PHAR 7632 Chapter 7

Routes of Drug Administration

Routes of Drug Administration

Student Objectives for this Chapter

After completing the material in this chapter each student should:-

- be able to describe various routes of drug administration including the concentration versus time profile that might expected from thier administration
- be able to describe the advantages and disadvantages of various routes of drug administration

One method of classifying routes of administration is ENTERAL and PARENTERAL. Enteral means to do with the GI tract and includes oral, buccal, and rectal. Parenteral means not through the alimentary canal and commonly refers to injections such as IV, IM, and SC; but could also include topical and inhalation. We can also distinguish IV from the rest, as with all others at least one membrane must be crossed, thus an absorption process is involved in the administration and the pharmacokinetics.

Table 7.1.1 Market and Share of Pharmaceuticals by ROA
Data from Viswanathan, 2004

ROA	Market Value	Market Share
Oral	$24.1B	32 %
Pulmonary	$20.0B	27 %
Nasal	$8.2B	11 %
Injection/Implants	$6.6B	9 %
Transdermal/Dermal	$5.7B	8 %
Transmucousal	$0.4B	0 %
Other ROA or Devices	$10.0B	13 %

References

- Dosage Form definitions from the FDA
- Routes of Administration at College of Veterinary Medicine at Cornell University
- Shargel, L. and Yu, A.B.C. 1999 **Applied Biopharmaceutics and Pharmacokinetics**, 4th ed., Appleton and Lange, Stamford, CT pp108-109, pp154-163.
- Gibaldi, M. 1984 **Biopharmaceutics and Clinical Pharmacokinetics**, 3rd ed., Lea and Febiger, Philadelphia, PA Chapters 3-7.
- Viswanathan, S. 2004 Advances in Drug Delivery, *Pharmaceutical Formulation Quality*, June/July, p20-28

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Oral (PO)

Oral administration will be covered in more detail in subsequent Chapters. Absorption after oral administration can be quite variable. Dosage form design may also be used modify the rate of absorption.

Advantages:

Convenient - portable, safe, no pain, easy to take.

Cheap - no need to sterilize (but must be hygienic of course), compact, multi-dose bottles, automated machines produce tablets in large quantities.

Variety of dosage forms available - fast release tablets, capsules, enteric coated, layered tablets, slow release, suspensions, mixtures

Disadvantages:

Sometimes inefficient - high dose or low solubility drugs may suffer poor availability, only part of the dose may be absorbed. Griseofulvin was reformulated about 1970 to include the drug as a micronized powder. The recommended dose at that time was decreased by a factor of two because of the improved bioavailability.
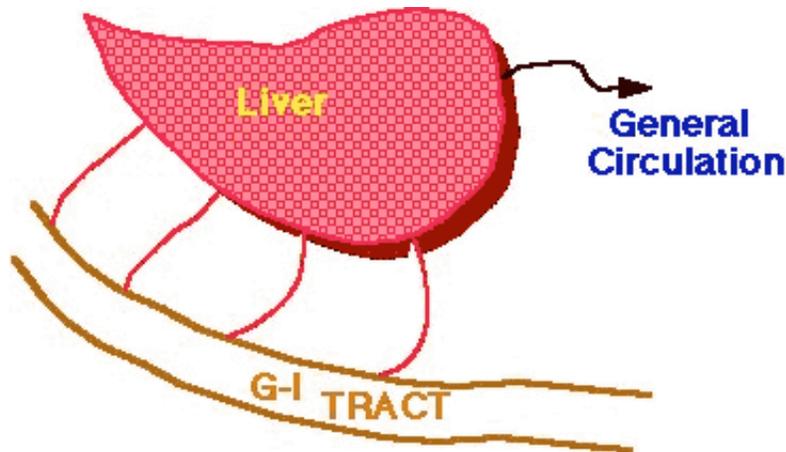
Figure 7.2.1 First Pass Effect

First-pass effect - drugs absorbed orally are transported to the general circulation via the liver. Thus drugs which are extensively metabolized will be metabolized in the liver during absorption.

e.g. the propranolol oral dose is somewhat higher than the IV, the same is true for morphine. Both these drugs and many others are extensively metabolized in the liver.

