**Subject: Pharmaceutical Sciences**

**Production of Courseware**

- **Content for Post Graduate Courses**

---

### Development Team

<table>
<thead>
<tr>
<th>Role</th>
<th>Name</th>
<th>Institution</th>
</tr>
</thead>
<tbody>
<tr>
<td>Principal Investigator</td>
<td>Prof. Farhan J Ahmad</td>
<td>Jamia Hamdard, New Delhi</td>
</tr>
<tr>
<td>Paper Coordinator</td>
<td>Dr. Javed Ali</td>
<td>Jamia Hamdard, New Delhi</td>
</tr>
<tr>
<td>Content Writer</td>
<td>Dr. Shrestha Sharma</td>
<td>K.R. Mangalam University, Gurgaon</td>
</tr>
<tr>
<td>Content Reviewer</td>
<td>Dr. Javed Ali</td>
<td>Jamia Hamdard, New Delhi</td>
</tr>
</tbody>
</table>
CONTENTS

1. Toxicokinetics
   1.1 Introduction
   1.2 Objectives of Toxicokinetics
   1.3 General principles for Toxicology
2. Important processes in Toxicokinetics/Pharmacokinetics
   2.1 Absorption
   2.2 Distribution
   2.3 Metabolism
   2.4 Excretion
3. Important terms dealing with Toxicokinetics
4. Toxicity studies
   4.1 Acute Toxicity
   4.2 Subchronic Oral toxicity
   4.3 Chronic oral toxicity
   4.4 Repeated dose toxicity
   4.5 Carcinogenicity testing
5. Case study
6. Summary
1. Toxicokinetics

1.1 Introduction

Toxicokinetics is an extension of pharmacokinetics which deals with the kinetic patterns of drug substances at higher doses. Toxicokinetics is an integral part of the non-clinical testing programme. Toxicokinetics studies play an important role in studying the metabolism and excretion pattern of xenobiotics. Animal toxicokinetic data help extrapolate physiologically based pharmacokinetics in humans. Toxicokinetic studies are mainly carried out in rodents, rabbits, dogs, nonhuman primates and swine using different types routes of administration. Blood sampling is done at previously determined various time points in order to analyze the pharmacokinetic data such as the area under the curve, drug distribution ratio, $C_{\text{max}}$, $t_{\text{max}}$ and other pharmacokinetic parameters. Pharmacokinetics is a term which is used to describe the rate at which a chemical will enter into the body and how the body will deal with it once it is inside the body. Toxicokinetics is an application of pharmacokinetic principles which are used to determine the relationship between the systemic exposure of a particular compound in experimental animals and its subsequent toxicity. These relations can be further extrapolated to determine their corresponding toxicity in humans.

1.1.1 Various objectives of toxicokinetics and the parameters which may be determined

The primary objectives of toxicokinetics are:

- To describe the systemic exposure achieved in animals and its relationship to dose level.
- To determine the time course of the toxicity study.

The secondary objectives of toxicokinetics are:

- To relate the exposure achieved in toxicity studies to toxicological findings and contribute to the assessment of the relevance of these findings to clinical safety.
- To support the choice of species and treatment regimen in non-clinical toxicity studies.
• To provide information which in conjunction with the toxicity findings, contributes to the design of subsequent non-clinical toxicity studies.

1.1.2 General principles to be considered for toxicology

• The toxicokinetic studies must conform to Good Laboratory Practice (GLP).
• When designing the toxicity studies, the exposure and dose-dependence in humans at therapeutic dose levels must be considered in order to achieve relevant exposure at various dose levels in the animal toxicity studies.
• The various time points for collecting body fluids in subsequent toxicokinetic studies should be as frequent as it is necessary, but should not be so frequent so that it interfere with the normal conduct of the study or to cause undue physiological stress to the animals.
• During toxicological study, the number of time points in the study should be justified on the basis that they are adequate to estimate exposure. This justification should be based on kinetic data which is gathered from toxicity studies, from pilot or dose range-finding studies, from separate studies in the same animal model or in other models allowing reliable extrapolation.
• The setting of various dose levels in toxicity studies is largely governed by the toxicology findings and the pharmacodynamic responses of the test species. These dose levels are classified into low dose levels, intermediate dose levels and high dose levels.
• **Low dose levels**: At low dose levels which is preferably a no-toxic-effect dose level, the exposure in the animals of any toxicity study should ideally be equal or just exceed the maximum expected level in patients.
• **Intermediate dose levels**: Exposure of test animals to intermediate dose levels should normally represent an appropriate multiple (or fraction) of the exposure at lower (or higher) dose levels dependent upon the objectives of the toxicity study.
• **High dose levels:** The high dose levels in toxicity studies will normally be determined by toxicological considerations. However, the exposure achieved at the dose levels used should be assessed.

