DOSAGE FORM DESIGN

Abstract

The design of dosage forms plays a pivotal role in optimizing drug delivery and efficacy. This chapter focuses on the significance of physiological properties of drugs in dosage form design. It explores how understanding the physicochemical characteristics, such as solubility, permeability, and stability, influences the selection of appropriate dosage forms. The interplay between drug properties and physiological conditions, including pH variations, enzymatic activity, and gastrointestinal transit times, shapes the formulation strategy. Addressing these factors ensures the dosage form's compatibility with the body's physiological environment, enhancing drug absorption, bioavailability, and therapeutic outcomes. This abstract underscores the pivotal role of comprehending drug-specific physiological properties in tailoring dosage forms for effective and targeted drug delivery.

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I. INTRODUCTION

Active Pharmaceutical Ingredient are never introduced to the body alone as pure chemical substances; they are always given as formulated preparations by adding some additives or excipients. Formulations can range from simple solutions to complex drug delivery systems with the help of suitable . Each excipients has its special pharmaceutical role. It's the property of formulation additives only that can help to solubilize, to suspend, to thicken, to preserve, to emulsify and to modify dissolution rate, to improve the compactability and flavor the drug substances to form various dosage forms. Each type of dosage form is unique in its physical, chemical and pharmaceutical characteristics. Various characteristics of drug substance and P'cal ingredient is required in designing a dosage form like physical, chemical and biological . The compatibility of API and excipients is prime for the production of dosage form that is efficacious, stable, safe and easy to administer. After that, several initial formulations of the drugs are prepared and evaluated for different properties like drug release profile and clinical effectiveness. The formulation that best suited the required goals for the drug product is selected as master formula. Every batch subsequently prepared should meet the specifications as per master formula record. There are so many different dosage forms in which an API can be included to treat the disease effectively.

II. NEED OF DOSAGE FORMS

The potency and very low dose of most of the drugs in use cause problem for general public to safely obtain the appropriate dose of a drug from bulk material. As few drug substances are administered only in milligram or microgram which is too small to be weighed. Besides this, dosage forms are required for some additional reasons that includes

1. Protection of the drug substance due to the presence of gastric acid after oral administration (best suited dosage form is enteric-coated tablets)
2. For concealing the bitter and salty taste or foul odor of a drug substance (best suited dosage forms are flavored syrups, capsules and coated tablets.)
3. For liquid preparations of substances which are not soluble or remains unstable in the vehicle of choice (best suited dosage form is suspensions)
4. For controlled rate-drug action (best suited dosage forms are capsules, controlled-release tablets, and suspensions)
5. For topical drug administration's (best suited dosage forms are creams, ointments, gels, transdermal patches etc.)
6. For insertion of a drug into the body's cavity (best suited dosage forms are vaginal suppositories, rectal suppositories, aurinaria, buginaria etc.)
7. For Delivering drug directly in to bloodstream or any body tissues (best suited dosage form is injections)
8. To Deliver drug in to lungs (best dosage form is inhalants and inhalation aerosols)

The main aim of dosage form design is to obtain a predictable therapeutic response of drug formulations which can be manufactured at a very large scale with reproducible quality. Various feature required for ensuring the product quality are chemical and physical stability, uniformity of dose of drug, preservatives used against microbial contamination, suitable packaging and labeling.

Dosage form should be free from inter subject variability but this is not possible because of different absorbtion, distribution, metabolism and excretion (ADME) of each individual. Attention should be given in removing variation in bioavailability.

For maximizing drug bioavailability this is mandatory to select such a chemical form that should meet the required solubility criteria, required particle size, compatible excipients, appropriate dosage form and most appropriate route of administration, manufacturing process and proper labeling and packaging. Therapeutic response can be maximize by altering route of administration

Formulations can be taken orally or injected in to the body, as well as can be applied to the skin for local action or inhaled, **Table1** lists the variety of dosage forms that can be used to deliver drugs by different administration routes.