Food - Food and G-I motility can effect drug absorption. Often patient instructions include a direction to take with food or take on an empty stomach. Absorption is slower with food for tetracyclines and penicillins, etc. However, for propranolol bioavailability is higher after food, and for griseofulvin absorption is higher after a fatty meal.

Local effect - Antibiotics may kill normal gut flora and allow overgrowth of fungal varieties. Thus, antifungal agent may be included

with an antibiotic.

Unconscious patient - Patient must be able to swallow solid dosage forms. Liquids may be given by tube.
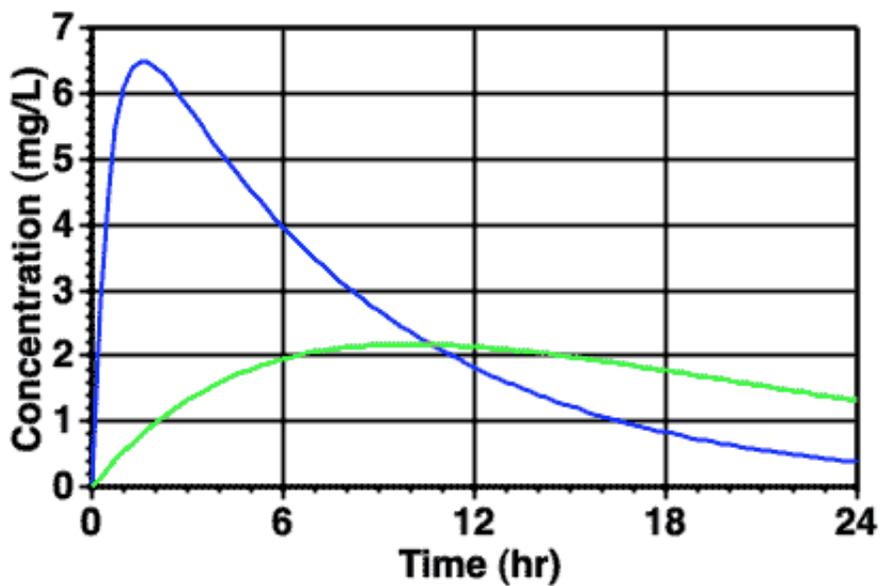
Figure 7.2.1 Typical Plot of Cp *versus* Time after Oral Administration Fast and Slow Release Dosage Forms

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Buccal and Sublingual (SL)

Some drugs are taken as smaller tablets which are held in the mouth or under the tongue. These are buccal or sublingual dosage forms. Buccal tablets are often harder tablets [4 hour disintegration time], designed to dissolve slowly. Nitroglycerin, as a softer sublingual tablet [2 min disintegration time], may be used for the rapid relief of angina. This ROA is also used for some steroids such as testosterone and oxytocin. Nicotine containing chewing gum may be used for cigarette smoking replacement.

Advantages:

First pass - The liver is by-passed thus there is no loss of drug by first pass effect for buccal or sublingual administration. Bioavailability is higher.

Rapid absorption - Because of the good blood supply to the area of absorption is usually quite rapid, especially for drugs with good lipid solubility.

Drug stability - pH in mouth relatively neutral (cf. stomach - acidic). Thus a drug may be more stable.

Disadvantages:

Holding the dose in the mouth is inconvenient. If any part of the dose is swallowed that portion must be treated as an oral dose and subject to first pass metabolism.

Usually more suitable for drugs with small doses.
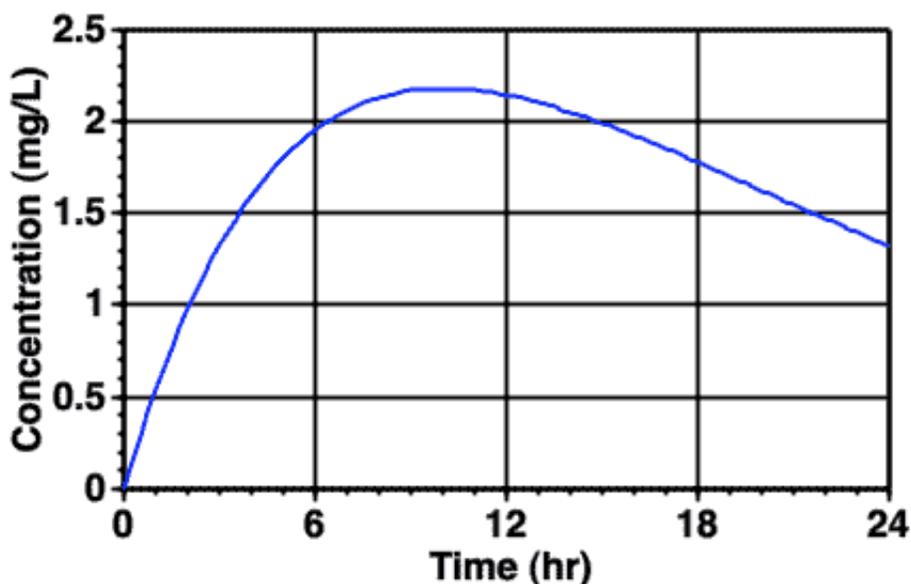
Drug taste may need to be masked.

