CALIFORNIA NORTHSTATE COLLEGE of PHARMACY

To Advance the Art and Science of Pharmacy

INTRODUCTION TO PHARM 632

&

ROUTES OF DRUG ADMINISTRATION

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This course deals with dosage forms and drug delivery systems:

- what they are,
- why we need them,
- how they are made,
- how they are tested,
- what goes into them (ingredients),
- what effect they have on the body (biological system),
- how the body affects them,
- the advantages and disadvantages of each type,
- their stability, and
- how to choose from the different types of dosage forms of the same drug.

In addition, we will also learn how the drug is released from the dosage form, how it is absorbed into the body (mechanisms), and which physiological factors affect absorption. A general approach is to outline the principles and give a few examples for illustrative purposes. Students should then find more examples by consulting the literature and appropriate websites.

We should start off with a very basic concept: what are dosage forms and why do we need them?

Need for Dosage forms

Dosage forms are the form in which each dose of the drug is supplied to the patient e.g. tablets, capsules, suppositories, injections, lozenges are dosage forms.

Why do we need dosage forms?

Suppose we did not have dosage forms, how would the drug be administered? Could we directly administer the drug in powder or liquid form (without any additives)? In some instances, it would be very difficult or practically impossible. If the dose of the drug is very small, such as 1 mg or less, it would be very difficult to administer in the form of the drug powder. In addition, many drugs would degrade if the drug alone is stored in a container for patient use. So, dosage forms provide an accurate amount of the drug in a stable physical form that is convenient to administer.

Fentora® (Fentanyl citrate) is a potent opioid that is available in several accurately controlled doses, including 100 micrograms (0.1 mg) per tablet. This is a very small dose and rigorous testing must show that the dose is accurate before the product can be released for sale. (Some of these tests will be discussed in the Tableting topic.)

Lanoxin® tablets are another example of a low dose tablet (from as little as 0.125 mg per tablet). Taking this tablet provides a far more accurate dose of the drug compared to the patient taking digitalis leaf (from which the active ingredient is obtained). Why? Plant materials may vary in their content of the drug, depending on soil conditions, where the plant was grown (geography), the condition of the soil, the amount of rain experienced that season etc. A Reserpine tablet has a far more accurate dose than an amount of the root of Rauwolfia serpentina (the plant from which reserpine is obtained).

Nitroglycerin is a highly volatile product. However, stabilized nitroglycerine tablets have a fair shelf life (if stored under proper conditions!). Similarly, Isordil® tablets contain a stable dose of Isosorbide dinitrate if properly maintained (store at room temperature away from light and moisture). Thus, in these cases, the formulation of the product provides a great deal of stability to a drug that is inherently unstable.

Modern dosage forms provide several additional benefits, beyond stability, accurate dose and convenience of administration, as the following examples indicate:

1. Separate Incompatible Drugs

The dosage form may contain two physically incompatible drugs that are separated in such a way as not to interact with each other e.g. in separate layers or with one or both drugs coated, thus preventing them from reacting with one another.

In the patent quoted below, Tramadol and Diclofenac are combined in one dosage form. Tramadol is a potent pain reliever and Diclofenac is a non-steroidal anti-inflammatory drug. The WHO claims that the combination of opioid analgesic and NSAID is a potent pain reliever and that the dose of opioid may be reduced if the combination is used. However, Tramadol and Diclofenac react chemically to form a poorly soluble complex that would reduce the absorption of the drug (most drugs must be in solution in order to be absorbed).

By incorporating the two drugs in separate layers with at least one placebo layer in between, a combination product that is effective may be produced.

United States Patent	6,558,701
Bartholomaeus , et al.	May 6, 2003

Many dietary supplements claim the separation of incompatible ingredients in multiple layered tablets. Since the layers are often colored differently, they look attractive and it is often not clear if these supplements and herbal products were produced as layered tablets mainly for aesthetic reasons. (Note: herbal products may also be presented as bilayered tablets where one layer is a sustained release layer and the other is a conventional release layer for fast onset of action. This is a different purpose than prevention of instability, as described above.)

