

Remington's Pharmaceutical Sciences

EDITED BY JAMES H. CLAYTON, JR.

Eighteenth Edition

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Table of Contents

Part 1 Orientation			
1	Scope	3	
2	Evolution of Pharmacy	8	
3	Ethics	20	
4	The Practice of Community Pharmacy	28	
5	Opportunities for Pharmacists in the Pharmaceutical Industry	33	
6	Pharmacists in Government	38	
7	Drug Information	49	
8	Research	60	
Part 2 Pharmaceutics			
9	Metrology and Calculation	69	
10	Statistics	104	
11	Computer Science	138	
12	Calculus	145	
13	Molecular Structure, Properties and States of Matter	158	
14	Complex Formation	182	
15	Thermodynamics	197	
16	Solutions and Phase Equilibria	207	
17	Ionic Solutions and Electrolytic Equilibria	228	
18	Reaction Kinetics	247	
19	Disperse Systems	257	
20	Rheology	310	
Part 3 Pharmaceutical Chemistry			
21	Inorganic Pharmaceutical Chemistry	329	
22	Organic Pharmaceutical Chemistry	356	
23	Natural Products	380	
24	Drug Nomenclature—United States Adopted Names	412	
25	Structure-Activity Relationship and Drug Design	422	
Part 4 Testing and Analysis			
26	Analysis of Medicinals	435	
27	Biological Testing	484	
28	Clinical Analysis	495	
29	Chromatography	529	
30	Instrumental Methods of Analysis	555	
31	Dissolution	589	
Part 5 Radioisotopes in Pharmacy and Medicine			
32	Fundamentals of Radioisotopes	605	
33	Medical Applications of Radioisotopes	624	
Part 6 Pharmaceutical and Medicinal Agents			
34	Diseases: Manifestations and Pathophysiology	655	
35	Drug Absorption, Action and Disposition	697	
36	Basic Pharmacokinetics	725	
37	Clinical Pharmacokinetics	746	
38	Topical Drugs	757	
39	Gastrointestinal Drugs	774	
40	Blood, Fluids, Electrolytes and Hematologic Drugs	800	
41	Cardiovascular Drugs	831	
42	Respiratory Drugs	860	
43	Sympathomimetic Drugs	870	
44	Cholinomimetic Drugs	889	
45	Adrenergic and Adrenergic Neuron Blocking Drugs	898	
46	Antimuscarinic and Antispasmodic Drugs	907	
47	Skeletal Muscle Relaxants	916	
48	Diuretic Drugs	929	
49	Uterine and Antimigraine Drugs	943	
50	Hormones	948	
51	Vitamins and Other Nutrients	1002	
52	Enzymes	1035	
53	General Anesthetics	1039	
54	Local Anesthetics	1048	
55	Sedatives and Hypnotics	1057	
56	Antiepileptics	1072	
57	Psychopharmacologic Agents	1082	
58	Analgesics and Antipyretics	1097	
59	Histamine and Antihistamines	1123	
60	Central Nervous System Stimulants	1132	
61	Antineoplastic and Immunosuppressive Drugs	1138	
62	Antimicrobial Drugs	1163	
63	Parasitocides	1242	
64	Pesticides	1249	
65	Diagnostic Drugs	1272	
66	Pharmaceutical Necessities	1286	
67	Adverse Drug Reactions	1330	
68	Pharmacogenetics	1344	
69	Pharmacological Aspects of Drug Abuse	1349	
70	Introduction of New Drugs	1365	
Part 7 Biological Products			
71	Principles of Immunology	1379	
72	Immunizing Agents and Diagnostic Skin Antigens	1389	
73	Allergenic Extracts	1405	
74	Biotechnology and Drugs	1416	
Part 8 Pharmaceutical Preparations and Their Manufacture			
75	Preformulation	1435	
76	Bioavailability and Bioequivalency Testing	1451	
77	Separation	1459	
78	Sterilization	1470	
79	Tonicity, Osmoticity, Osmolality and Osmolarity	1481	
80	Plastic Packaging Materials	1499	
81	Stability of Pharmaceutical Products	1504	
82	Quality Assurance and Control	1513	
83	Solutions, Emulsions, Suspensions and Extractives	1519	
84	Parenteral Preparations	1545	
85	Intravenous Admixtures	1570	
86	Ophthalmic Preparations	1581	
87	Medicated Applications	1596	
88	Powders	1615	
89	Oral Solid Dosage Forms	1633	
90	Coating of Pharmaceutical Dosage Forms	1666	
91	Sustained-Release Drug Delivery Systems	1676	
92	Aerosols	1694	
Part 9 Pharmaceutical Practice			
93	Ambulatory Patient Care	1715	
94	Institutional Patient Care	1737	
95	Long-Term Care Facilities	1758	
96	The Pharmacist and Public Health	1773	