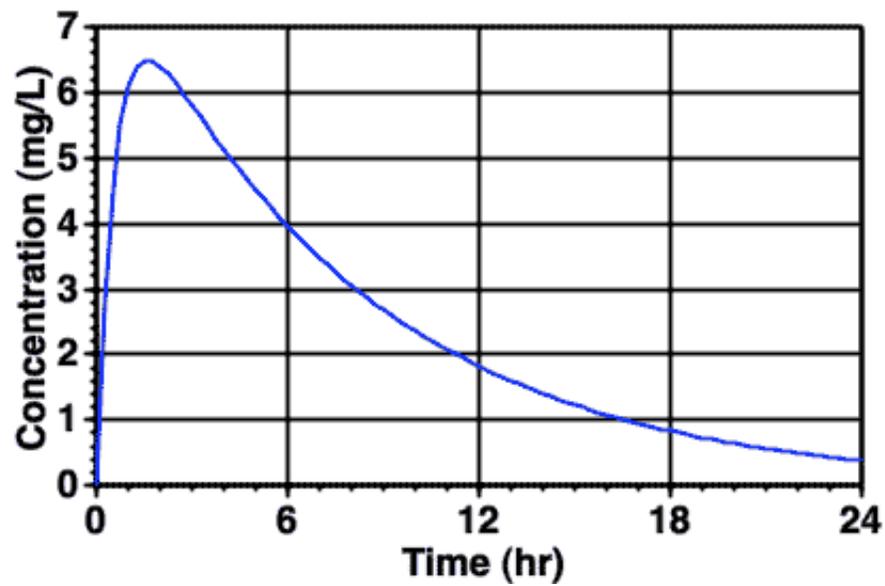**Figure 7.3.1 Typical Plot of Cp *versus* Time after Buccal Administration**

Figure 7.3.2 Typical Plot of Cp *versus* Time after Sublingual Administration

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Rectal (PR)

Drugs given by the rectal route a most commonly given as suppository or enema. Some drugs given by this route include aspirin, theophylline, chlorpromazine and some barbiturates.

Advantages:

By-pass liver - Some (but not all) of the veins draining the rectum lead directly to the general circulation thus by-passing the liver. Therefore there may be a reduced first-pass effect.

Useful - This route may be most useful for patients unable to take drugs orally or with younger children.

Disadvantages:

Erratic absorption - Drug absorption from a supppository is often incomplete and erratic. However for some drugs it is quite useful. There is research being conducted to look at methods of improving the extent and variability of rectal administration. Absorption from solutions used as an enema may be more reliable.
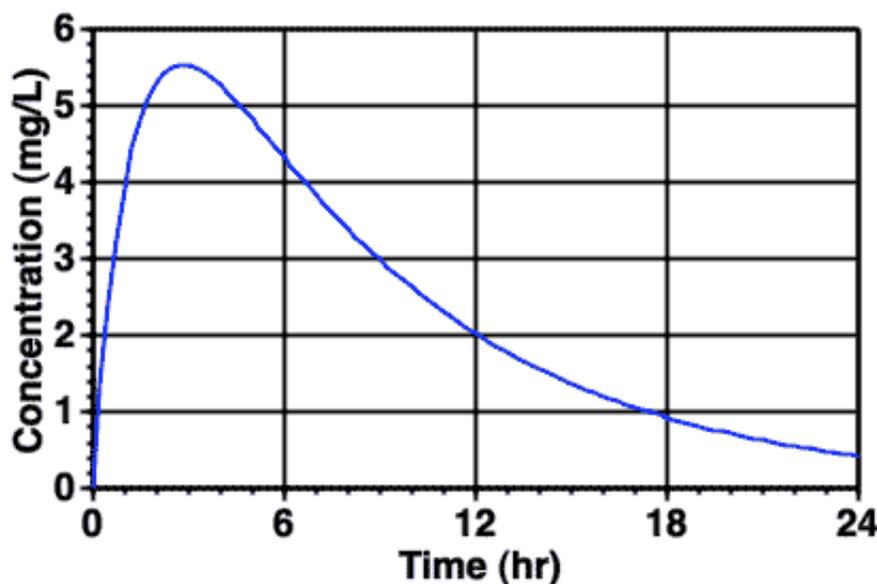
Not well accepted. May be some discomfort.