2. Provide a mechanism to enhance the absorption of a poorly absorbed drug.

Cyclosporin has been used for many years to counteract rejection in transplant patients. The old formulation (Sandimmune®) was replaced a few years ago by a microemulsion formulation, Neoral®, which shows much improved absorption and better control of rejection. The nature of the microemulsion allows the drug to be absorbed to a much greater extent.

When Griseofulvin tablets were reformulated many years ago, micronized drug particles were utilized and absorption was increased so greatly that the dose was reduced to the 500 mg usually used at present for an adult. Hence, the type of formulation is important. In some instances, big differences in the amount of drug absorbed, or of side effects, can be seen with different formulations of the same drug.

3. Reduce degradation in biological fluids

The dosage form may be constructed to reduce the natural tendency for the drug to be degraded in a biological fluid. All enteric-coated tablets and capsules protect sensitive drugs from the acid of the stomach. In the less acidic conditions of the small intestines, the coating dissolves to release the drug for absorption. Nexium® (esomeprazole) is an example ("the purple pill"). Enteric coating will be briefly discussed in the section on tableting.

The above examples illustrate how it may be possible to pass a dosage form through the part of the body that would have degraded the drug, without actually causing significant deterioration to it.

Of course, another approach would be to introduce the drug into the body by another route which does not have the harsh conditions that destroy the drug e.g. deliver the drug through the buccal membrane of the mouth (without swallowing the drug) since the oral cavity does not have the acidic conditions of the stomach). Is this an easier approach? Often, it is not since the drug may not naturally permeate the biological membrane of the alternate route (oral cavity). Peptides are very susceptible to the action of gastric acid and are rapidly broken down in the stomach. They are not degraded during transdermal delivery but will not penetrate the skin easily. Oralyn® is an oral transmucosal spray containing insulin (peptide) that penetrates the lining of the mouth. The product is available in some South American countries and is awaiting registration in the US.

4. Controlled Release

The dosage form may contain mechanisms to control the rate at which the drug is released for a steady, predetermined rate of drug absorption. This produces the desired effect without intense side effects caused by high drug levels. The product may be an oral (swallowed) dosage form (such as Sudafed 12 hour extended release tablets or Ambien CR). The pharmaceutical product may, alternately, utilize permeation of the drug through another part of the body (e.g. the Fentanyl patch or Scopolamine patch which both utilize permeation through the skin).

The Scopolamine patch provides sustained release of this drug to eliminate or reduce motion sickness without causing drowsiness (which would occur with a conventional dosage form of this drug).

Fentanyl patches are available for administration once in 3 days. Not only is this much more convenient than taking injections every 6 hours (the alternative since this drug is not well absorbed through the GIT).The patch also provides more or less constant blood levels for better control of pain. Other transdermal patches provide convenience of administration, offer several days therapy in one patch (e.g. hormonal replacement therapy), and steady release of the drug to achieve nearly constant blood levels. (Why is it important to achieve blood levels that do not fluctuate greatly (go high, and then low, only to go high again some hours later)? Patches will be discussed in more detail in the Transdermal topic.

5. Reduce Irritation caused by the Drug

The dosage form could be developed to decrease irritation normally caused by the drug. Microfined Aspirin has smaller aspirin particles to reduce the irritation caused by the crystals abrading the stomach surface. Buffered Aspirin reduces the acidity caused by aspirin in the local area of the drug particles.

6. Provide Tamper Resistance

Gel tabs (capsule-shaped tablets with a thin coating of gelatin) offer the ease of swallowing of capsules with a far greater tamper resistance than capsules. These products were developed by the McNeil company after incidents of willful tampering with capsules. This represents a convenience to the patient while assuring his safety.