• In toxicity studies, the extent of exposure should be estimated in an appropriate number of animals and dose groups which provides a basis for risk assessment.

• Simultaneous toxicity studies could be performed either in all or a particular proportion of the animals which are used in the main study or in special satellite groups.

• The number of animals to be used in toxicity studies should be the kept minimum which are sufficient consistent with generating adequate toxicokinetic data.

• In toxicological studies where both male and female animals are being utilized, it is necessary to estimate exposure in animals of both sexes unless some proper justification is made.

• Various complicating factors such protein binding need to be considered while interpreting the toxicological results.

• The strategy made for using of alternative routes of administration, for example by inhalation, topical or parenteral delivery, must be based on the pharmacokinetic properties of the drug substance administered by the intended route.

• Integration of pharmacokinetic principles into toxicity studies suggests the early development of analytical methods for which the choice of analytes and matrices should be continually reviewed as information gathered on metabolism and species differences.

• The analytical methods to be used in toxicokinetic studies should be specific for the drug substance to be measured and must be of an adequate accuracy and precision. The limit of quantification must be adequate for the measurement of the range of concentrations predicted to occur in the generation of the toxicokinetic data.
2. **Important processes in Toxicokinetics/Pharmacokinetics**

There are basically four processes that play their role when a particular chemical enters inside the body of an animal. These processes are absorption, distribution, metabolism and excretion which are collectively referred to as ADME processes. These processes mainly determine the time course when the drug appears in the blood and for how long it is left over in the blood. Therefore, the time duration of drug action is directly correlated with the concentration of the drug in the blood stream. These processes are discussed in detail below:

![Diagram of ADME processes]

*Figure 1: Various processes dealing with ADME*
2.1 Absorption
Absorption process can be described as movement of a compound or drug moiety from its site of administration into the blood stream. There are several absorption mechanisms by which the drug can be absorbed including passive diffusion, active transport, facilitated transport, convective transport, Ion pair transport and pinocytosis. There are several factors which are associated with absorption process. These factors are divided into drug related and patient related factors. The drug related factors include aqueous solubility, molecular size, degree of ionization and chemical nature of the drug. Patient related factors include area of absorptive surfaces, vascularity, food, pH of the gastrointestinal tract (GIT), GIT mobility and diseased state.

Figure 2: Factors affecting drug Absorption
2.2 Distribution
Distribution is defined as the movement of drugs throughout the body. It is determined by the blood flow to the tissues, it is ability of the drug to enter the vasculature system and the ability of the drug to enter the cell if required. It is a reversible process. The distribution of drug from the bloodstream to the site of action depends primarily on blood flow to that organ, capillary permeability, protein binding, and the relative lipophilic character of the drug molecule. It is well known that blood flow to various organs is not equal. The most vital organs of the body receive the greatest supply of blood i.e. brain, liver and kidneys. But the blood supply to the organs is not the only factor which is responsible for distribution. Besides, for freely penetration of drugs into the brain, they must be small and lipid soluble and must be picked up by the carrier-mediated transport mechanism in the central nervous system.

Factors affecting Distribution
- Protein binding
- Blood flow to that organ
- Vd Volume of distribution

2.3 Metabolism
The process of undergoing chemical changes is called biotransformation or metabolism. Once a chemical is inside a body, it can be distributed to other areas of the body through diffusion or other biological processes. At this point, the chemical may undergo metabolism and be biotransformed into other chemicals (metabolites). These metabolites can be less or more toxic than the parent compound. After this potential biotransformation occurs, the metabolites may leave the body, be transformed into other compounds, or continue to be stored in the body compartments.

2.4 Excretion
After the drug is sufficiently absorbed and metabolized throughout the body, it must be subsequently removed and eliminated from the body. The two terms ‘elimination’ and ‘excretion’ have been used interchangeably in pharmacokinetics. The term elimination is
used to indicate removal or loss of drug from the body and the term excretion is used to mean drug removal from body by all processes including elimination. The elimination or excretion of drugs from the blood can take place through a variety of pathways.