Figure 7.4.1 Typical Plot of Cp *versus* Time after Rectal Administration

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Intravenous (IV)

Drugs may be given into a peripheral vein over 1 to 2 minutes or longer by infusion. Rapid injections are used to treat epileptic seizures, acute asthma, or cardiac arrhythmias.
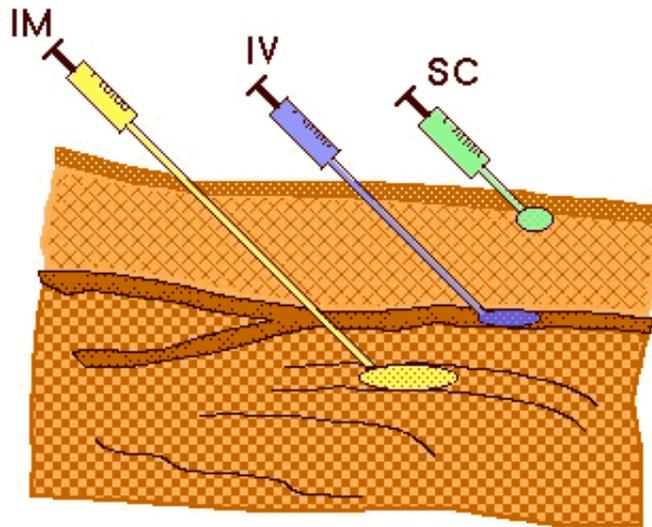

Figure 7.5.1 Showing IV, IM, and SC Injection

Advantages:

Rapid - A quick response is possible. Plasma concentration can be precisely controlled using IV infusion administration.

Total dose - The whole dose is delivered to the blood stream. That is the bioavailability is generally considered to 100% after IV administration. Larger doses may be given by IV infusion over an extended time. Poorly soluble drugs may be given in a large r volume over an extended time period.

Veins relatively insensitive - to irritation by irritant drugs at higher concentration in dosage forms.

Disadvantages:

Suitable vein - It may be difficult to find a suitable vein. There may be some tissue damage at the site of injection.

Maybe toxic - Because of the rapid response, toxicity can be a problem with rapid drug administrations. For drugs where this is a particular problem the dose should be given as an infusion, monitoring for toxicity.

Requires trained personnel - Trained personnel are required to give intravenous injections.

