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Prodrugs
Do They Have Advantages in Clinical Practice?

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Summary

Prodrugs are pharmacologically inactive chemical derivatives of a drug molecule that require a transformation within the body in order to release the active drug. They are designed to overcome pharmaceutical and/or pharmacokinetically based problems associated with the parent drug molecule that would otherwise limit the clinical usefulness of the drug.

The scientific rationale, based on clinical, pharmaceutical and chemical experience, for the design of various currently used prodrugs is presented in this review. The examples presented are by no means comprehensive, but are representative of the different ways in which the prodrug approach has been used to enhance the clinical efficacy of various drug molecules.

The term 'prodrug' is used to describe compounds which must undergo chemical transformation within the body prior to exerting their pharmacological or therapeutic action. The term 'prodrug' or 'proagent' was first used by Albert (1958) who suggested that this approach could be used to alter the properties of drugs, in a temporary manner, to increase their usefulness, and/or to decrease associated toxicity.

1. The Prodrug Concept

The prodrug concept is illustrated in figure 1. A drug whose usefulness is limited by adverse physicochemical properties, such that it is not capable of overcoming a particular barrier, is chemically modified via the attachment of a promoiety to generate a new chemical entity, the prodrug, whose properties are such that it is capable of traversing the limiting barrier. Ideally, the promoiety/drug bond will be designed to be cleaved efficiently by enzymatic or non-enzymatic means (Kupchan et al., 1965), followed by the subsequent rapid elimination of the released promoiety.

The term 'drug latentiation' has also been applied to this concept. Harper (1959, 1962) described drug latentiation as the chemical modification of a biologically active agent to form a new compound which upon *in vivo* enzymatic attack will liberate the parent compound. The chemical alteration of the parent compound is such that the change in physicochemical properties will affect the absorption, distribution and enzymatic metabolism. Such compounds have also been called bioreversible derivatives and congeners, but 'prodrug' is now the most commonly accepted term (Higuchi and Stella, 1975; Roche, 1977a; Sinkula and Yalkowsky, 1975).

Clinically relevant prodrugs are abundant. Many of the drugs that were developed as early as the

late nineteenth century are in fact prodrugs: for example, hexamine (methenamine) and aspirin are prodrugs of formaldehyde and salicylic acid, respectively. Aspirin is less corrosive than salicylic acid to the gastrointestinal mucosa and quantitatively releases salicylic acid *in vivo* by the action of esterases. Formaldehyde, as a contact antibacterial, could not be used as a urinary tract antiseptic until it was formulated as an enteric-coated tablet of hexamine. After absorption, hexamine is excreted in the urine, which if acidified, provides a medium in which formaldehyde is generated. Here the problem overcome was one of transport limitation, and site-specific delivery was achieved.

