**Lecture II**

**The role of pharmacokinetic principles in creation of new**

 **medicinal substances.**

The degree of drug activity is directly related to the concentration of the drug in the aqueous medium in contact with the substrate molecules. The factors affecting this concentration in a biological system can be classified into the phar- macokinetic phase and the pharmacodynamic phase of drug action.

The pharma- cokinetic phase concerns the study of the parameters that control the journey of the drug from its point of administration to its point of action. The pharmaco-dynamic phase concerns the chemical nature of the relationship between the drug and its target: in other words, the effect of the drug on the body.

The physical form in which a medicine is administered is known as s dosage form. Dosage forms normally consist of the active constituent and other ingredi- ents known as excipients. Excipients can have a number of functions, such as fillers (bulk providing agent), lubricants, binders, preservatives and antioxidants. A change in the nature of the excipients can significantly affect the the stability of the active ingredient as well as its release from the dosage form. Similarly, changes in the preparation of the active principle, such as the use of a different solvent for purification, can affect its bioavailability (see Section 2.7.2 and 8.5) and consequently its effectiveness as a drug. This indicates the importance of quality control procedure for all drugs especially when they reach the manufacturing stage.

*ENTERAL*

*route,*

*e.g. via oral administration.*

**GI TRACT**

*PARENTERAL*

*route,*

*e.g. intravenous injection.*

**TISSUE DEPOTS**

Desired biological activity



Target site

**BLOOD STREAM**

  

GI tract

**Absorption**

GI tract  

Membrane

**LIVER**

First pass metabolism

**BLOOD STREAM**

**METBOLISM**

Other sites

Membrane

**EXCRETION**

**EXCRETION**

Unabsorbed material through the GI tract (faeces)

Membrane



Unwanted side effects

 

**KIDNEY**

(urine)

**LUNGS**

exhaled gases

Figure 2.3 The main routes of drug administration and distribution in the body. The distribution of a drug is also modified by metabolism, which can occur at any point in the system

The design of dosage forms lies in the field of the pharmaceutical technologist but it should also be considered by the medicinal chemist when developing a drug from a lead compound. It is no use having a wonder drug if it cannot be packaged in a form that makes it biologically available as well as acceptable to the patient.

Drugs are usually administered topically or systemically. The routes are classified as being either parenteral or enteral (Figure 2.3). Parenteral routes are those that avoid the gastrointestinal tract (GI. tract), the most usual method being intramuscular injection (IM). The enteral route is where drugs are absorbed from the alimentary canal (PO per oral), rectal and sub-lingual routes. The route selected for the administration of a drug will depend on the chemical stability of the drug, both when it is transported across a membrane (absorption) and in transit to the site of action (distribution). It will also be influenced by the age, and physical and mental abilities, of the patients using that drug. For example, age related metabolic changes often result in elderly patients requiring lower dosages of the drug to achieve the desired clinical result. Schizophrenics and patients with conditions that require constant medication are particularly at risk of either overdosing or underdosing. In these cases, a slow release intra- muscular injection, which need only be given once in every two to four weeks, rather than a daily dose, may be the most effective use of the medicine.

Consequently, at an appropriately early stage in its development, the design of a drug should also take into account the nature of its target groups.

Once the drug enters the bloodstream it is distributed around the body and, so, a proportion of the drug is either lost by excretion metabolism to other products or is bound to biological sites other than its target site. As a result, the dose administered is inevitably higher than that which would be needed if all the drug reached the appropriate site of biological action. The dose of a drug administered to a patient is the amount that is required to reach and maintain the concentration necessary to produce a favourable response at the site of biological action. Too high a dose usually causes unacceptable side effects whilst too low a dose results in a failure of the therapy. The limits between which the drug is an effective therapeutic agent is known as its therapeutic window (Figure 2.4.). The amount of a drug the plasma can contain coupled with processes that irreversibly eliminate (see Section 2.7.14) the drug from its site of action results in the drug concentration reaching a so called plateau value. Too high a dose will give a plateau above the therapeutic window and toxic side effects. Too low a dose will result in the plateau below the therapeutic window and ineffective treatment.

The dose of a drug and how it is administered is called the dosage regimen.