Table1: List of Dosage Forms Available for Different Route of Administration

Administration Routes	Dosage Forms
Oral	Solutions, syrups, emulsions, powders, tablets, capsules, elixirs, magmas, cachets, pills etc.
Sublingual	Tablets & lozenges,
Intra-respiratory	Aerosols
Rectal	Suppositories, tablets, ointments, creams, douches, foams.
Urethral	Suppositories
Parenteral	Solutions, emulsions and suspensions
Transdermal	Creams, pastes, lotions, ointments, powders, plaster
Intranasal	Sprays, inhalations, solutions
Intra-ocular	Solutions
Conjunctival	Ointments

Several drugs are prepared into many dosage forms, each having different strengths, with different p'cal characteristic which are required for a specific application. e.g glucocorticoid prednisolone which is used to lower the inflammation and allergic reaction disease. With the use of different chemical forms and different excipients, a range of effective anti-inflammatory formulations are available like tablet, injections, enteric-coated tablet, eye drops.

In contrast to the soluble form of prednisolone, sodium phosphate salt, which can be used to create soluble tablet form, solutions for ear and eye drops, and intravenous injection, the very low aqueous solubility of the base prednisolone and acetate salt can be used to create sustained release tablets and slowly absorbed intramuscular suspension injection as dosage forms.

For the formulation of dosage form of a drug substance the factors that needs to be considered are majorly divided into following categories:

- Biopharmaceutical considerations, it includes factors affecting absorption of the drug from different administration routes.
- Physicochemical properties of drug.
- Therapeutic considerations

III. BIOPHARMACEUTICAL FACTORS AFFECTING DOSAGE FORM DESIGN

Biopharmaceutics can be defined as the study of the rate and factor affecting drug absorption. It include study of pharmacokinetic and pharmacodynamic. Pharmacokinetics means simply absorption, distribution, metabolism and excretion i.e ADME of drug. Pharmacodynamic deals with therapeutic response of the drug. A Drug substance must be present in solution form to be absorbed through absorbing membranes and epithelia of the skin. Drugs are absorbed via passive diffusion or via carrier mediated transport. Driving force for passive diffusion is concentration gradient exist across cell membrane. Most of the drugs are absorbed through passive diffusion.

When dosage form is given through buccal route, rectally and respiratory route, intra muscular or sub-cutaneous the drug directly reaches in to systemic circulation. When dosage form is delivered by oral route, onset of drug action is delayed because of required transit time in the gastrointestinal tract. The physical form of the dosage form influences the absorption rate, solution being absorbed faster than suspension or granules, or tablets. Various dosage forms are listed in table 2 showing different time of action onset.

Table 2: Variation in Time of Onset of Action for Different Dosage Forms

Dosage Forms	Time of Onset of Actions
Intravenous injections	In Seconds
Intramuscular, subcutaneous injections, buccal tablets, aerosols, gases	In Minutes
Short-term depot injections, solutions, suspensions, powders, granules, capsules, tablets, modified-release tablets	It can take Minutes to hour
Enteric-coated formulations	It can take Several Hours
Implants, Depot Injection	Shows effect from Days to weeks

IV. ROUTES FOR ADMINISTRATION OF DRUGS

The absorption pattern of drugs depends on type of dosage form given and route of drug administration opted. Dosage forms are mean by which drug is delivered in a suitable form for absorption in the body from selected route of drug administration.

Drug administration Routes are divided majorly into two main categories i.e. local route and systemic which can be further sub categorized as Figure 1.