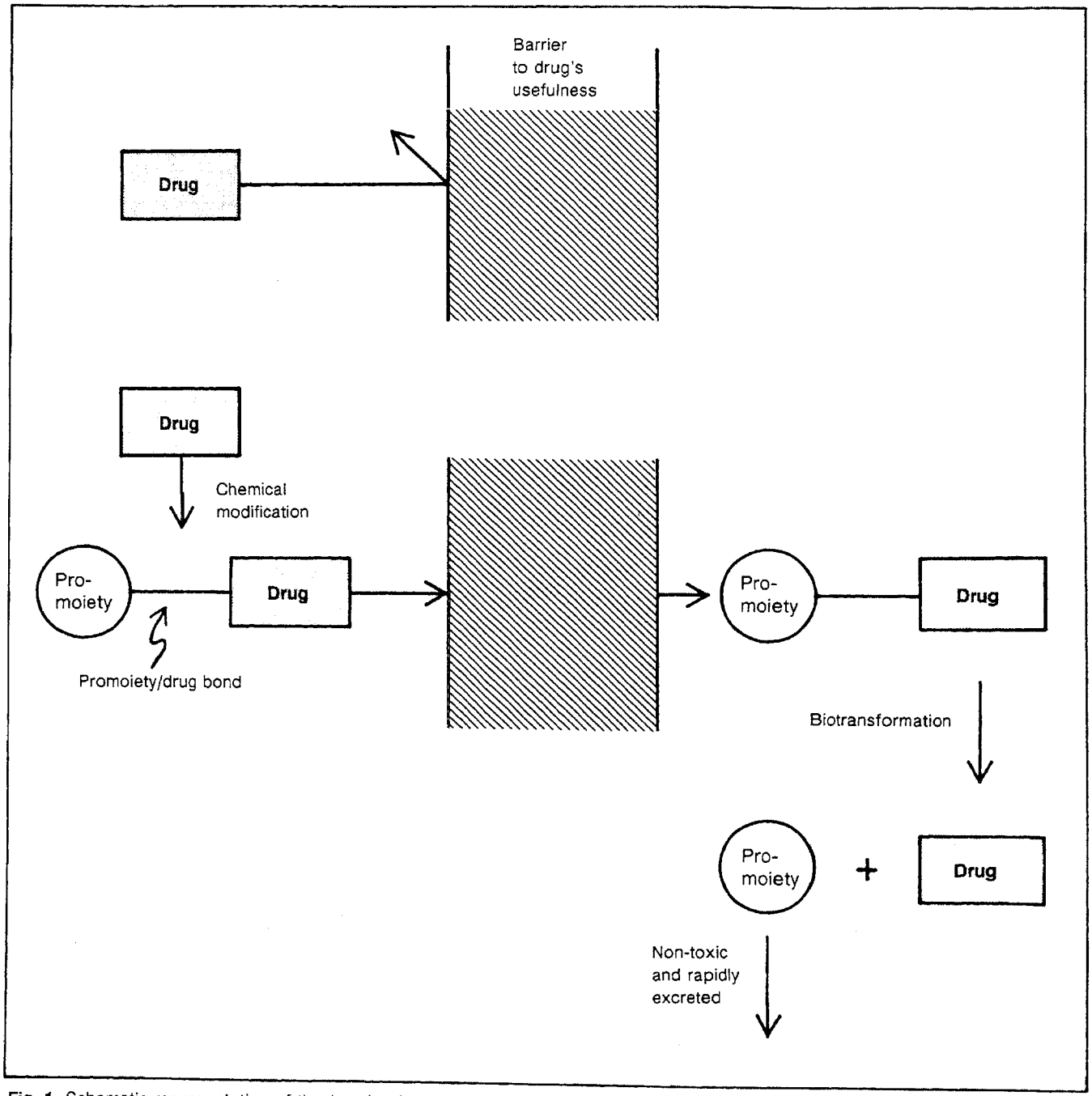


Fig. 1. Schematic representation of the 'prodrug' concept.

2. *Barriers to Drug Development*

In figure 1, the term 'barrier' is used rather loosely. It is easy to envisage a true biological barrier, such as the blood-brain barrier, when discussing the problems of drug delivery to the central nervous system (CNS). However, there are various other barriers that are not always recognised by end-users of a drug product that must be resolved before a new chemical entity can become a useful drug. Ariens and Simonis (1974) described the process of drug development as occurring in three phases: the pharmaceutical, pharmacokinetic, and pharmacodynamic phases. The pharmacodynamic phase, which involves the drug/receptor interaction, is not a phase where prodrugs are usually considered to act, although Bey (1978) has suggested that suicide substrates or K_{cat} inhibitors (compounds containing latent reactive groupings which are specifically unmasked by the action of target enzymes) can be considered as prodrugs.

2.1 Pharmaceutical Phase

The pharmaceutical phase can be considered as the phase of development which occurs between the identification of a new chemical entity with measured or proposed therapeutic potential and its incorporation into a drug delivery system. The delivery system may be one of the traditional forms such as tablets, capsules, injections, creams/ointments etc., or one of the new drug delivery modes, e.g. transdermal delivery patches or implanted devices. Two barriers in this phase to the development of a commercially usable drug product are:

1. The aesthetic properties of the new molecule may limit its usefulness, e.g. odour, taste, pain upon injection, gastrointestinal irritability, etc.
2. Formulation problems may become apparent, e.g. the drug is unstable, or because of its physicochemical properties, cannot be incorporated into a particular type of dosage form.

2.2 Pharmacokinetic Phase

The pharmacokinetic phase can be considered as that phase involving the study of the absorption, distribution, metabolism and excretion of the drug. These studies provide valuable information about the *in vivo* properties of a drug's limitations such as poor absorption, too rapid elimination, and presystemic metabolism. If these properties can be related back to the physicochemical and dosage form properties of the system, then correction can be made. Occasionally, these corrections will require prodrug interventions.

