PHARMACEUTICAL DOSAGE FORMS AND DRUG DELIVERY SYSTEMS

fifth edition

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4 Dosage Form Design: Pharmaceutic Ingredients, Product Formulation, and Current Good Manufacturing Practice

DRUG SUBSTANCES are seldom administered alone, but rather as part of a formulation in combination with one or more nonmedical agents that serve varied and specialized pharmaceutical functions. Through selective use of these nonmedicinal agents, referred to as *pharmaceutic ingredients*, dosage forms of various types result. The pharmaceutic ingredients solubilize, suspend, thicken, dilute, emulsify, stabilize, preserve, color, flavor, and fashion medicinal agents into efficacious and appealing dosage forms. Each type of dosage form is unique in its physical and pharmaceutical characteristics. These varied preparations provide the manufacturing pharmacist with the challenges of formulation and the physician with the choice of drug and drug delivery system to prescribe. The general area of study concerned with the formulation, manufacture, stability, and effectiveness of pharmaceutical dosage forms is termed *pharmaceutics*.

The proper design and formulation of a dosage form requires consideration of the physical, chemical and biological characteristics of all of the drug substances and pharmaceutic ingredients to be used in fabricating the product. The drug and pharmaceutic materials utilized must be compatible with one another to produce a drug product that is stable, efficacious, attractive, easy to administer and safe. The product should be manufactured under appropriate measures of quality control and packaged in containers that contribute to product stability. The product should be labeled to promote correct use and be stored under conditions that contribute to maximum shelf life.

Methods for the preparation of specific types of dosage forms and drug delivery systems are described in subsequent chapters. This chapter presents some general considerations regarding pharmaceutic ingredients, drug product formulation, and standards for good manufacturing practice.

The Need for Dosage Forms

The potent nature and low dosage of most of the drugs in use today precludes any expectation that the general public could safely obtain the appropriate dose of a drug from the bulk material. The vast majority of drug substances are administered in milligram quantities, much too small to be weighed on anything but a sensitive laboratory balance. For instance, how could the layman accurately obtain the 325 mg or 5 gr of aspirin found in the common aspirin tablet from a bulk supply of aspirin? He couldn't. Yet, compared with many other drugs, the dose of aspirin is formidable (Table 4–1). For example, the dose of ethinyl estradiol, 0.05 mg, is 1/6500 the amount of aspirin in an aspirin tablet. To put it another way, 6500 ethinyl estradiol tablets, each containing 0.05 mg of drug, could be made from an amount of ethinyl estradiol equal to the amount of aspirin in just one 5 gr aspirin tablet. When the dose of the drug is minute, as that for ethinyl estradiol, solid dosage forms such as tablets and capsules must be prepared with fillers or diluents so that the size of the resultant dosage unit is large enough to pick up with the fingertips.

Besides providing the mechanism for the safe and convenient delivery of accurate dosage, dosage forms are needed for additional reasons:

Table 4–1. Examples of Some Drugs with Relatively Low Usual Doses

Drug	Usual Dose, mg	Category
Lithium Carbonate	300	Antidepressant
Ferrous Sulfate	300	Hematinic
Cimetidine	300	Antiulcer
Ibuprofen	300	Antinflammatory
Amoxicillin	250	Antibacterial
Erythromycin	250	Antibacterial
Nitrofurantoin	100	Antibacterial (urinary)
Propoxyphene HCl	65	Analgesic
Thyroid	60	Thyroid
Hydrochlorothiazide	50	Diuretic
Codeine Phosphate	30	Analgesic
Phenobarbital	30	Sedative
Chlorpromazine HCl	25	Tranquilizer
Diphenhydramine HCl	25	Antihistaminic
Morphine Sulfate	10	Narcotic analgesic
Prednisolone	5	Adrenocortical steroid
Chlorpheniramine maleate	4	Antihistaminic
Colchicine	0.5	Gout Supressant
Nitroglycerin	0.4	Antianginal
Digoxin	0.25	Cardiotonic (maintenance)
Levothyroxine	0.1	Thyroid
Ethinyl Estradiol	0.05	Estrogen

1. For the protection of a drug substance from the destructive influences of atmospheric oxygen or humidity (e.g., coated tablets, sealed ampuls).
2. For the protection of a drug substance from the destructive influence of gastric acid after oral administration (e.g., enteric-coated tablets).
3. To conceal the bitter, salty, or offensive taste or odor of a drug substance (e.g., capsules, coated tablets, flavored syrups).
4. To provide liquid preparations of substances that are either insoluble or unstable in the desired vehicle (e.g., suspensions).
5. To provide clear liquid dosage forms of substances (e.g., syrups, solutions).
6. To provide time-controlled drug action (e.g., various controlled-release tablets, capsules, and suspensions).
7. To provide optimal drug action from topical administration sites (e.g., ointments, creams, transdermal patches, ophthalmic, ear, and nasal preparations).
8. To provide for the insertion of a drug into one of the body's orifices (e.g., rectal or vaginal suppositories).
9. To provide for the placement of drugs directly into the bloodstream or into body tissues (e.g., injections).
10. To provide for optimal drug action through inhalation therapy (e.g., inhalants and inhalation aerosols).

There are many different forms into which a medicinal agent may be placed for the convenient and efficacious treatment of disease (Table 3–6). Most commonly, a pharmaceutical manufacturer prepares a drug substance in several dosage forms and strengths for the efficacious and convenient treatment of disease (Fig. 4–1). Before a medicinal agent is formulated into one or more dosage forms, among the factors considered are such therapeutic matters as: the nature of the illness, the manner in which it is generally treated, locally or through systemic action, and the age and anticipated condition of the patient.

If the medication is intended for systemic use and oral administration is desired, tablets and/or capsules are generally prepared. These dosage units are easily handled by the patient and are most convenient in the self-administration of medication. If a drug substance has application in an emergency situation in which the patient may be comatose or unable to take oral medication, an injectable form of the medication may also be prepared. Many other examples of therapeutic situations affecting dosage form design could be cited, including the preparation of agents for motion sickness, nausea, and vomiting into tablets and skin patches for prevention and suppositories and injections for treatment.

The age of the intended patient also plays a role in dosage form design. For infants and children under 5 years of age, pharmaceutical liquids rather than solid dosage forms are preferred for oral administration. These liquids, which are generally flavored aqueous solutions, syrups or suspensions, are usually administered directly into the infant's or child's mouth by drop, spoon, or oral dispenser (Fig. 4–2) or incorporated into the child's food. A single liquid pediatric preparation may be used for infants and children of all ages, with the dose of the drug varied by the volume administered. When an infant is in the throes of a vomiting

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