**Routes of drug excretion**

- Excretion through kidneys
- Excretion through lungs
- Excretion through bile
- Excretion through intestine
- Excretion through saliva
- Excretion through perspiration or skin
- Excretion through milk

Among all routes, kidney is the main route for excretion of most drugs from the body.

**Figure 3: Basic processes of Pharmacokinetics**
3 Important terms dealing with toxicokinetics

3.1 Therapeutic index (TI)

Therapeutic index (TI) also named as therapeutic ratio is mainly used to assess the amount of a drug that causes the desired therapeutic effect. Mathematically, TI can also be expressed as the proportion of the dose of drug that lead to the adverse effects to the dose of drug that leads to the desired pharmacological effect. TI is mainly determined in animals as the lethal dose of a drug for 50% of the population also called as LD$_{50}$, divided by the minimum effective dose for 50% of the population also called as ED$_{50}$.

$$\text{Therapeutic index} = \frac{\text{LD}_{50}}{\text{ED}_{50}} \text{ in animal studies}$$

or  $$\text{Therapeutic index} = \frac{\text{TD}_{50}}{\text{ED}_{50}} \text{ for humans}$$

A higher therapeutic index is always preferred over a lower one i.e. the toxic effects of a drug are lower with a drug having higher TI and a patient would have to consume a much higher dose of such drug to reach toxicity rather than the dose required to elicit the desired therapeutic effect. Dose adjustment is often required for the drugs which have a narrow therapeutic range (i.e. show small difference between the toxic and therapeutic doses). For this purpose, therapeutic drug monitoring (TDM) protocols are followed. Such drug candidates which have potentially suboptimal TI should be recognized as early as possible. TI can be easily understood by the following graph:
3.2 Maximum tolerated dose (MTD)

The maximum tolerated dose (MTD) is defined as the maximum dose of the prescribed drug that will lead to the desired pharmacological effect without unacceptable toxicity. The main purpose of determining MTD is to determine if long-term exposure to a particular drug would lead to undesirable or adverse effects in a population specially when the extent of the exposure is insufficient enough to produce short-term toxic effects. Maximum tolerated dose studies are also performed during the clinical trials. Now a days, MTD is considered as an essential component of a drug profile since all modern healthcare systems exhibit a maximum safe or effective dose for the particular drug. It has been observed that the patients are not able tolerate the theoretical MTD of a drug due to the prevalence of side-effects and can lead to distress and/or discomfort to result in non-compliance with treatment.

Maximum tolerated dose (MTD) do not include the following:
(a) Overt toxicity which might cause appreciable death of cells or organ dysfunction.
(b) Toxic manifestations that are predicted materially to reduce the life span of the animals except as the result of neoplastic development.
(c) 10% or greater retardation of body weight gain as compared with control animals.

3.3 No-observed-adverse-effect level (NOAEL)

NOAEL (no-observed-adverse-effect level) plays an important role in non-clinical assessment. It is determined or proposed by a qualified personnel (pharmacologist, toxicologist) depending on the study, drug indications and its pharmacological therapeutic or side/adverse effects. NOAEL is defined as the highest experimental point that is not showing any adverse effect. In relation to toxicology, NOAEL is the highest tested dose or concentration of a particular drug at which no such adverse effect is found in exposed animal models where higher doses or concentrations might result in an adverse effect. NOAEL may also be used in the process of creating a dose-response relationship which is considered to be a fundamental step in most risk assessment methodologies. In drug development process, NOAEL of a newly discovered drug is particularly assessed in laboratory animals before the start of clinical trials to establish a safe clinical starting dose in humans.

3.4 No-observed-effect level (NOEL)

No-observed-effect level is the highest concentration or amount of a drug substance, found by experiment or observation, that causes no alterations of morphology, functional capacity, growth, development, or life span of target organisms distinguishable from those observed in normal (control) organisms of the same species and strain under the same defined conditions of exposure.
3.4 Lowest-observed-adverse-effect level (LOAEL)

Lowest-observed-adverse-effect level (LOAEL) is the lowest concentration or amount of a drug substance found by experimentation or practical observation, which might cause an adverse effect on morphology, functional capacity, growth, development or life span of a target organism which are quite distinguishable from normal (control) organisms of the same species and strain under defined conditions of exposure.