The principal barriers identified in the pharmacokinetic phase are:

1. Incomplete absorption of the drug from the delivery system or across biological barriers such as the gastrointestinal mucosal cells and the blood-brain barrier
2. Too rapid or too slow transport of the drug to the body, i.e. the *rate* of drug action onset needs to be optimised
3. Incomplete systemic delivery of an agent due to presystemic metabolism in the gastrointestinal lumen, mucosal cells, and liver
4. Toxicity problems associated with local irritation or distribution into tissues other than the desired target organ
5. Poor site specificity of the drug.

There are numerous clinical examples and literature references on the use of prodrugs attempting to solve the problems mentioned above. Many of these examples have appeared in comprehensive reviews (see table I). Some of the clinically or potentially clinically relevant examples, as well as some of the problems associated with the use of prodrugs, are presented in this article. The reviews listed in table I should be consulted for extensive coverage of the subject.

3. *Use of Prodrugs to Overcome Pharmaceutical Barriers*

The formulation of a new chemical entity with suspected therapeutic benefits requires that the drug be formulated into a delivery form that is chemically stable, free from taste and odour problems (particularly if it is for paediatric use or intended for parenteral administration), and the drug/form-

Table I. Comprehensive review articles on prodrugs

Selective toxicity	Albert (1973)
Molecular pharmacology as a basis for drug design	Ariens (1966)
Modulation of pharmacokinetics by molecular modulation	Ariens (1971)
Novel approaches in prodrug design	Bodor (1982)
Novel bioreversible derivatives of amides, imides, ureides, amines and other chemical entities not readily derivatisable	Bundgaard (1982)
Drug latentiation	Digenis and Swintosky (1975); Harper (1959, 1962)
Prodrugs as novel drug delivery systems	Higuchi and Stella (1975)
Prodrug design	Notari (1981)
Design of biopharmaceutical properties through prodrugs and analogues	Roche (1977a)
Rationale for design of biologically reversible drug derivatives	Sinkula and Yalkowsky (1975)
Prodrug approach in drug design	Sinkula (1975)
Chemical modification of drugs to overcome pharmaceutical problems	Stella (1973)
Drug substances in particular prodrugs: problems and methods or approaches	Stella (1977)
Prodrugs and site specific delivery	Stella and Himmelstein (1980)
A physical chemical basis for the design of orally active prodrugs	Yalkowsky and Morozowich (1980)

ulation must be relatively free of irritation on administration. For intravenous usage, the drug should have adequate water solubility and remain in solution for sufficient time to permit administration of the complete dose.

3.1 Masking Taste or Odour Problems

Chloramphenicol is an extremely bitter substance inhibiting its usage in paediatric formulations. Chloramphenicol palmitate, a sparingly soluble ester of chloramphenicol, is practically tasteless because of its low aqueous solubility (Glazko et al., 1952). Since the interaction of a drug or prodrug with taste receptors requires the drug to be sufficiently soluble in saliva, by lowering the aqueous solubility to mask a taste problem, one runs the risk of creating a more serious problem, i.e. incomplete dissolution of the prodrug in the gastrointestinal tract, resulting in incomplete absorption. However, the commercially used form of cloramphenicol palmitate is efficiently hydrolysed to active chloramphenicol by the action of pancreatic lipase on solid chloramphenicol palmitate particles (Andersgaard et al., 1974). Interestingly, other polymorphs – different crystalline forms of chloramphenicol palmitate – which are also tasteless, do not provide good plasma concentrations of chloramphenicol because of poor solubility and the fact that the solid-to-solution transition is not catalysed by lipase. Other examples of the use of prodrugs to mask taste are listed in table II.

Odour is another aesthetic concern for some drugs. Such compounds are often volatile liquids, or solids with significant vapour pressure that makes them difficult to formulate. A classic example of this are the volatile mercaptans used as tuberculostatic agents and for the treatment of leprosy. Ethyl mercaptan has a boiling point of 25°C and a strong disagreeable odour. Diethyldithioisophthalate, a prodrug of ethylmercaptan, has a higher boiling point, is relatively odourless (Davies et al., 1956; Davies and Driver, 1957) and has been used topically (as an enunction) for the systemic delivery of ethylmercaptan which is generated from the prodrug by the action of systemic thioesterases.