Dosage regimens may vary from a single dose taken to relieve a headache through regular daily doses taken to counteract the effects of epilepsy and diabetes to continuous intravenous infusions for seriously ill patients. Regimens are designed to maintain the concentration of the drug within the thera- peutic window at the site of action for the period of time that is required for therapeutic success. The design of the regimen depends on the nature of the medical condition and the medicant. The latter requires not just a knowledge of a drug’s biological effects but also its pharmacokinetic properties, that is, the rate of its absorption, distribution, metabolism and eliminination from the body.

Too toxic, too many side effects

**The plateau**

Drug concentration in the plasma

*x x x*

*x x x x*

Time

Therapeutic window

Too little to be effective

Figure 2.4 A simulation of the therapeutic window for a drug given in fixed doses at fixed time intervals X.

The action of a drug is believed to be due to the interaction of that drug with endogenous and exogenous substrate molecules found in the body (see Chapter 7). When one or more active drug molecules bind to the target en- dogenous and exogenous molecules, they cause a change or inhibit the bio- logical activity of these molecules. The effectiveness of a drug in bringing about these changes normally depends on the stability of the drug–substrate complex, whereas the medical success of the drug intervention usually depends on whether enough drug molecules bind to sufficient substrate molecules to have a marked effect on the course of the disease state.

**The pharmacokinetic phase**

#####  The pharmacokinetic phase of drug action includes the Absorption, Distribu- tion, Metabolism and Elimination (ADME) of the drug. Many of the factors that influence drug action apply to all aspects of the pharmacokinetic phase. Solubility (see Section 3.3), for example, is an important factor in the absorp- tion, distribution and elimination of a drug. Furthermore, the rate of drug dissolution, that is, the rate at which a solid drug dissolves in the aqueous medium, controls its activity when a solid drug is administered by enteral routes (see Section 2.6) as a solid or suspension.

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#####  **Absorption**

Absorption is the passage of the drug from its site of administration into the plasma after enteral administration. It involves the passage of the drug through the appropriate membranes. Good absorption normally requires that a drug molecule has the correct balance between its polar (hydrophilic) and nonpolar (hydrophobic) groups. Drugs that are too polar will tend to remain in the bloodstream, whilst those that are too nonpolar will tend to be absorbed into and remain within the lipid interior of the membranes (see Appendix 3). In both cases, depending on the target, the drug is likely to be ineffective.

The degree of absorption can be related to such parameters as partition coefficient, solubility, p*K*a, excipients and particle size. For example, the ioniza- tion of the analgesic aspirin is suppressed in the stomach by the acids produced from the parietal cells in the stomach lining. As a result, it is absorbed into the bloodstream in significant quantities in its unionized and hence uncharged form through the stomach membrane.

#####

#####  **Distribution**

#####  Distribution is the transport of the drug from its initial point of administration or absorption to its site of action. The main route is the circulatory syste; however, some distribution does occur via the lymphatic system. In the former case, once the drug is absorbed, it is rapidly distributed throughout all the areas of the body reached by the blood.

#####  Drugs are transported dissolved in the aqueous medium of the blood either in a ‘free form’ or reversibly bound to the plasma proteins.

#####  Drug molecules bound to plasma proteins have no pharmacological effect until they are released from those proteins. However, it is possible for one drug to displace another from a protein if it forms a more stable complex with that protein. This may result in unwanted side effects, which could cause compli- cations when designing drug regimens involving more than one drug. Moreover, low plasma protein concentrations can affect the distribution of a drug in some diseases, such as rheumatoid arthritis.

#####  Major factors that influence distribution are the solubility (see Section 3.3) and stability (see Biological half life, Section 8.4.1) of drugs in the biological environment of the blood. Sparingly water soluble compounds may be deposited in the blood vessels, leading to restriction in blood flow. Drug stability

is of particular importance in that serum proteins can act as enzymes that catalyse the breakdown of the drug. Decompositions such as these can result in a higher dose of the drug being needed in order to achieve the desired pharmacological effect, which increases the risk oftoxic side effects in the patient. However, the active form of some drugs is produced by the decom- position of the administered drug. Drugs that function in this manner are known as prodrugs (see Section 9.8). For example, the bacteriacide prontosil, discovered in 1935, is not active but is metabolized *in situ* to the antibacterial sulphanilamide.