3.5 Lowest-observed-effect level (LOEL)

It is the lowest concentration or amount of a drug substance which is found by experimentation or practical observation, which might cause no any alteration in morphology, functional capacity, growth, development, or life span of target organisms which are quite distinguishable from normal (control) organisms of the same species and strain under the same defined conditions of exposure.

4. Toxicity studies

4.1 Acute toxicity

Acute toxicity refers to the adverse or toxic effects of a drug substance that might result either from a single exposure of the particular drug or from multiple exposures of the same drug in a short span of time (usually less than 24 hours). To be defined as acute toxicity, the adverse effects should occur within 14 days of the administration of the substance. Acute toxicity can be differentiated from the chronic toxicity, which describes the adverse health effects from repeated exposures, often at lower levels, to a substance over a longer time period (months or years). Determination of acute toxicity studies in animals are usually necessary for any drug which is intended for human use. The LD$_{50}$ value is a useful parameter for determining the acute toxicity. But determining acute toxicity using LD$_{50}$ value, mortality ratio was found to be
high as the study involves the use of large number of animals are involved and mortality ratio is high. Due to these drawbacks, following modified methods are used:

a) **The fixed dose procedure (FDP):** This method predicts acute toxicity by calculating the non-lethal toxicity rather than the lethal dose at fixed dose levels of 5, 50, 500 and 2000 mg/kg.

b) **The acute toxic category (ATC) method:** In this method, a sequential procedure is followed in which three animals of same sex are used in each step and four pre-identified starting doses are generally used.

c) **The up and down (UDP) method:** The UDP method is also named as staircase design. This method is most recommended by various regulatory agencies as this method involved fewer animals than other methods. In this method, firstly a dose less than the LD₅₀ is selected and administered to the test animal which is kept under observation for 48 h. If the animal survives then higher dose (twice the original dose) is administered. But in case if the animal dies, the testing is further conducted on a lower dose with another animal of the same sex. UDP method can be used only for doses up to 2000 mg/kg.

The information gathered from these studies is useful in choosing doses for repeat-dose studies, providing preliminary identification of target organs of toxicity, and, occasionally, revealing delayed toxicity. Acute toxicity studies may also aid in the selection of starting doses for Phase 1 human studies, and provide information relevant to acute overdosing in humans.

**Testing procedure:**

The test drug compound should be administered to animals to identify doses which do not cause any adverse effect and doses causing major (life-threatening) toxicity. The use of vehicle control groups should be considered. For compounds with low toxicity, the maximum feasible dose should be administered. Acute toxicity studies in animals are conducted using two routes of drug administration; the route intended
for human administration, and Intravenous administration. When intravenous dosing is proposed in humans, use of this route alone in animal testing is sufficient. Studies should be conducted in at least two mammalian species, including a non-rodent species when reasonable. The objectives of acute studies can usually be achieved in rodents using small groups of animals (for instance, three to five rodents per sex per dose). Where nonrodent species are appropriate for investigation, use of fewer animals may be considered. Any data providing information on acute effects in nonrodent species, including preliminary dose-range finding data for repeat-dose toxicity studies, may be acceptable.

**Observations**

Animals should be observed for 14 days after pharmaceutical administration. All mortalities, clinical signs, time of onset, duration, and reversibility of toxicity should be recorded. Gross necropsies should be performed on all animals, including those sacrificed moribund, found dead, or terminated at 14 days.

### 4.1.1 Acute toxicity testing for topical preparations

The acute toxicity testing for topical preparations is usually performed using the eye irritation test and skin irritation test using Draize tests. Draize tests are used as a tool to measure the deadliness of drug substances in rabbits and guinea pigs. In the Draize eye irritation test, rabbit is used as model animal and 0.5 ml of the test substance is administered in the rabbit's eyes. The animal is then left undisturbed under standard laboratory conditions and examined for 4 h for various signs of redness, swelling, discharge, ulceration, hemorrhage and blindness for a period of not less than 14 days. In Draize skin irritation test, 0.5 g of the test substance is taken and applied evenly to the surface of an animal's skin and kept under observation in the standard laboratory conditions for a period of not less than 14 days and assessed for prevailing signs of erythema and
edema. After the specified period, the complete batch of animals is sacrificed and various histopathological changes are evaluated.