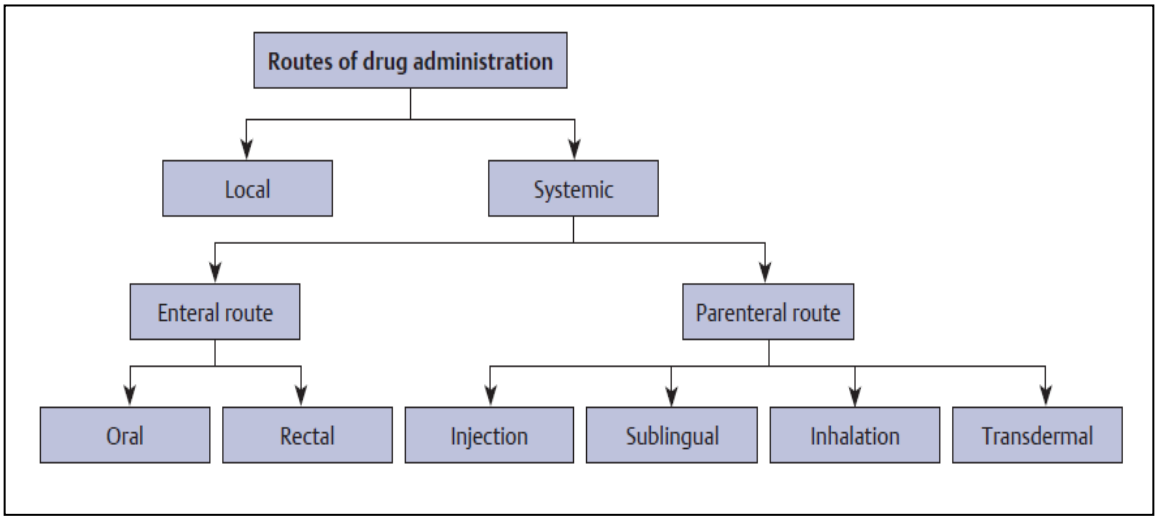


Figure1: Routes of Drugs Administration

V. ENTERAL ROUTE

This route comprises of two route i.e oral & rectal.

1. **Oral Route:** Oral route of drug administration is most widely used. Dosage forms given by oral routes are capable of achieving systemic effects that results from medication absorption passing via the gastrointestinal tract's different membranes. The disadvantages associated with oral route are slow onset of action, deterioration of several drugs because of the presence of enzymes and acids of the gastrointestinal tract. For example, insulin-containing preparations are inactivated due to stomach fluids.

   Another factor that affect drug absorption from intestine is Gastric emptying time. Slow gastric emptying can be detrimental to drugs inactivated by the gastric juices and can delay absorption of drugs more effectively absorbed from the intestine.

   Environmental pH affect the ionization and lipid solubility of drugs, the pH gradient exists in GIT range from pH 1.2 as found in stomach to pH 7 or 8 as found in the large intestine which plays role in both the degree and site of drug absorption.

   Membranes are more permeable to unionized form rather than ionized forms and most of the drugs being largely unionized at site of absorption, are well absorbed from the stomach.

   Tablets, capsules, suspensions, solutions and emulsions are few of the most popular used oral dosage forms.

   - **Parenteral Route:** This route is other than the enteral route of drug administration. In parenteral route drugs can be introduced in body using injection, transdermal route and , inhalation. Parenteral route has its own advantages like fast onset of action, so it is one of the choice used in emergency, in uncooperative patients and the ones with severe diarrheaor vomiting etc.. Parenteral route is also best suited for drugs that are

irritant, drugs with high first-pass metabolism, such drugs that are non-absorbable orally, and drugs which can be destroyed by digestive juices.

- **Injection:** On the basis where the drug is injected we have various route like **Intradermal** when Drug is injected into upper layer of skin, **Sub Cutaneous** when Drug is injected into Sub Cutaneous tissue, **Intramuscular** when Drug is injected into deltoid, gluteus maximum muscles. **Intravenous** when drug is directly injected into veins. By this route we can administer the Drugs as bolus administration or as an intra venous infusion given slowly. Bolus administration include either asingle large dose rapidly or a single unit dose injected slowly, whereas slow IV injection include addition of drug into dextrose/saline. **Intra-articular when** Drug is injected into the spaces between joints