Drug Delivery Systems

The more complex dosage forms are referred to as “drug delivery systems”. Their complexity has increased with each passing year. Such complex dosage forms are usually patented.

The patent allows the company producing them protection from competition for a limited period, usually 20 years but also forces the company to disclose the nature of the invention in a publically accessible document. The mere reading of a patent may stimulate another scientist to develop additional drug delivery systems (without infringing the patent). Of course, once the patent period has expired, other companies may produce the same formulation. Thus the patenting system ultimately makes new inventions accessible to everyone. It will be readily understood that patents are valuable documents and are therefore frequently the subject of litigation. Company A may claim that Company B infringed its patent by producing a similar product. It would then be

Company B's responsibility to show that their product is different from that of company A and that they do not infringe the patent.

If we appreciate and accept the need for a dosage form as the suitable unit in which to present the drug for delivery into the body, then it becomes obvious that many different types of presentations are possible. While the oral route has historically been the most important route of drug delivery, it was not the only route known to man in that ointments, creams etc have been in use for a very long time (with variable effectiveness). In recent times, other routes of drug delivery such as the oral mucosal (lining of the mouth) have become increasingly important. The transdermal route has become more important in recent years and many novel dosage forms have been developed to deliver drugs through the skin.

This course, therefore, describes the different routes of drug administration. Since many different dosage forms are currently in vogue to administer drugs through these different routes, this course goes on to describe the formulation, production and testing of modern dosage forms. **This will provide the pharmacist with an intimate knowledge of the products he sells and enable him to talk to both industrial formulation scientists and clinical scientists with an understanding of the issues.**

After the introductory discussion on the routes of drug administration, selected routes will be discussed in more detail:

- the advantages and disadvantages of the selected route (such as the sublingual, or under the tongue, route),
- the biological barriers to overcome in order that the drug can be absorbed,
- the rate of drug absorption via that route (are some routes faster than others?),
- the formulation factors that will give enhanced results (what can the formulator put into the product that will make it work better?),
- the limitations of the route (will it only work with a particular chemical class of drugs, or only with molecules below a certain molecular weight?)

This approach of understanding the influence of the body on the dosage form (including the drug) and the influence of the dosage form on the body, falls into the subject area of Biopharmaceutics. It also includes the biological mechanisms of drug absorption etc. In this course, we will also deal with pharmaceutical calculations and will touch on some aspects of compounding.To some extent, formulation and manufacturing processes will be covered. You are expected, for board examination purposes, to know some fundamental aspects of manufacturing e.g. how manufacturing processes may influence the rate of absorption of a drug.

ROUTES OF DRUG ADMINISTRATION

The ideal therapy would be to administer to a patient one drug which has a single desired effect and no unwanted or side effects. Such a drug, in the ideal situation,

would pass directly to the site of action (the organ or part of the organ where the effect is required) so that it brings about the desired response (such as the relief of pain) in that part of the body only and does not affect other organs. Such an ideal drug does not exist. In the first place all drugs have multiple effects and the pain-relieving drug may also cause euphoria and drowsiness. Or, a pain medication may irritate the stomach and increase bleeding time.

Since medicinal chemistry has not progressed to the point where we have drugs with a single effect (pin-point pharmacology), we have to contend with drugs with multiple effects. The drug's beneficial effects and its side effects are a "package deal". Generally, the drug is administered at some convenient site (historically through the mouth to the GIT), the drug is absorbed, reaches a central compartment (the blood) and is distributed by this central compartment throughout the body. The vascular system has been described as the body's highway system that is able to deliver drugs to all parts of the body. The diluted drug in this central compartment is the source of the drug that is supplied to the site of action. Can you see any inefficiency or problems with this system?