4.2 Subchronic oral toxicity testing

In subchronic oral toxicity study, both rodents and nonrodents species are employed and the test drug substance is given by the oral route for a stated period of 90 days and week by week body weight variations were observed. Subsequently, biochemical, cardiovascular parameters and behavioural changes are observed after a periodic cycle of 30 days. After the stated period of 90 days, whole batch of animals is sacrificed and histopathological analysis of tissues is done. The maximum allowable weight variation among the animals is ±20%. In the study, a satellite group can be included in the study protocol which might serve as either a control group or a high-dose group.

4.3 Chronic oral toxicity testing

This study is conducted with a minimum of one rodent and one nonrodent species. The test compound is first administered orally to the stated animal model and periodic observation was performed for a period of 90 days. The chronic oral toxicity testing is important IA chronic toxicology study provides interpretations about the long-term effect of a test substance in animals, and it may be extrapolated to the human safety of the test substance. The allowable weight variation between the animals is ±20%. A satellite group may be included in the study protocol which serves both as a control group and a high-dose group.

4.4 Repeated dose toxicity testing

Repeated dose toxicity studies are carried out for a minimum period of 28 days. The test drug substance to be tested is administered daily for a certain period through the oral route if found to beconvenient. The test drug is regularly administered for 28 days to a rodent species of any gender. The age of the rodent species must lie between 5–6 weeks. The individual variation
between the animals should be minimum. The percentage weight variation which is allowed between the animals is ±20%. A satellite group can also be incorporated in the study protocol which may serve both purposes (as a control group and a high-dose group). During the study, various behavioural and biochemical parameters of the animals are recorded. These studies are important for the interpretation of human safety details. After the stated period, animals are sacrificed. The histopathological changes in various tissues are then recorded. If suggested, immunotoxicity (adverse effects on the immune system) studies are also performed on the same animals. These studies are carried out for several immunotoxicological parameters such as delayed-type hypersensitivity (DTH), mitogen- or antigen-stimulated lymphocyte proliferative responses, macrophage function, and primary antibody response to T-cell dependent antigens. The major difference between repeated dose and subchronic toxicity studies is the time duration of the studies. Repeated dose toxicity studies are conducted for a period of 28 days whereas subchronic toxicity studies are done for over a period of 90 days.

4.5 Carcinogenicity testing

In carcinogenicity testing, both rodents and nonrodent animal species are utilized. These studies are very long and carried out over the greater portion of an animal's lifespan that is roughly estimated to be around 24 months. The animals under observation are examined for various signs of toxicity and development of tumors during and after the exposure of test drug substances. If the initial observations shows no signs of tumors, then the carcinogenic test can be terminated after 18 months if the test animal is mice and hamsters and if the test animals are rats the duration of the study is 24 months. If the animals are found to be healthy, hematological analysis is performed after the 12 months and 18 months duration and the study is terminated. After the stated time period, the animals are sacrificed and histopathological studies are done out on all the tissues.
7. Case study

1. The pharmacokinetics of sertraline in overdose and the effect of activated charcoal

Antidepressant drugs are one of the major category of drugs which are taken in overdose for deliberate self-poisoning. After oral administration, sertraline is absorbed slowly with the maximum concentration ($C_{\text{max}}$) occurring 4 to 6 hours after oral administration. It undergoes extensive first pass metabolism via a number of cytochrome P450 (CYP) isoenzymes to produce a weakly active metabolite for serotonin re-uptake, N-desmethylsertraline. Sertraline appears to follow linear kinetics in therapeutic dose ranging from 50–200 mg/day. In the study, 77 timed sertraline concentrations were measured in 28 patients with sertraline overdoses ranging between (250–5000 mg) with a median dose of 1550 mg. Pharmacokinetic data for sertraline following overdose in 28 patients and the effect of activated charcoal, based on the median overdose of 1500 mg.