97	The Patient: Behavioral Determinants	1788	106	Poison Control	1905
98	Patient Communication	1796	107	Laws Governing Pharmacy	1914
99	Drug Education	1803	108	Community Pharmacy Economics and Management	1940
100	Patient Compliance	1813	109	Dental Services	1957
101	The Prescription	1828			
102	Drug Interactions	1842			
103	Clinical Drug Literature	1859			
104	Health Accessories	1864			
105	Surgical Supplies	1895			

Index

Alphabetic Index	1967
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CHAPTER 91

Sustained-Release Drug Delivery Systems

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The goal of any drug delivery system is to provide a therapeutic amount of drug to the proper site in the body to achieve promptly, and then maintain, the desired drug concentration. This idealized objective points to the two aspects most important to drug delivery, namely, *spatial placement* and *temporal delivery* of a drug. Spatial placement relates to targeting a drug to a specific organ or tissue, while temporal delivery refers to controlling the rate of drug delivery to the target tissue. An appropriately designed sustained-release drug delivery system can be a major advance toward solving these two problems. It is for this reason that the science and technology responsible for development of sustained-release pharmaceuticals have been and continue to be the focus of a great deal of attention in both

industrial and academic laboratories. There currently exist numerous products on the market formulated for both oral and parenteral routes of administration that claim sustained or controlled drug delivery. The bulk of research has been directed at oral dosage forms that satisfy the temporal aspect of drug delivery, but many of the newer approaches under investigation may allow for spatial placement as well. This chapter will define and explain the nature of sustained-release drug therapy, briefly outline relevant physicochemical and biological properties of a drug that affect sustained-release performance and review the more common types of oral and parenteral sustained-release dosage forms. In addition, a brief discussion of some methods currently being used to develop targeted delivery systems will be presented.

Conventional Drug Therapy

To gain an appreciation for the value of sustained drug therapy it is useful to review some fundamental aspects of conventional drug delivery.¹ Consider single dosing of a hypothetical drug that follows a simple one-compartment pharmacokinetic model for disposition. Depending on the route of administration, a conventional dosage form of the drug, eg, a solution, suspension, capsule, tablet, etc, probably will produce a drug blood level versus time profile similar to that shown in Fig 91-1. The term "drug blood level" refers to the concentration of drug in blood or plasma, but the concentration in any tissue could be plotted on the ordinate. It can be seen from this figure that administration of a drug by either intravenous injection or an extravascular route, eg, orally, intramuscularly or rectally, does not maintain drug blood levels within the therapeutic range for extended periods of time. The short duration of action is due to the inability of conventional dosage forms to control temporal delivery. If an attempt is made to maintain drug blood levels in the therapeutic range for longer periods by, for example, increasing the dose of an intravenous injection,

as shown by the dotted line in the figure, toxic levels may be produced at early times. This obviously is undesirable and the approach therefore is unsuitable. An alternate approach is to administer the drug repetitively using a constant dosing interval, as in multiple-dose therapy. This is shown in Fig 91-2 for the oral route. In this case the drug blood level reached and the time required to reach that level depend on the dose and the dosing interval. There are several potential problems inherent in multiple-dose therapy:

1. If the dosing interval is not appropriate for the biological half-life of the drug, large "peaks" and "valleys" in the drug blood level may result. For example, drugs with short half-lives require frequent dosings to maintain constant therapeutic levels.
2. The drug blood level may not be within the therapeutic range at sufficiently early times, an important consideration for certain disease states.
3. Patient noncompliance with the multiple-dosing regimen can result in failure of this approach.

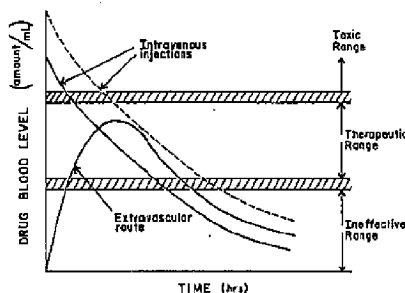


Fig 91-1. Typical drug blood level versus time profiles for intravenous injections and an extravascular route of administration.

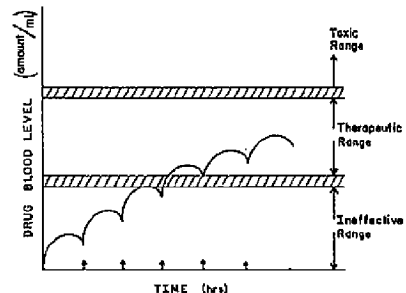


Fig 91-2. Typical drug blood level versus time profile following oral multiple-dose therapy.

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