3.2 Reduction of Pain or Irritation at Injection Sites

Pain or irritation at an injection site may be caused by precipitation of the drug, by cell lysis due to either hypo- or hyperosmotic solutions, the properties of the drug itself, or the corrosive action of the drug at nerve endings. Some of these prob-

Table II. Some examples of prodrugs designed to mask taste problems

Drug	Prodrug	Reference
Chloramphenicol	Palmitate	Glazko et al. (1952)
Clindamycin	Palmitate	Sinkula et al. (1973)
Erythromycin	Ethyl succinate	Murphy (1953)
	Ethyl carbonate	Clark and Varner (1957)
Oleandamycin	Acyl ester and N-oxide	Celmer (1968)
Lincomycin	Phosphate ester	Morozowich et al. (1969, 1973)
	Carbonate ester	Sinkula and Lewis (1973)
Sulphafurazole (sulfisoxazole)	N'-Acetyl	McEvoy (1974)
Dextro-propoxyphene	Napsylate[a]	Gruber et al. (1971)

a Sparingly soluble salt.
Note: In the case of salts, the promoiety/drug linkage is ionic, and not covalent. However, these specialised salts can still be called prodrugs (Stella, 1975).

lems may relate to the vehicle composition or vehicle pH needed for formulation purposes.

Clindamycin hydrochloride, an antibiotic with an aqueous solubility of 3 mg/ml, produces a great deal of pain upon intramuscular injection, while clindamycin 2-phosphate, a prodrug of clindamycin with a solubility of > 150 mg/ml, does not cause irritation or pain upon intramuscular administration (Edmondson, 1973; Gray et al., 1974). The prodrug has no intrinsic antibacterial activity and is converted to clindamycin *in vivo* with a half-life of approximately 10 minutes by the action of phosphatase enzymes (DeHaan et al., 1973). Figure 2 shows serum concentrations of clindamycin 2-phosphate and free clindamycin *versus* time after a 20mg intravenous infusion (10 min) of clindamycin 2-phosphate. Although the phosphate ester is detected in the serum for a substantial length of time, most of it is ultimately cleaved to clindamycin, with only 1 to 2% of the dose appearing as unchanged prodrug in the urine (DeHaan et al., 1973). The clinical advantage here is that an intramuscular clindamycin preparation may not have been commercially viable without the development of the phosphate prodrug.

A further example is provided by the anticonvulsant drug phenytoin (5,5-diphenylhydantoin) which is formulated for intravenous or intramuscular use in 40% propylene glycol, 10% alcohol and 50% water with the pH adjusted to $\approx$ 12. At this pH, phenytoin is present in its anionic form (sodium phenytoin). These formulation conditions are necessary because phenytoin has an aqueous solubility of only 0.02 mg/ml and is weakly acidic (pK_a 8.3). Therefore, a high pH and the presence of cosolvents are necessary to provide a 50 mg/ml

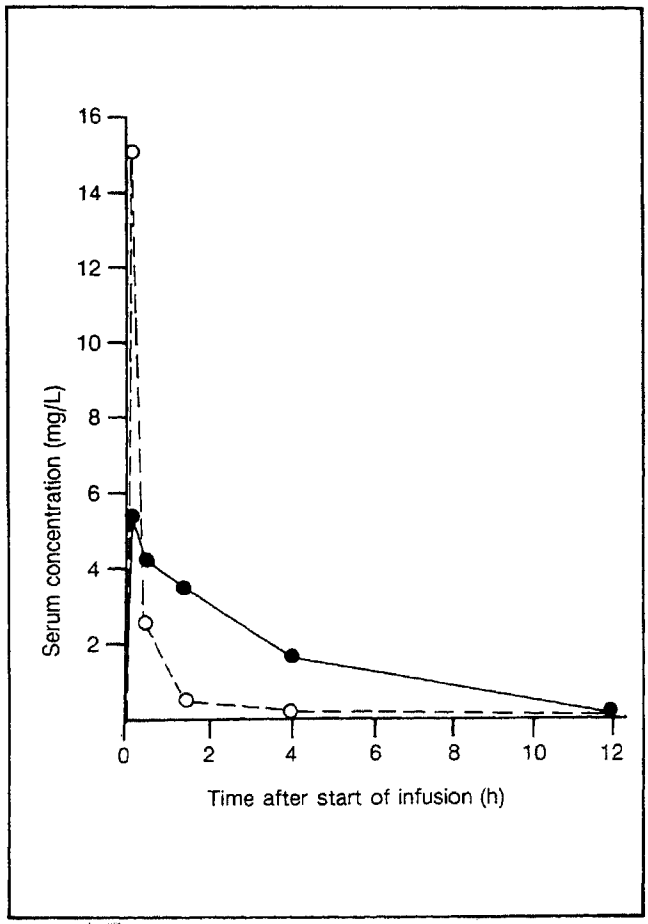


Fig. 2. Mean serum concentration (mg/L) of clindamycin (●—●) and clindamycin 2-phosphate (as clindamycin equivalent) (○----○) after a 20mg intravenous infusion of clindamycin phosphate over a 10-minute period (after DeHaan et al., 1973).