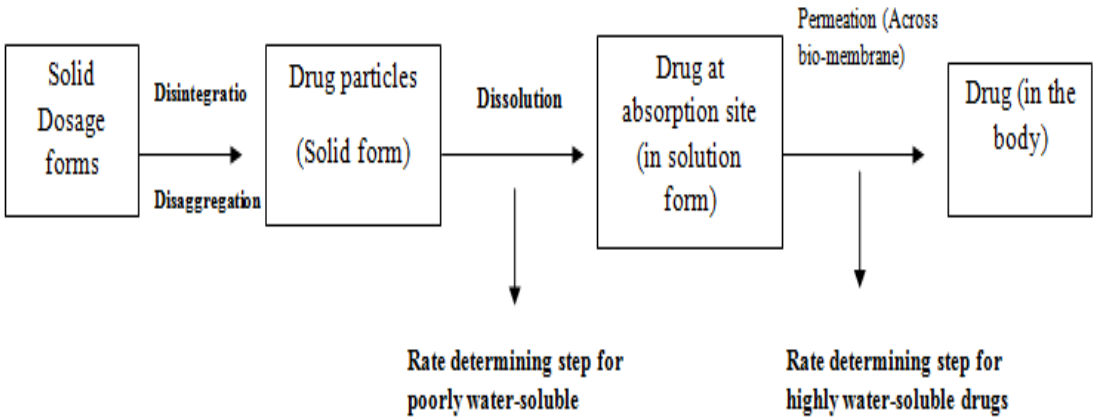
- **Sublingual:** In this type Dosage form is placed under the tongue or is applied to buccal mucosa from where it is getting absorbed into blood vessels surrounding oral mucosa and reaches in systemic circulation. The drugs having high first-pass metabolism can be given by this route so that they can reach in systemic circulation.

- **Inhalation:** This route is used for volatile liquids, vapors and gases. The drugs is Inhaled and is absorbed in alveoli present in lungs because of their large surface are, hence action is rapid.

2. **Transdermal Route:** In this route drugs reaches in systemic circulation across the skin. Patches deliver the drugs. Patches have multilayer like drug present as reservoir, for rate control a rate controlling membrane, backing film, and an adhesive layer containing primary drug dose.

VI. DRUG PHYSICOCHEMICAL FACTORS

1. **Solubility of Drugs and Dissolution Rate:** Dosage forms given by oral route are disaggregated or disintegrated before being dissolved; drugs in solution are then passed through the bio-membranes and are absorbed in body.



The following two processes are critical in the absorption of drugs from dosage forms given orally

- Dissolution rate, and
- The rate at which drugs permeate across the bio membrane (i.e. gastrointestinal membrane)

- Because the rate of dissolution is the rate determining step for poorly water-soluble drugs, absorption in such cases are said to be dissolution rate limited. e.g., Acyclovir
- Because dissolution of water-soluble drugs is rapid, for such drugs permeation is rate limiting step, so absorption is permeation rate limited. e.g., Diclofenac sodium

2. **Particle Size of Drug and Effective Surface Area:** From Noyes-Whitney's equation of dissolution:
dc/dt = DAKo/w(Cs-Cb)/VH

where,
D: Diffusion coefficient, in cm^2/s
A: Surface area of the dissolving solid exposed to the dissolution medium, in cm^2
$K_{O/W}$: Partition coefficient of the drug between water/oil in cm/s
$Cs - C_B$: Concentration gradient of the diffusing drug molecule, in g/ml.
V: Volume of dissolution medium
H: Thickness of the stagnant layer, in cm

According to this equation more the surface area, the faster will be the distribution
The surface area of a drug increases when the particle size is reduced. As a result, decreasing particle size increases dissolution rate.

Surface area can be classified into following two types:

- Absolute surface area: This is the total surface area of any particle's solid surface
- Effective surface area: This is the exposed area of the solid surface to the dissolution medium.

e.g. Superior dissolving rates are obtained by micronizing pharmaceuticals with low water solubility, such as chloramphenicol, griseofulvin, and salts of tetracycline.