**Metabolism**

Drug metabolism is the biotransformation of the drug into other compounds referred to as metabolites. These biotransformations occur mainly in the liver but they can also occur in blood and other organs such as the brain, lungs and kidneys (see Section 9.3). Metabolism of a drug usually reduces the concen- tration of that drug in the systemic circulation, which normally leads to either a lowering or a complete suppression of the pharmacological action and toxic effects of that drug. Exceptions are prodrugs (see Section 9.8), such as prontosil, where metabolism produces the active form of the drug.

Metabolism usually involves more than one route and results in the forma- tion of a sucession of metabolites (Figure 2.5). Each of these metabolites may have a different or similar activity to the parent drug (see Section 9.2). Consequently, the activities of all the metabolities of a drug must be considered in the development of a potential drug. Metabolities are frequently more water soluble than their parent drug and because of this are usually excreted in the urine.

##### **Elimination**

Elimination is the collective term used for metabolic and excretion processes that irreversibly remove a drug from the body during its journey to its site of action. It reduces the medical effect of the drug by reducing its concentration at its site of action. A slow elimination process can result in a build-up of the drug concentration in the body. This may benefit the patient in that the dose required to maintain the therapeutic effect can be reduced, which in turn reduces the chances of unwanted side effects. Conversely, the rapid elimination of a drug means that the patient has to receive either increased doses, with a greater risk of toxic side effects, or more frequent doses, which carries more risk of under- or over-dosing. The main excretion route for drugs and their metabolites is through the kidney in solution in the urine. However, a significant number of drugs and their metabolic products are also excreted via the bowel in the faeces.

Drugs are eliminated in the kidneys by either glomerular filtration or tubular secretion. However, some of the species lost by these processes are reabsorbed by a recycling process known as tubular reabsorption. Tubular reabsorption is a process normally employed in returning compounds such as water, amino acids, salts and glucose that are important to the well-being of the body from the urine to the circulatory system, but it will also return drug molecules. The reabsorp- tion of acidic and basic drugs is reduced if the pH favours salt formation as charged molecules are not readily transported across membranes (see Appendi- ces 3 and 5).

Elimination occurs in the liver by biliary clearance, very large molecules being metabolized to smaller compounds before being excreted. However, a fraction of some of the excreted drugs is reabsorbed through the enterohepatic cycle. This reabsorption can be reduced by the use of suitable substances in the dosage form, for example, the ion exchange resin cholestyramine is used to reduce cholesterol levels by preventing its reabsorption.

#### **Bioavailability of a drug**

#### The bioavailability of a drug is defined as the fraction of the dose of a drug that is found in general circulation (see Section 8.5). It is influenced by such factors as ADME. Bioavailability is not constant but varies with the body’s physio- logical condition.

####  **The pharmacodynamic phase**

#### Pharmacodynamics is concerned with the result of the interaction of drug and body at its site of action, that is, what the drug does to the body. It is now known that a drug is most effective when its shape and electron distribution, that is, its stereoelectronic structure, is complementary to the steroelectronic structure of the active site or receptor.

The role of the medicinal chemist is to design and synthesize a drug structure that has the maximum beneficial effects with a minimum of toxic side effects. This design has to take into account the stereoelectronic characteristics of the target active or receptor site and also such factors as the drug’s stability *in situ*,

its polarity and its relative solubilities in aqueous media and lipids. The stereo- chemistry of the drug is particularly important, as stereoisomers often have different biological effects, which range from inactive to highly toxic (see Table 2.1).

**8.1 *Drug distribution and 'survival'***

In Chapter 7, we concentrated on the interaction of drugs with binding sites. However, the compound which has the best binding interaction with its receptor is not

necessarily the best drug to use in medicine. There are other variables which have to

be taken into account.

The drug has to be stable enough to survive a rather tortuous journey through the

body's circulatory system. It also has to be capable of negotiating barriers put in its

way and not be diverted from its target.

For example, consider a drug taken as a pill. It has to dissolve in aqueous solution.

It has to survive the acid of the stomach, then be absorbed from the gastrointestinal

tract into the bloodstream. To do that it has to negotiate barriers in the form of cell

membranes. It has to survive the destructive tendencies of the liver and its enzymes.

It has to survive the enzymes present in the blood. If it is a lipophilic drug, it may be

taken up by fat tissue. If it is anionic, it may get bound by plasma protein and if it is

canonic, it may be bound by nucleic acids. It has to avoid being excreted by the

kidneys or the bile duct. If the drug is aimed at the brain, it has to cross another cell

barrier known as the blood-brain barrier. If it is to react with an enzyme, it has to

negotiate another cell membrane to reach that.