sodium phenytoin injection preparation suitable for intravenous or intramuscular usage. However, this formulation is very toxic after rapid intravenous injection due to possible precipitation of phenytoin in the vein as the pH adjusts to the physiological value of 7.4, and due to the fact that propylene glycol is a cardiac depressant (Atkinson and Davison, 1974). Similarly, on intramuscular injection, phenytoin precipitates at the injection site. Recently, Varia et al. (1984a,b,c,d) evaluated a series of prodrugs of phenytoin that have superior solubility and potential therapeutic benefits over the current sodium phenytoin injectable form. The disodium salt of the phosphate ester of 3-hydroxymethylphenytoin was found to be pharmacologically inert, generated phenytoin rapidly and quantitatively *in vivo* in rats and dogs, and on intramuscular administration gave no apparent irritation while rapidly releasing phenytoin. This prodrug is currently undergoing evaluation as a possible alternative to the use of sodium phenytoin.

3.3 Alteration of Drug Solubility

The prodrug approach can be used to increase or decrease the solubility of a drug depending on its ultimate use. One advantage of making a less soluble prodrug (to mask taste) and the possible problems it can create – i.e. compromised bioavailability – has already been discussed (section 3.1). There are numerous examples where solubility needs to be increased. The prime examples involve drugs whose solubility is so low that a solution dosage form for intravenous usage is not possible.

3.3.1 Chloramphenicol and Corticosteroids

Whereas the palmitate ester of chloramphenicol has proved useful for oral formulations, a more water-soluble form, chloramphenicol sodium succinate, has been developed for parenteral administration (Glazko et al., 1957). Chloramphenicol sodium succinate has no antibacterial activity but is hydrolysed in the body to free chloramphenicol by the action of esterases.

Steroids are another group of compounds having poor water solubility. Glucocorticoids such as betamethasone, prednisolone, methylprednisolone, hydrocortisone and dexamethasone are available as water-soluble disodium phosphate or sodium succinate prodrugs. The sodium succinate forms are available only as lyophilised powders for reconstitution because of their relatively poor chemical stability compared with the phosphate esters. The lyophilisation is also an expensive process.

Ideally, when a prodrug is used to improve aqueous solubility to allow intravenous administration of a drug, it should be rapidly and quantitatively hydrolysed in the body, and it should also have no intrinsic therapeutic activity or toxicity. If a very water-soluble prodrug is not rapidly converted to the parent drug after administration, it may be significantly eliminated in the urine thereby reducing drug bioavailability. The possibility of prodrug accumulation in the body, particularly in patients with impaired renal function, may also be a problem. Studies with chloramphenicol sodium

Table III. Plasma cortisol $AUC_{0\text{-}240}$ values after intravenous and intramuscular injections of hydrocortisone sodium succinate and hydrocortisone disodium phosphate in humans (after Melby and St Cyr, 1961)

Prodrug[a]	Route of administration	Plasma cortisol $AUC_{0\text{-}240}$ (mg/L · min)
Hydrocortisone sodium succinate	IV	1.42×10^4
Hydrocortisone disodium phosphate	IV	2.12×10^4
Hydrocortisone sodium succinate	IM	1.55×10^4
Hydrocortisone disodium phosphate	IM	2.18×10^4

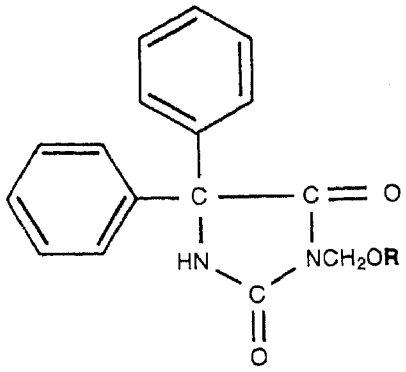
a Both prodrugs have essentially the same molecular weight, so even though the dose administered (1 mg/kg) was on a weight basis, comparison of AUCs is possible.

Abbreviations: $AUC_{0\text{-}240}$ = area under the plasma concentration-time curve over 240 minutes; IV = intravenous; IM = intramuscular.

succinate have shown that 30 to 40% of the prodrug is excreted in the urine as such (Nahata and Powell, 1981), thus complicating chloramphenicol therapy.