Size reduction, however, has some limitations. Micronization reduces the effective surface area of hydrophobic drugs such as phenacetin,, phenobarbital etc. because the hydrophobic surface of the drugs absorb air onto their surface thus decreasing their wettability, due to which the powders float on dissolution medium.

- Due to their high surface free energy, the particles reaggregate to form larger particles.
- Surface charges imparted by extreme particle size reduction prevent wetting; and electrically induced agglomeration prevent the drug from making contact with the dissolution medium.

3. **Amorphism and Polymorphism:** A solid can be either crystalline or amorphous, depending on its internal structure.

When a substance exists in more than one crystalline form, the different forms are known as polymorphs and the phenomenon as polymorphism. Each polymorphic form has different physical and chemical properties.

Different polymorphs can be produced by crystallizing the medication under various circumstances and in various solvents. Depending on their relative stability, one of the polymorphic forms will be physically more stable than the others. The lowest energy state, greatest melting point, and lowest aqueous solubility are all possessed by this stable polymorph. The remaining polymorphs, which stand for higher energy levels, are referred to as metastable forms. There is a thermodynamic propensity for the metastable forms to change into the stable form. If kept dry, a metastable form will stay stable for years. Compared to the stable polymorphs, it is more bioavailable due to its higher water solubility.

e.g. Chloramphenicol palmitate comes in three different polymorphs: A, B, and C. The B-form is physiologically active, but the A-form has a low bioavailability.Dosage forms containing metastable forms of the drug, converted to a less soluble, stable polymorph form up on aging.

e.g. In an aqueous suspension, the more soluble crystalline form-III of cortisone acetate converts to the less soluble form-V, resulting in solid caking.

Amorphous form

These drugs have the highest energy level and can be thought of as supercooled liquids. Amorphous forms have more aqueous solubility than crystalline forms.

Novobiocin, for example, is ten times more soluble in amorphous form than in crystalline form.

4. **Pseudopolymorphism (Hydrates / Solvates):** These crystals are known as solvates, and the trapped solvent molecules are referred to as the solvent of crystallization. This occurs sometimes during the crystallization process when the solvent molecules may be absorbed into the solid's crystal lattice in a stoichiometric proportion.

Once more, the solvates can display several pseudopolymorphic states of polymorphism. The condition is referred to as pseudopolymorphism.

When water is used as the solvent, the drug's solvate is referred to as a hydrate.Effect of absorption:

- Typically, a drug's anhydrous form is more soluble than its hydrates. This is because the hydrates have less need for water because they are already in equilibrium with water.

e.g. theophyline and ampicillin are more soluble in water, dissolve more quickly, and have superior bioavailability in their anhydrous forms than in their monohydrate and trihydrate forms, respectively.

- However, compared to nonsolvates, non aqueous solvates are more soluble in water.

e.g. fludrocortisone and succinyl sulfathiazole n-pentanol solvates, as well as the griseofulvin chloroform solvates, are more water soluble than their non-solvate forms.

5. **Salt Form of the Drug:** In general, drugs are weak bases or acids. These medications' solubility and rate of dissolution can be accelerated by saltifying them.

As a result of salt production, weak acid HA becomes more soluble in basic pH, whereas weak base B gets more soluble in acidic pH.

- **Size of Counter Ion:** The salt will be more soluble the smaller the counter ion is (of a drug's salt form). The bioavailability of Novobiocin's sodium salt, calcium salt, and free acid forms, for instance, is as follows:

Novobiocin Na	Novobiocin Ca	Novobiocin free acid
50	20	1

- **The Counter Ion's Ionic Strength:** The solubility may be much lower than the free drug itself when the counter ion is particularly big in size and/or has a weak ionic strength (as in the case of ester versions of the medications). For instance, weak base pamoates and palmitates with limited aqueous solubility

6. **pKa of the Drug and pH**

- According to the pH partition theory, passive diffusion accounts for the majority of the transport of medicinal molecules with molecular weights larger than 100 across the biomembrane. The unionized drug's
- lipid solubility (Ko/w) controls the absorption process.
- The drug's dissociation constant (Ka)
- The pH at the point of absorption

Handerson-Hasselbach Equation: The medication's dissociation constant (pKa) and the pH of the fluid at the absorption site dictate how much of the drug is present in unionized form. Below are a few instances.