Accepting that, at the present time, drugs with multiple effects is our reality, the following questions are posed:

1. ***Is it possible to administer the drug only to the site of action?***

2. ***Is it possible to have such a drug exert effects (beneficial and unwanted) only at the site of action?***

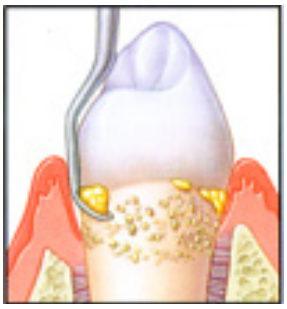
If we could achieve these goals, it would spare the rest of the body the impact of the drug's effects and side effects. Unfortunately, even this is not a totally realistic expectation as shown by the following examples. However, pharmaceutical scientists may, through knowledge of the drug's properties and an intimate understanding of the human body, try to develop drug delivery systems that get us a little closer to these ideals.

A drug may be delivered by **catheterization** i.e. by inserting a tube into a particular organ and administering the drug through the tube with the intention of treating only that organ. This may produce a higher drug level in the organ concerned, without administering the drug to the general blood circulation, as it would occur if an intravenous injection is given. This saves the cost of the drug (a bigger dose would have to be given if it is to be distributed throughout the body.) It also saves the rest of the body from having to experience the high dose of the drug. However, there are problems

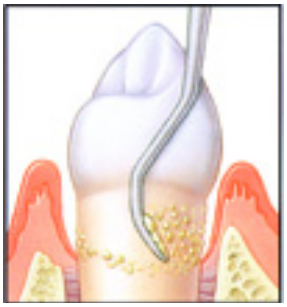
associated with this. To some extent, the drug will leak out of the organ to the blood circulation and reach other organs. Hence, the drug effect is not totally located to one organ. There are also other issues which make this impractical: the catheter exposes the patient to the possibility of infections related to inserting the catheter, it would require a clinic stay etc. So, the idea of dosing only one organ by means of a catheter is not only impractical, it also may not work very well in confining the drug to one area of the body.

Periodontal films are thin strips or films of biocompatible material that are impregnated with drug for the treatment of periodontal disease. For example, the Periochip® is a thin film containing chlorhexidine for the adjunctive treatment of periodontal disease. A dentist inserts the chip into the periodontal sulcus where it releases chlorhexidine over a period of approximately 10 days. Repeat visits, at 3-monthly intervals, are required for the insertion of additional chips for long term treatment. By the use of this device high concentrations of the antiseptic, chlorhexidine, can be reached in the periodontal sulcus (gum socket in which the tooth sits) to effectively kill off bacteria. This device allows high concentrations of this compound without causing systemic toxicity. (Nevertheless, a small amount of drug will diffuse out of the gum socket into surrounding tissues but does not cause significant side effects).

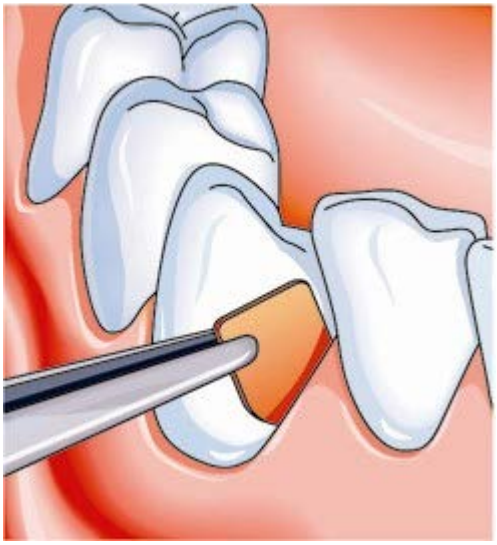
Scaling
Scaling is a type of cleaning. It removes plaque and tartar from around and below the gum line.



Root Planing
Root planing involves scraping and smoothing the root surfaces of your teeth. Gum tissue can more firmly reattach to roots that are clean and smooth.