Only then will the drug interact with its receptor or enzyme. As far as the drug is

concerned, it is a long, strenuous, and dangerous journey. Many of these problems can be avoided by giving the drug as an intravenous or intramuscular injection, but clearly orally administered drugs are preferred by the patient and if at all possible, drug design aims at an orally active compound. Let us look again at the journey which has to be followed by an orally administered drug. The success of the journey depends principally on the physical properties of the drug. First of all, it has to be chemically stable and not break down in the acid conditions of the stomach. Secondly, it has to be metabolically stable so that it survives the hydrolytic enzymes present in the digestive system, liver, and blood stream. Thirdly, it has to have the correct balance of hydrophilic to hydrophobic character. Let us consider each of these factors in turn.

**8.1.1 Chemical stability**

There are several useful drugs with chemically labile functional groups. Penicillins have a chemically labile (3-lactam ring which is susceptible to acid hydrolysis. Cholinergic

agents have a susceptible ester group which is also susceptible to acid hydrolysis. One way round the problem is to inject the drug in order to avoid the acid conditions of the stomach. However, there are strategies available which can be used to make the offending functional group less labile (see Section 8.3.2.).

**8.1.2 Metabolic stability**

Drugs are foreign substances1 as far as the body is concerned and the body has its own method of getting rid of such chemical invaders. Non-specific enzymes (particularly

in the liver) are able to add polar functional groups to a wide variety of drugs. Once the polar functional group has been added, the overall drug is more polar and water soluble, and is therefore more likely to be excreted when it passes through the kidneys.An alternative set of non-specific enzymatic reactions can reveal 'masked' polar functional groups which might be present in a drug. For example, there are enzymes which can demethylate a methyl ether to reveal a more polar hydroxyl group. Once again, the more polar product (metabolite) is excreted more efficiently. These reactions are classed as phase I reactions in the overall process of drug

metabolism. They generally involve oxidation, reduction, and hydrolysis (Fig. 8.1).

The structures most prone to oxidation are Af-methyl groups, aromatic rings, the

terminal positions of alkyl chains, and the least hindered positions of alicyclic rings. Nitro and carbonyl groups are prone to reduction by reductases, whilst amides and esters are prone to hydrolysis by esterases.

There is also a series of metabolic reactions classed as phase II reactions (Fig. 8.2).

These are conjugation reactions whereby a polar molecule is attached to a suitable

polar 'handle' which is either already present on the drug or has been placed there by a phase I reaction. The resulting conjugate has increased polarity, thus increasing its excretion rate in urine or bile even further.

Phenols, alcohols, and amines form O- or Af-glucuronides by reaction with UD Pglucose such that the highly polar glucose molecule is attached to the drug. Phenols, epoxides, and halides can react with the tripeptide glutathione to give mercapturic acids and some steroids can react with sulfates.

**Prodrugs to improve membrane permeability**

Prodrugs have proved very useful in temporarily masking an 'awkward' functional

group which is important to receptor binding, but which hinders the drug from crossing cell membranes. For example, a carboxylic acid functional group may have an important role to play in binding the drug to a receptor via ionic or hydrogen bonding. However, the very fact that it is an ionizable group may prevent it from crossing a fatty cell membrane. The answer is to protect the acid function as an ester. The less polar ester can cross fatty cell membranes and once in the bloodstream, it will be hydrolysed back to the free acid by esterases in the blood. An example of such a prodrug is the antibacterial agent pivampicillin-a prodrug for ampicillin (Chapter 10).

N-Demethylation is a common metabolic reaction in the liver. Therefore, primary

or secondary amines could be N-methylated to improve their membrane permeability. Several hypnotics and antiepileptics take advantage of this reaction (e.g. hexobarbitone (Fig. 8.12)).

 

Another way round the problem of membrane permeability is to design a prodrug which can take advantage of a carrier protein in the cell membrane, such as the one responsible for carrying amino acids into a cell. The best known example of such a prodrug is levodopa (Fig. 8.13).

 

Levodopa is a prodrug for the neurotransmitter dopamine and as such has been used in the treatment of Parkinson's disease—a condition due primarily to a deficiency of the neurotransmitter dopamine. Dopamine itself cannot be pig used since it is too polar to cross the blood-brain barrier.