Drugs	pKa	pH at the Site of Absorption
Very weak bases Theophyline Caffeine	*(pKa < 5.0)* 0.7 0.9	Unionized across the board: integrated all the way through the GIT.
Moderately weak bases Heroin Codeine	*(5 < pKa < 11)* 7.6 8.3	Ionized at the pH of the stomach, unionized at the pH of the colon for improved absorption

Amitriptyline	9.7	
Stronger base Mecamylamine Guanethidine	*(pKa > 11.0)* 11.4 12.23	Ionized at all pH levels, resulting in poor GIT absorption.

Only the unionized medication, if sufficiently lipophilic, is absorbed into the systemic circulation at a certain pH, as indicated by the drug's pKa.

In order to be absorbed as effectively as possible, a medicine must have sufficient aqueous solubility to dissolve in the liquids at the absorption site, as well as lipid solubility (Ko/w) in the lipoidal biomembrane and into the systemic circulation.

VII. THERAPEUTIC CONSIDERATIONS

When choosing a drug's dose form, the nature and kinds of the condition are crucial considerations. Most of the time, a single medication ingredient is manufactured in a variety of dose forms to accommodate both patient preferences and the unique requirements of a particular clinical setting. Angina pectoris sufferers might get relief by taking nitroglycerine tablets sublingually after buccal absorption. Topical dose forms, such as cream, gels, ointments, and others that may be applied to the skin, eyes, and throat, are utilized for a drug's local impact. Few medications can be effectively absorbed via one route but not by another, thus each case must be taken into account.

Designing a dose form must take the patient's age into consideration. For babies and kids under five, liquid dosage form is recommended after oral administration. A single liquid pediatric preparation is used for infants and children of all age groups with various doses that depend on the volume of liquid. These liquids are flavored aqueous solutions, syrups, or suspensions that are supplied directly into the mouth of infants or children by drop or spoon.

REFERENCES

[1] Bourne DW, Banker GS, Rhodes CT. Modern Pharmaceutics. New York: Informa Healthcare. 2002:67-92.
[2] Niazi SK. Handbook of preformulation: chemical, biological, and botanical drugs. CRC Press; 2006 Sep 18.
[3] Gibson M. Pharmaceutical preformulation and formulation. Drugs Pharm Sci. 2001;199:199.
[4] Ansel H, Allen L. Pharmaceutical Dosage Forms and Drug Delivery Systems. Tenth Edit.
[5] Sastry SV, Nyshadham JR, Fix JA. Recent technological advances in oral drug delivery–a review. Pharmaceutical science & technology today. 2000 Apr 1;3(4):138-45.
[6] Mahato RI, Narang AS. Pharmaceutical dosage forms and drug delivery. CRC Press; 2017 Nov 22.
[7] Tekade RK. Dosage Form Design Considerations: Volume I. Academic Press; 2018 Jul 28.
[8] Junginger HE, editor. Drug targeting and delivery: concepts in dosage form design. CRC Press; 1992 Oct 31.
[9] Patel P, Ahir K, Patel V, Manani L, Patel C. Drug-Excipient compatibility studies: First step for dosage form development. The Pharma Innovation. 2015 Jul 1;4(5, Part A):14.
[10] Hom FS, Miskel JJ. Oral dosage form design and its influence on dissolution rates for a series of drugs. Journal of pharmaceutical sciences. 1970 Jun;59(6):827-30.
[11] Ace Jr LN. Pharmaceutical dosage forms and drug delivery systems. American Journal of Pharmaceutical Education. 2001 Apr 1;65(1):104.
[12] York P. The design of dosage forms. Pharmaceutics: the science of dosage form design. 2013 Jul 29:1-2.
Davis SS. Recent developments in dosage form design. Drug Development Communications. 1976 Jan