Source: http://www.timtelliosdmd.com/scalingandrootplaning.html



Source: Periochip website: www.periochip.com/

A **drug eluting stent** is a device placed into the coronary artery to help keep it open. The stent may also contain drugs that prevent the artery from becoming blocked again (restenosis). This arrangement places the drug at the site of action. Even in such a case the drug will slowly diffuse into the blood and to other organs to a small extent. While not perfect, such administration is better than *systemic administration* of a high dose of a drug which will permeate the whole body to enable a small amount to be taken up by the affected organ.

The periodontal chip and the drug eluting stent are two extreme examples which reflect drug delivery close to the site of action. The Periodontal Chip and other, similar devices delivering drug to the periodontal sulcus, have been quite successful in keeping most (not all) of the drug in one area. Usually, it is either not possible, or not practical, to administer the drug at, or very close to, the site of action.

Traditionally, drugs were administered, for example by swallowing, and resulted in the drug being absorbed and circulated throughout the general circulation. This transferred some of the drug to a part of the body where it is needed. Some of the limitations of this process are:

- How much drug is required to circulate throughout the body to overcome pain in one area of the body?
- What side effects are caused by this drug perfusing the entire body although it is only needed in one spot?
- What is the limitation in dose due to a side effect in one part of the body (e.g. the kidneys) for a drug that is needed to relieve a symptom in another part of the body (the head in the cases of headache)?

For most drugs, we are far from the ideal situation of delivering a drug at a controlled rate to one location only, at the present time. Nevertheless, **Pharmaceutical Scientists may try to improve the therapeutic effect by controlling where the drug is administered; how fast the drug is released; and at what rate it is absorbed etc.** To be able to develop such dosage forms, especially to administer the drug at other sites besides the mouth, and *have it absorbed advantageously,* takes scientific knowledge, skill and inventiveness.

By **route of drug administration** is meant the passage or path by which the drug is introduced into the body. An example is the oral route where the drug is swallowed passes into the stomach and then the small intestine from where it is absorbed into the blood stream. The blood carries the drug to the liver where a portion of it is degraded. The remaining intact drug passes into the general circulation and is carried to the site of action where it reacts with receptors to bring about a pharmacological response.

The oral route is also known as the ***enteral route.*** The term "enteral" refers to the "enteron" or gastrointestinal tract (GIT). Any drug that is absorbed through the GIT has entered the body via the enteral route. All other routes are **parenteral.** Note that the injection route is one example of a parenteral route. In common usage, the term parenteral is taken to mean any type of injection route i.e. intravenous (IV) or into a vein, intramuscular (IM) or into the muscle, subcutaneous (sc) or under the skin, intrathecal or into the spinal cord.

The recent increase in popularity of drugs delivered through the lining of the mouth has also caused some confusion in terminology. Since the drug is delivered through the mouth, can we use the term "oral" to describe this type of delivery? Some authors have used the term ***oral transmucosal*** to describe drugs placed in the mouth for absorption through the lining of the mouth. This is the more appropriate description and enables one to distinguish these drugs from "oral" drugs which are swallowed for absorption through the GIT.

Often there is a choice of route of drug administration, depending on factors such as the nature of the drug, the therapeutic need and the condition of the patient e.g.:

a) Is the drug water soluble or oil soluble, a small molecule or a peptide?
b) Do we want a rapid onset or a slower delivery of the drug?
c) Is the patient ambulatory or hospitalized?

Through which routes is the drug absorbed to a reasonable extent? If a drug is not absorbed through the skin but is absorbed through the oral cavity, the nasal cavity, and the rectum, then the formulator must think of the 3 latter routes and decide which is best for the condition being treated. If the patient is nauseous, for example, the oral cavity route may not be a good idea. The following overview of the different routes will help to understand the complexities.