Levodopa is even more polar and seems an unlikely prodrug. However, it is an amino acid and as such can make use of the special arrangements' made in order to move amino acids across the blood-brain barrier.

Amino acids are essential building blocks for all cells, but are incapable of crossing

hydrophobic membranes by themselves. There is, however, a process by which amino acids can be shuttled through membranes such as the blood-brain barrier. This involves a protein carrier system which is embedded in the membrane and 'smuggles its passengers from one side to the other (Chapter 5). Once across the barrier, a decarboxylase enzyme removes the acid group and generates dopamine (Fig. 8.14).



Another means of taking advantage of the transport proteins is to attach the active drug to an amino acid or nucleic acid base such that the drug gets a 'piggyback' across the membrane. Uracil mustard (Fig. 8.23) is one such example.

**Prodrugs for prolonged activity**

6-Mercaptopurine (Fig. 8.15) suppresses the body's immune response and is therefore

useful in protecting donor grafts. However, the drug tends to be eliminated from then body too quickly. The prodrug azathioprine (Fig 8.15) lasts far longer. Azathioprine is slowly converted to 6-mercaptopurine, allowing a more sustained activity. Since the conversion is chemical and unaffected by enzymes, the rate of conversion can be altered, depending on the electron withdrawing ability of the heterocyclic group. The greater the electron withdrawing power, the faster the breakdown. The NO2 group is therefore present to ensure an efficient conversion to 6-mercaptopurine, since it is strongly electron withdrawing.



There is a belief that the well-known sedatives Valium (Fig. 8.16) and Librium might be prodrugs and are only active because they are metabolized by *N* demethylation to no dazepam. Nordazepam itself has been used as a sedative, but loses activity quite quickly due to etabolism and excretion. Valium, if it is a prodrug for nordazepam, demonstrates again how a prodrug can be used to lead to a more sustained action.



One approach to maintaining a sustained level of drug over long periods is to deliberately associate a very lipophilic group with an active drug. This means that the majority of the drug is stored in fat tissue, and if the lipophilic group is only slowly removed, then the drug is steadily released into the bloodstream over a long period of time. The antimalarial agent cycloguanil pamoate (Fig. 8.17) is one such agent. The active drug is bound ionically to an anion with a large lipophilic group.



**Prodrugs masking drug toxicity and side-effects**

Prodrugs can be used to mask the side-effects and toxicity of drugs. For example, salicylic acid is a good painkiller, but causes gastric bleeding due to the free phenolic group. This is overcome by masking the phenol as an ester (aspirin) (Fig. 8.18).



The ester is later hydrolysed by esterases to free the active drug. Prodrugs can be used to give a slow release of drugs which would be too toxic to give directly. Propiolaldehyde is useful in the aversion therapy of alcohol, but is not used itself since it is an irritant. However, the prodrug pargylene can be converted to propiolaldehyde by enzymes in the liver (Fig. 8.19).



An extension of this tactic is to design a prodrug such that it is converted to the active drug at the target site itself. If this can be achieved successfully, it will greatly reduce the side-effects of highly toxic drugs such as the anticancer agents. Cyclophosphamide is a successful anticancer drug which is not toxic itself, but which is converted in several steps to the toxic phosphoramide mustard (Fig. 8.20).



This is a strong alkylating agent which will alkylate a cell's DNA and thus kill the cell. Since there is a high level of phosphoramidase enzyme in some tumour cells, it was hoped that the drug could be directed selectively against these cells. Some selectivity has indeed been observed and it is hoped that complete selectivity can eventually be achieved.

**8.3.6 Bioisosteres**

A bioisostere is a chemical group which can replace another chemical group without

affecting biological activity. Many peptides and polypeptides are chemical messengers in the body, yet using such compounds as medicines is impractical since the body's own digestive enzymes can hydrolyse the peptide links. One answer to the problem has been to replace the peptide bond with another functional group which is stable to these hydrolytic

enzymes. For example, a peptide bond might be replaced with a double bond. If the compound retains activity, then the double bond represents a bioisostere for the peptide link *in this particular case.* Note that bioisosteres are not general. They are specific for the drug and the protein with which it interacts. A successful bioisostere in one field of medicinal chemistry may be useless in a different field. Note also that bioisosteres are different from isosteres. It is the retention of important biological activity which determines whether a group is a bioisostere, not the valency.