There are similar indications that the succinate esters of corticosteroids (Melby and St Cyr, 1961) are incompletely broken down to the parent steroid. Melby and St Cyr (1961) compared plasma concentrations of hydrocortisone, prednisolone and dexamethasone after intravenous and intramuscular administration of the phosphate and succinate esters. The areas under the 0 to 240 minute plasma concentration-time curves (AUCs) [table III] clearly demonstrate that the hydrocortisone was more efficiently released from the phosphate ester (disodium salt). The rapid hydrolysis of the phosphate esters can probably be attributed to the abundance of phosphatase enzymes, while the poorer performance of the succinate esters, i.e. their inability to be rapidly and quantitatively cleaved by esterases, may be due to the presence of an anionic site (the free carboxylate) near the ester bond (Krish, 1971).

Table IV. Aqueous solubilities of various phenytoin prodrugs (derivatives of 3-hydroxymethylphenytoin) relative to phenytoin

Prodrug (−R)	Relative solubility (phenytoin = 1)
	
$-COCH_2NH^+(CH_3)_2 \cdot CH_3CO_3^-$	8810
$-CO(CH_2)_2NH^+(C_2H_5)_2 \cdot$ napsylate	39
$-COO(CH_2)_2NH^+(CH_3)_2 \cdot CH_3SO_3^-$	4730
$-PO_3^{2-}Na_2^+$	4500

3.3.2 Phenytoin

As discussed above (section 3.2), some water-soluble prodrugs of phenytoin have recently been developed (Varia et al., 1984a,b,c,d). Phenytoin has a high melting point indicating strong crystal lattice energy, which on dissolution is not compensated for by the release of solvation forces. Therefore, phenytoin is very water-insoluble and can only be dissolved at a high pH, as sodium phenytoin, and with the help of cosolvents. We have found that phenytoin reacts with an excess of formaldehyde to produce 3-hydroxymethylphenytoin which can be further derivatised to give the water-soluble prodrugs listed in table IV.

Dramatic increases in aqueous solubility are seen with the disodium phosphate ester, which has also been determined to be the most desirable phenytoin prodrug based on chemical stability, as well as *in vivo* performance (Varia and Stella, 1984c,d). Upon cleavage of the phosphate group, the 3-hydroxymethyl derivative is formed, which in the absence of formaldehyde rapidly looses formaldehyde ($t_{1/2}$ < 2 sec at 37°C and pH 7.4) to generate phenytoin. Table V illustrates the advantages of this phosphate ester in delivering phenytoin after intramuscular administration of the prodrug to rats in comparison with sodium phenytoin. The lower phenytoin concentrations from sodium phenytoin are probably the result of phenytoin precipitation after the cosolvent is diluted and the pH has adjusted to physiological pH. The higher phenytoin concentrations from the prodrug reflect its rapid release from the intramuscular site and subsequent *in vivo* cleavage to phenytoin.

This solution to the phenytoin problem raises an interesting question: does the formaldehyde produced cause toxicity? As with any prodrug solution to a problem, the prodrug itself and its decomposition product must be safe, or at least should not add to possible toxicity. Although in theory the formaldehyde produced by the 3-hydroxymethylphenytoin could be toxic, in practice the prodrug will only be used in acute cases where the patient,

Table V. The relative areas under the blood concentration-time curves over 210 minutes (AUC_{0-210}) and maximum blood concentrations of phenytoin after a 10 mg/kg intramuscular dose of sodium phenytoin and a 7 mg/kg intramuscular phenytoin equivalent dose of its phosphate prodrug to rats (± SD)

Compound	Dose[a] (mg/kg)	Maximum blood concentration (mg/L)	t_{max} (min)	AUC_{0-210} (mg/L · min)
Sodium phenytoin[b]	10	1.05 (± 0.40)	30	97.8 (± 82.0)
Phosphate prodrug[c]	7	2.95 (± 0.60)	45	339.8 (± 9.7)

a Phenytoin equivalents.
b In a 40% propylene glycol, 10% alcohol, 50% water vehicle (pH ≈ 12).
c In sterile distilled water.

over a week, will receive less than 2g equivalents of phenytoin or approximately 200mg of formaldehyde, which would rapidly convert to CO_2. Most drugs that undergo N- or O-demethylation produce larger quantities of formaldehyde than the 3-hydroxymethylphenytoin conversion, and many of these drugs are used clinically. Therefore, the amount of formaldehyde produced from this system is not anticipated to cause any serious problems.