Oral or Enteral Route

The oral route has been used from the earliest times for the ingestion of drugs. It is the most obvious route for substances considered beneficial. It is considered a very safe route and this route is easy for self administration. The dosage forms for the oral route are relatively cheap to manufacture (compare tablets to transdermal patches). However, it is not without its problems:

1. Children and geriatric patients may have difficulty swallowing and this is a distinct problem with larger doses. It also needs the active cooperation of the patient and in instances of uncooperative patients, this easy administration route can prove to be extremely difficult. Think of young children or mentally impaired patients.

2. The taste of the drug may present a problem. However, this is partially overcome with flavors and may be completely overcome by coating the tablet. The formulation scientist has to ensure that the coating does not delay absorption of the drug.

3. The drug may cause nausea, irritation and vomiting.

4. The drug will experience a very acidic environment in the stomach which may degrade the drug. (We may get around this by enteric coating the drug.)

5. Enzymes in the GIT may degrade the drug.

6. Absorption may be limited, especially with respect to poorly soluble drugs.

7. Absorption may be variable from patient to patient and even within the same patient, depending, for example, on whether food is taken with the drug and also on the nature of the meal. A fatty meal with a few glasses of wine may change absorption significantly from the amount absorbed after a light salad.

8. There may only be a short absorption window i.e. only a small part of the GIT is capable of absorbing the drug. The drug, mixed with intestinal contents, may pass the window too rapidly for significant absorption.

Buccal and Sublingual Delivery

While there are some differences between these routes of drug delivery (which will be dealt with in the Buccal and Sublingual Dosage Forms topic), we can consider these to be essentially the same and discuss the route in broad outline. The blood vessels from the mucosa lead into the systemic circulation, thus avoiding the liver during the first pass. Therefore, the degradation normally experienced in the liver will not occur and more of the drug will reach the systemic circulation. (The role of the liver is to degrade, or make less harmful, any toxins ingested; the liver sees the drug as a foreign substance that must be eliminated or detoxified.)

Disadvantages include the taste of the drug (imagine holding a bitter tablet under your tongue for several minutes while it is slowly absorbed). The advantage is the fact that it is possible to get rapid absorption of the drug; often this is much faster than absorption via the oral route. Since absorption is more efficient, a much lower dose can usually be administered. Special delivery systems may be needed to enable the drug to be transferred across the barrier (oral mucosa). This will be discussed in more detail in the topic covering these dosage forms.

Colonic Delivery

Some drugs may be destroyed by the harsh conditions of the stomach (acidic pH) or the small intestines (enzymes) but be effectively absorbed in the colon. Peptides are a group of drugs that fall into this category (insulin for diabetes; calcitonin for osteoporosis). The colon contains little enzymes but bacteria are present which help break down residual matter from food. Hence, if we had a material to coat the drug that is resistant to acidic pH and enzymes but succumbs to bacterial breakdown, it would be possible to deliver the drug in the colon without degradation in the stomach or small intestines.

A drug product, such as a tablet containing the sensitive drug, is coated with the resistant material. When the tablet is swallowed, it is not affected by the acid and passes intact through the stomach (does not disintegrate). It continues down the small intestines unaffected by the enzymes of the small intestines. When the tablet reaches the colon, the coating is broken down by the bacteria and the tablet disintegrates to release the drug for absorption by the colon.

Rectal Delivery

The rectum is well supplied with blood vessels and drugs applied to the rectum may be absorbed readily and rapidly. Aminophylline suppositories for the treatment of asthma attacks were popular. Generally, suppositories are not popular in the US but they remain popular in Europe and South America. They are still used for nausea and vomiting e.g. Stemetil® Suppositories and Cyclizine Suppositories. The pharmacist may be called upon to make suppositories for a particular patient.

Nasal Administration

The nasal mucosa is relatively permeable to small molecular weight compounds. If the drug is able to pass the mucosa, it is rapidly taken into the general circulation. Although the surface area is small, it is large enough for adequate absorption of many drugs (cocaine is rapidly and extensively absorbed!!). Small peptides can be sufficiently well absorbed for this route to be useful. Larger peptides may not cross the barrier sufficiently well. Miacalcin® is a preparation of salmon calcitonin that is administered intranasally to treat osteoporosis and Paget's disease.