<table>
<thead>
<tr>
<th></th>
<th>Total ($n = 28$)</th>
<th>No Activated Charcoal ($n = 21$)</th>
<th>Activated Charcoal ($n = 7$)</th>
</tr>
</thead>
<tbody>
<tr>
<td>$t_{1/2}$ (h)</td>
<td>27.6 [19.3–30.6]</td>
<td>29.4 [26.4–30.8]</td>
<td>15 [10.7–22.2]</td>
</tr>
<tr>
<td>$C_{\text{max}}$ (mg l$^{-1}$)</td>
<td>0.25 [0.18–0.42]</td>
<td>0.33 [0.18–0.43]</td>
<td>0.22 [0.18–0.42]</td>
</tr>
<tr>
<td>$t_{\text{max}}$ (h)</td>
<td>2.8 [2.1–3.6]</td>
<td>2.9 [2.3–3.6]</td>
<td>2.5 [1.9–3.6]</td>
</tr>
</tbody>
</table>

2. The pharmacokinetics of paracetamol in overdose

Paracetamol, also known as acetaminophen, belongs to the category of non-steroidal anti-inflammatory drug. It is most commonly prescribed drug for the treatment of pain and fever. In case of overdosage of paracetamol, hepatotoxicity is the commonest cause of death due to acute liver failure (ALF). A study of paracetamol toxicity with different doses has been
conducted on over 500 patients. Of all patients, (75.4%) had taken an intentional paracetamol overdose, whilst 110 patients (16.6%) had taken an unintentional overdose. The results showed that patients with unintentional overdoses had significantly lower admission paracetamol and alanine aminotransferase concentrations in comparison to intentional overdoses. The poisoning results in acute liver failure (ALF) which lead to sudden extensive loss of liver cell mass, resulting in hepatic encephalopathy (HE) and coagulopathy. It can also lead to multiple organ failure with a high associated mortality rate. ALF was restricted to those patients developing hepatic encephalopathy (HE). Paracetamol overdose was prospectively assigned as the cause of acute severe liver injury if there was a clear history of ingestion of potentially toxic amounts of paracetamol (<4 g day\(^{-1}\)) within 7 days of presentation, serum paracetamol concentrations were <10 mg l\(^{-1}\) or serum ALT concentration was <1000 IU l\(^{-1}\) within 7 days of a history of paracetamol ingestion irrespective of the serum paracetamol concentration.
8. Summary

Toxicokinetics is the study of the time course of toxicant absorption, distribution, metabolism and excretion. It is basically an extension of pharmacokinetics which deals with the kinetic patterns of higher doses of chemicals/toxins/xenobiotics. Toxicokinetics is an integral part of the non-clinical testing programme. Toxicokinetic studies are done to describe the systemic exposure achieved in animals and its relationship to dose level. Another objective of toxicokinetics is to relate the exposure achieved in toxicity studies to toxicological findings and contribute to the assessment of the relevance of these findings to clinical safety. When designing the toxicity studies, the exposure and dose-dependence in humans at therapeutic dose levels must be considered in order to achieve relevant exposure at various dose levels in the animal toxicity studies. During toxicological study, the number of time points in the study should be justified on the basis that they are adequate to estimate exposure. The setting of various dose levels in toxicity studies is largely governed by the toxicology findings and the pharmacodynamic responses of the test species. These dose levels are classified into low dose levels, intermediate dose levels and high dose levels. In toxicity studies, the extent of exposure should be estimated in an appropriate number of animals and dose groups which provides a basis for risk assessment. The number of animals to be used in toxicity studies should be kept minimum which are sufficient consistent with generating adequate toxicokinetic data. There are basically four processes that play their role when a particular chemical enters inside the body of an animal. These processes are absorption, distribution, metabolism and excretion which are collectively referred to as ADME processes. These processes mainly determine the time course when the drug appears in the blood and for how long it is left over in the blood. Several key parameters or indices govern the toxicity of drug candidates. These include therapeutic index (TI); maximum tolerated dose (MTD); NOAEL (no-observed-adverse-effect level); No-observed-effect level (NOEL); Lowest-observed-adverse-effect level (LOAEL) and Lowest-observed-effect level (LOEL). Out of all parameters consideration of
therapeutic index is most important. TI can be expressed as the ratio of the dose of drug that causes adverse effects (e.g. toxic dose in 50% of subjects, TD$_{50}$) to the dose of drug that leads to the desired pharmacological effect (e.g. efficacious dose in 50% of subjects, ED$_{50}$). Toxicity can be distinguished as acute toxicity, subacute toxicity, chronic toxicity and repeated dose toxicity studies. So it can be concluded that toxicokinetic study involves the study of various pharmacokinetic principles in case of excess dose of that particular drug and how the excess dose effect the ADME processes in the body.