Expensive - Sterility, pyrogen testing and larger volume of solvent means greater cost for preparation, transport and storage.
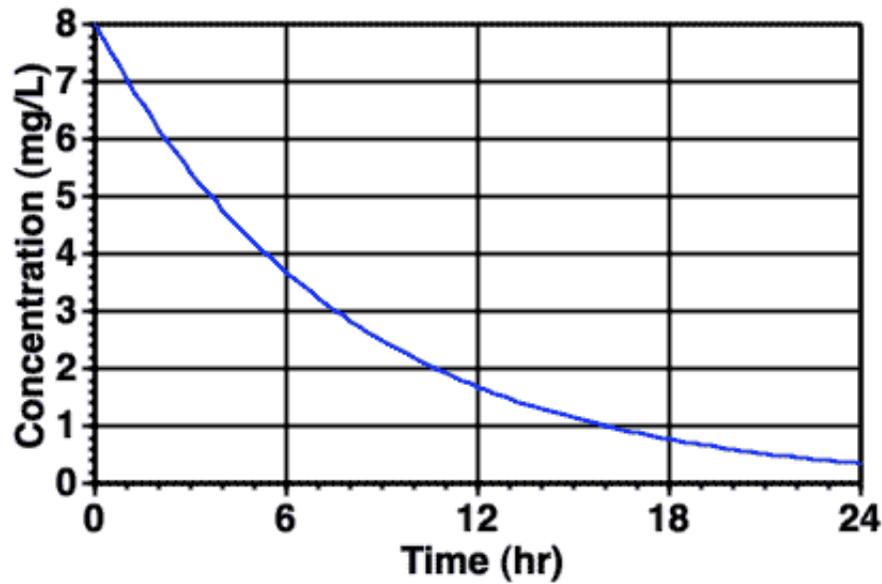
Figure 7.5.2 Typical Plot of Cp *versus* Time after IV Bolus Administration
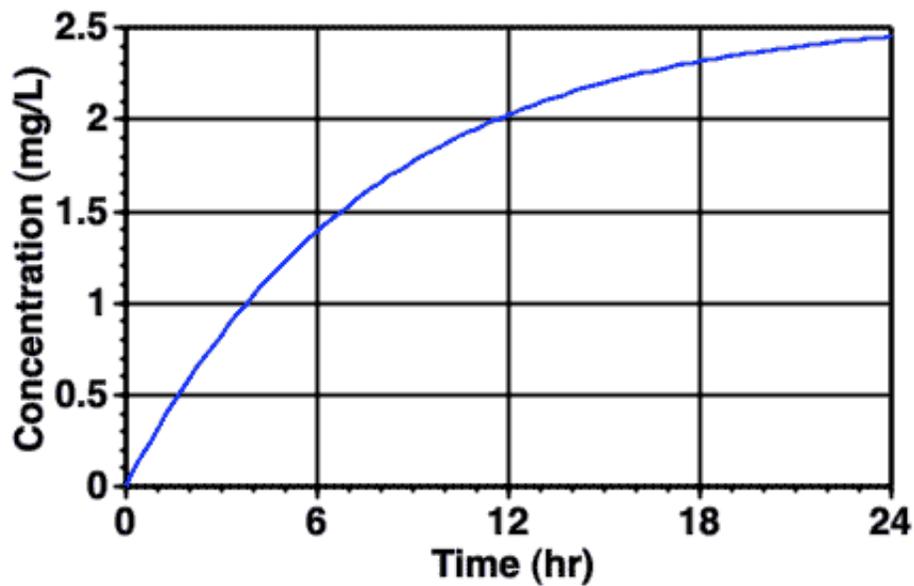

Figure 7.5.3 Typical Plot of Cp *versus* Time during an IV Infusion Administration

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Subcutaneous (SC)

This involves administration of the drug by injection just under the skin. Commonly used for insulin injection.

Advantages:

Can be given by patient, e.g. in the case of insulin.

Absorption can be fast from aqueous solution but slower with depot formulations. Absorption is usually complete. Improved by massage or heat. Vasoconstrictor may be added to reduce the absorption of a local anesthetic agent, thereby prolonging its effect at the site of interest.

Disadvantages:

Can be painful. Finding suitable sites for repeat injection can be a problem.

Irritant drugs can cause local tissue damage.

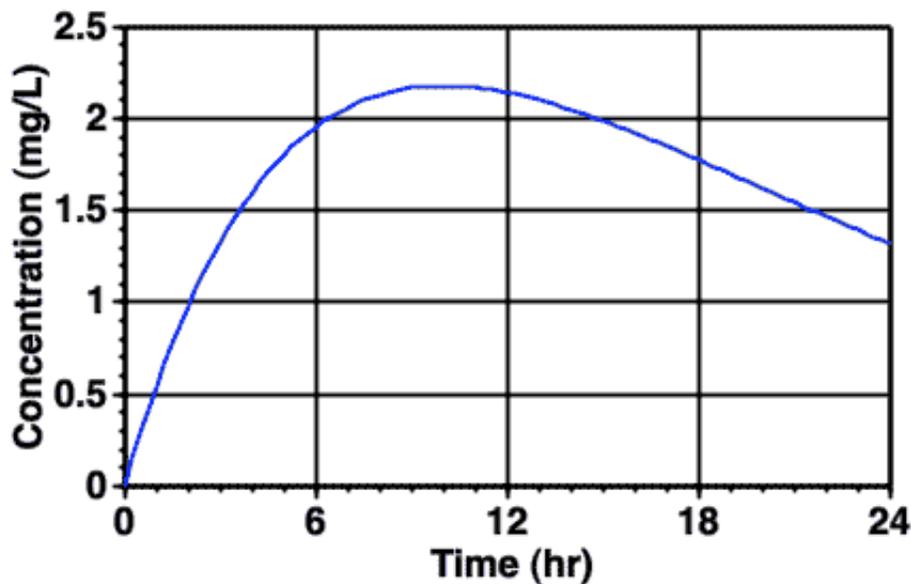Maximum of 2 ml injection thus often small doses limit use.