Transdermal Absorption

The skin has a very large surface area, a part of which can be utilized for the administration of drugs. However, the epidermis of the skin contains densely packed cells which contain keratin and this layer is a barrier to drug absorption. Lipophilic drugs pass through the skin but the transit time may be long. (Is the long transit time good or bad for drug delivery?)

Nitroglycerin, fentanyl, scopolamine, nicotine and progesterone are some of the drugs that have been studied for transdermal delivery. If there is minimal metabolism as the drug passes through the skin, then the net effect would be similar to a subcutaneous injection. Hydrophilic drugs, generally, will not permeate the skin unless special techniques are used. If a drug does get past the barrier, this is an effective means to delivery that drug since it avoids the GIT (irritation, metabolism or degradation) and the liver (metabolism). This route provides a long duration of action e.g.72 hours for fentanyl patches.

Pulmonary Delivery

Presently the lungs are used mostly for local action of the drug i.e. bronchodilators and anti-inflammatory steroids for asthma. However, there is interest in using this organ to deliver drugs to the general circulation:

1. The surface area is large
2. It is well supplied with blood vessels
3. The drug passes directly into the blood stream and the effect is, therefore, very rapid.

The size of particles administered to the lung affects the part of the lung to which they are delivered, and, therefore, the usefulness of the therapy.

Intravenous Administration

When a drug is injected intravenously, it enters directly into the blood stream i.e. there is no absorption phase. From here it is pumped throughout the body, including to the site of action very rapidly and that is why IV injections have a fast onset of action. However, one must not assume that the drug passes directly to the site of action.

The venous blood returns to the heart and is then pumped to the lungs where some drugs are metabolized and some (those that have a high vapor pressure) are excreted. (Can you think of a drug with a high v.p. that is excreted through the lungs?) From the lungs, the blood with remaining drug (that portion that is not metabolized or excreted), flows back to the heart for circulation to the entire body, including the organ where the drug is needed. From this brief picture we can see:

1. that the drug is diluted tremendously before it reaches the site of action, and

2. the rest of the body must also experience the effect of the drug (and its side effects)
3. other organs may participate in the elimination (excretion and metabolism) of the drug

Subcutaneous Injection

When a drug solution is injected into the subcutaneous space (under the skin), the drug diffuses to blood vessels and is absorbed into these blood vessels. Thus the drug does not go directly into vessels as in the case of IV injection. There is an uptake or absorption phase. Therefore, there is a slower pharmacological response than in the case of an IV injection. After the drug passes into the veins, it is carried to the heart, the lungs, back to the heart and then distributed throughout the body.

The sc route is good for peptides (which are degraded to a large extent in the GIT) e.g. Insulin is administered this way. The slower absorption is not bad from one perspective: a sudden drop in blood sugar does not occur. The delayed absorption means, however, that the rapid rise in blood glucose level after a meal, will not be rapidly counteracted by an insulin injection that is administered at about the same time as the meal. The injection has to be well timed and/ or other drugs have to be given as will be further discussed in the Therapeutics class on insulin.

Intramuscular Injection

Intramuscularly administered drugs (i.e. drugs administered into the muscle tissue), diffuse slowly, reach blood vessels, are absorbed into these vessels etc as for sc injections. The absorption rate is slower than that from the subcutaneous area largely because the muscle tissue is dense. This can result in a slower initial response but the pharmacological response will occur over a longer period. This may be many days in some instances e.g. some chemical forms of penicillin.

The absorption rate is influenced by the blood flow rate which, in turn, is affected by the muscle into which the drug is injected. The deltoid muscle has a much faster blood flow rate, and therefore faster absorption, than the gluteus muscle.