic vein at the anterior surface of the elbow. The volume can vary from less than 1 ml to in excess of 500 ml. Small volumes may be administered for a rapid effect (e.g. anaesthetics) and large volumes (perfusion or infusion fluids) to replace body fluid loss in shock, severe burns, vomiting and diar-

DOCKET ALARM

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.