Figure 7.6.1 Typical Plot of Cp *versus* Time after Subcutaneous Administration

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Intramuscular (IM)

Advantages:

Larger volume than SC can be given by IM. They may be easier to administer than IV injections.

A depot or sustained release effect is possible with IM injections, e.g. procaine penicillin.

Disadvantages:

Trained personnel required for injections. The site of injection will influence the absorption, generally the deltoid muscle provides faster and more complete absorption.

Absorption can be rapid from aqueous solution. Absorption is sometimes erratic, especially for poorly soluble drugs, e.g. diazepam, phenytoin. The solvent maybe absorbed faster than the drug causing precipitation of the drug at the site of injection.
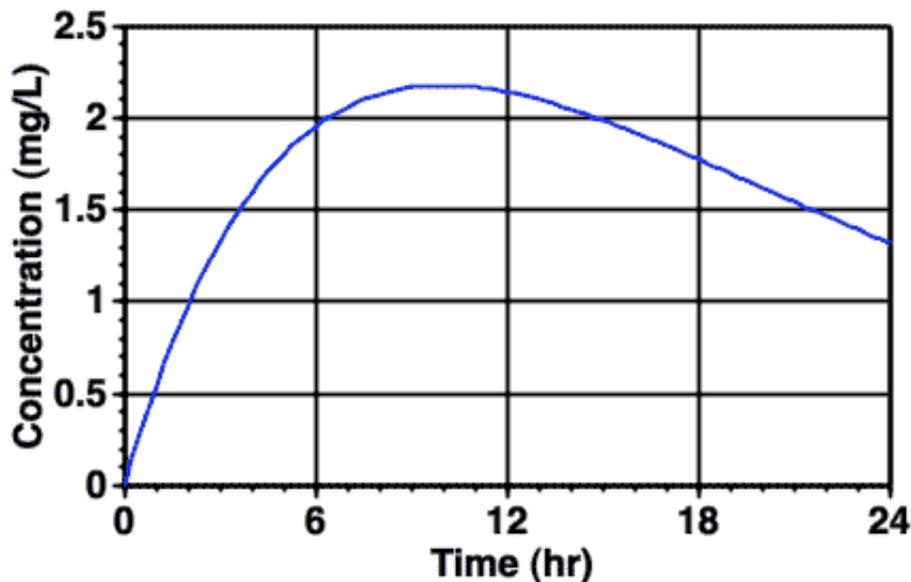
Irritiating drug may be painful.

Figure 7.7.1 Typical Plot of Cp *versus* Time after Intramuscular Administration

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Inhalation

May be used for a local effect, e.g. bronchodilators.

Can be used for systemic effect, e.g. general anesthesia.

Rapid absorption by-passing the liver.