3.3.3 Sulindac

In contrast to parenteral dosage forms, there are surprisingly few examples of a clinically relevant nature where the prodrug approach has been used to increase aqueous solubility in order to improve the oral absorption of drugs. This can partly be traced to how drugs were screened for activity up until about 10 years ago. Screening usually involved the oral and/or subcutaneous administration of the drug to rats or mice, and the measurement of a pharmacological response. If the drug had poor aqueous solubility, it was often given as a suspension, so the only drugs which showed activity were those with sufficient solubility or high intrinsic bioactivity to elicit a response. Thus, the screening procedures not only eliminated inactive drugs, but also those drugs with limited aqueous solubility. Those drugs which did give a response had some solubility in water. Therefore, when these compounds were formulated into tablets and the tablet formulation optimised for release characteristics, they often performed fairly well. With the knowledge of how solubility can affect screening results, and the use of biochemically based screens, current analogue and prodrug approaches to solving solubility problems are becoming an integral part of the drug design process. An example of this is the recent development of the indene non-steroidal anti-inflammatory agent sulindac as a prodrug of sulindac sulphide (Shen and Winter, 1977) [fig. 3]. Sulindac was developed primarily to reduce gastrointestinal toxicity (see also section 4.4.1) and is 100 times more water soluble than the sulphide. At pH 7.4, the solubility of sulindac is 3.3 mg/ml while that of the sulphide is 0.03 mg/ml (Shen, personal communication). Because of this greater solubility and the fact that it still maintains sufficient lipophilicity for gastrointestinal absorption (octanol : water partition coefficient at pH 7.2 is 1.52; Shen and Winter, 1977), sulindac is well absorbed after oral administration (Duggan et al., 1977).

One should always remember that increased aqueous solubility does not necessarily result in improved bioavailability for dissolution rate-limited, poorly bioavailable drugs. Because of the lipophilic nature of most cell membranes, including those of the gastrointestinal mucosal cells, a proper balance between changes in aqueous solubility and drug lipophilicity must be maintained. This is discussed in greater detail in section 4.1.

3.4 Enhancement of Chemical Stability

A very important requirement of all drug products is that they must be chemically stable over a reasonable period. Except for products like vaccines, some cytotoxic agents, and other life-saving products, a shelf-life of at least 2 years is desirable. If a drug is chemically very unstable and the instability problem cannot be resolved by formulation means, it is sometimes possible to develop a prodrug with enhanced stability over the parent drug. This usually takes the form of chemical modification of the functional group responsible for the instability, or a change in the physical properties of the drug (via prodrug modification) resulting in the reduction of contact between the drug and the media in which it is unstable.

Aqueous sodium ampicillin is chemically very unstable in concentrated solution due to autoaminolysis, i.e. the side chain primary amino group of the ampicillin molecule is capable of attacking the β-lactam ring of a second ampicillin molecule to give various polymeric species (Bundgaard, 1974; Stewart, 1967, 1968). Hetacillin is a prodrug of ampicillin formed by its reaction with acetone. When hetacillin is diluted for intravenous infusion (< 20 mg/ml ampicillin equivalents) it readily dissociates to ampicillin and acetone. However, in concentrated solutions, the hetacillin only partially dissociates. Since the interaction of the side chain of ampicillin and acetone 'ties up' the amino group, hetacillin does not undergo the autoaminolysis reaction and is a relatively stable prodrug form of ampicillin sodium (Schwartz and Hayton, 1972). In the body, hetacillin readily dissociates to produce ampicillin.

As stated in the footnote to table II, salts of a drug may or may not be considered prodrugs, since the promoiety/drug linkage in this instance is ionic and not covalent. However, assuming that they are considered prodrugs (i.e. the properties of the new salt are unique), then the sparingly soluble benzathine and procaine salts of penicillin G can be termed prodrugs. Penicillin G is very unstable in aqueous solution and it is not possible to formulate penicillin G as a stable aqueous solution. The rate of inactivation of drugs in solution usually follows pseudo first-order kinetics. The procaine and benzathine salts of penicillin have poor aqueous solubility. When these salts are formulated as suspensions, only the fraction of penicillin G in solution, given by its solubility product, will degrade, so these sparingly soluble salts give suspensions of penicillin G quite long shelf lives. The napsylate salt of dextropropoxyphene also is more stable than the corresponding hydrochloride salt.