An example of how bioisosteric groups have been used successfully is provided by

the cholinergic drug bethanechol described in Chapter 11.

**8.3.7 'Sentry' drugs-synergism**

In this approach, a second drug is administered along with the drug which is 'going

into action'. The role of the second drug is to guard or assist the principal drug. Usually, the second drug is an antagonist of an enzyme which metabolizes the principal drug. For example, clavulanic acid inhibits the enzyme p-lactamase and is therefore able to protect penicillins which are labile to that particular enzyme (Chapter 10).

Another example is to be found in the drug therapy of Parkinson's disease. The use of L-dopa (levodopa) as a prodrug for dopamine has already been described. However, to be

effective, large doses of L-dopa (3-8 g per day) are required, and over a period of time these dose levels lead to side-effects such as nausea and vomiting. L-Dopa is susceptible to the enzyme dopa decarboxylase and as a result, much of the L-dopa administered is decarboxylated to L-dopamine before it reaches the central nervous system (Fig. 8.21).



As stated earlier, dopamine is unable to cross the blood-brain barrier. As a result, an excess of dopamine builds up in the peripheral blood supply and this is what leads to the nausea and vomiting side-effects.

If an antagonist was administered to dopa decarboxylase, then it would inhibit the

decarboxylation of L-dopa and less would be required. The drug carbidopa has been used successfully in this respect and effectively inhibits dopa decarboxylase. Furthermore, since it is a highly polar compound containing two phenolic groups, a hydrazine moiety, and an acidic group, it is unable to cross the blood-brain barrier and so cannot prevent the conversion of L-dopa to dopamine in the brain.

Adrenaline is an example of a 'sentry drug' which acts on a receptor rather than an

enzyme. This drug is used along with the injectable local anaesthetic procaine to prolong its action (Fig. 8.22). Adrenaline constricts the blood vessels in the vicinity of the injection and so prevents procaine being 'washed away' by the blood supply.



**8.3.8 'Search and destroy' drugs**

A major goal in cancer chemotherapy is to target drugs efficiently against tumour cells

rather than normal cells. One method of achieving this is to design a drug transport system. The idea is to attach the active drug to a molecule which is needed in large amounts by the rapidly dividing tumour cells. One approach has been to attach the active drug to an amino acid or a nucleic acid base, e.g. uracil mustard (Fig. 8.23).



Of course, normal cells require these building blocks as well, but tumour cells often

grow more quickly than normal cells and require the building blocks more urgently. Therefore, the uptake of these drugs should be greater in tumour cells than in normal cells. This approach has the added advantage that the drug can enter the cell more efficiently by using the transport proteins for the particular building block.

The tactic has been reasonably successful, but has not yet lived up to expectation.

A more recent idea has been to attach the active drug to monoclonal antibodies which can recognize antigens unique to the tumour cell. The difficulty is in finding suitable antigens and producing the antibodies in significant quantity. However, the approach has great promise for the future.

**8.3.9 Self-destruct drugs**

Occasionally, the problems faced are completely the opposite of those mentioned

above. A drug which is extremely stable to metabolism and very slowly excreted can pose just as many problems as one with the opposite properties. It is usually desirable to have a drug which performs what it is meant to do, then stops doing it within a reasonable time. If not, the effects of the drug could last far too long and cause toxicity and lingering side-effects.

Therefore, designing drugs with decreased chemical and metabolic stability can be useful on occasions. The neuromuscular drug atracurium (Chapter 11) is a good example of this.

**8.3.10 Delivery systems**

Continuous minipumps have been developed which can release insulin at varying rates depending on blood-glucose levels. This appears to be the best answer to the problem of providing insulin at the correct levels at the correct times. Some acid-sensitive drugs can be protected by the way they are formulated. For example, it is possible to coat pills with an acid-resistant polymer which protects the drug from the acids in the stomach. The polymer is designed to be removed under the slightly alkaline conditions of the large intestine. Unfortunately, absorption in the large intestine is not so efficient as the small intestine and so the applications are limited.

A physical way of protecting drugs from metabolic enzymes in the bloodstream is to

inject small vesicles called liposomes filled with the drug. These vesicles or globules consist of a bilayer of fatty molecules in the same way as a cell membrane and will travel round the circulation, slowly leaking their contents.