Absorption of gases is relatively efficient, however solids and liquids are excluded if larger than 20 micron and even then only 10 % of the dose may be absorbed. Cromolyn is taken as a powder with 50 % of the particles within the range of 2 to 6 micron. Larger than 20 micron and the particles impact in the mouth and throat. Smaller than 0.5 micron and they aren't retained. Some portion of the dose may be swallowed.
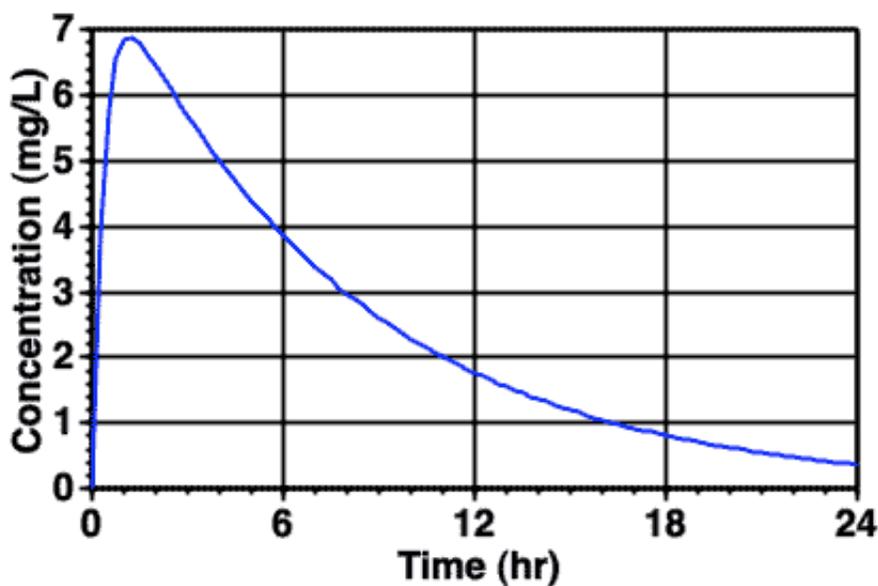

Figure 7.8.1 Typical Plot of Cp *versus* Time after Inhalation Administration

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Topical or Transdermal

Local effect - ear drops, eye drops or ointment, antiseptic creams and oinments, sunscreens, callous removal products, etc.

Systemic effect - e.g., nitroglycerin ointment.

Generally absorption is quite slow. Absorption through the skin especially via cuts and abrasions or from sites were the skin is quite thin can be quite marked. This can be a real problem in handling toxic materials in the laboratory or pharmacy. This can also be a serious problem with garden chemicals.

An occlusive dressing may be used to improve absorption.

Transdermal patches can provide prolonged or controlled (iontrophoresis) drug delivery.

There may be some skin irritation. Drug absorption will vary by site of administration, skin condition, age and gender.

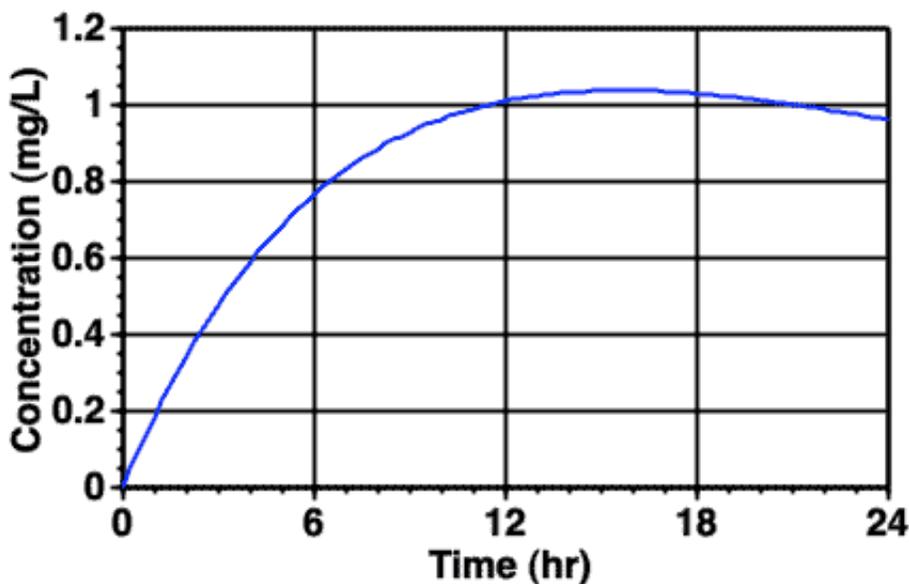Systemic absorption (transdermal) is better with low dose, low MWt, lipid soluble drugs.

Figure 7.9.1 Typical Plot of Cp *versus* Time after Topical Administration

Examples of drugs delivered by the transdermal route include estradiol, fentanyl, nicotine (various forms), nifedipine and nitroglycerin.

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Other ROA's

Other routes of administration include: nasal, some systemic absorption has been demonstrated for propranolol and some low dose hormones; intra-arterial for cancer chemotherapy to maximize drug concentrations at the tumor site; and intrathecal directly into the cerebrospinal fluid. Others routes with limited systemic absorption but with local utility include topical, ocular, aural, vaginal, urethral and intrasynovial

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Student Objectives for this Chapter

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