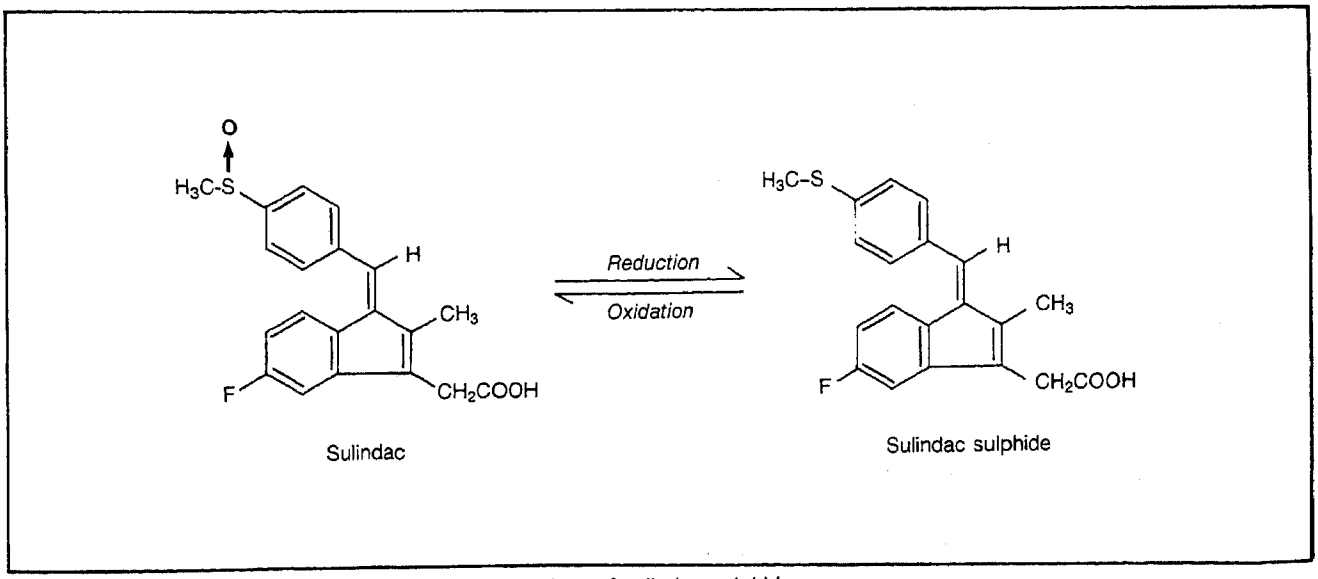


Fig. 3. Sulindac was specifically developed as the prodrug of sulindac sulphide.

4. Use of Prodrugs to Overcome Pharmacokinetic Barriers

The absorption, distribution, metabolism and excretion of a drug are all dynamic processes that are affected by the physicochemical properties of the drug. Variations in bioavailability, for example, can lead to variations in patient response to a drug, and in animals can lead to ambiguous interpretation of the efficacy of the drug.

4.1 Enhancement of Oral Absorption

If a drug is very water insoluble, bioavailability after oral dosing is often dissolution rate limited. As stated above (section 3.3.3) there are only a few examples where prodrugs have been used to improve drug absorption of dissolution rate-limited drugs.

For agents that are highly polar in nature, it is often the transport of the drug across the gastrointestinal mucosal cell membranes that limits drug absorption. Since most drugs are absorbed by passive diffusion, a degree of lipophilicity is necessary for efficient absorption through the gastrointestinal barrier (Ho et al., 1977). For highly polar compounds, the administration of a less polar, more lipophilic prodrug may help promote gastrointestinal absorption. This approach has been successfully applied with various penicillin derivatives.

4.1.1 Ampicillin

Ampicillin is highly polar and at the pH of the gastrointestinal tract is mostly present in a zwitterionic form. Its bioavailability after oral dosing is only 20 to 60% (Bolme et al., 1976). A number of less polar prodrugs of ampicillin have been prepared by esterifying the carboxyl group of ampicillin. Those currently receiving the most attention are bacampicillin, pivampicillin and talampicillin (fig. 4).

These ester prodrugs of ampicillin are efficiently absorbed and are cleaved by general esterase enzymes in the body, most often in the mucosal cells themselves, releasing ampicillin. In the case of bacampicillin, the products of the cleavage are acetaldehyde, carbon dioxide and ethanol. For pivampicillin, it is formaldehyde (see earlier discussion of the toxicity question, section 3.3.2) and pivalic acid. The bioavailability characteristics of all these prodrugs are significantly superior to ampicillin itself (Ehrnebo et al., 1979; Loo et al., 1974; Sjovall et al., 1978). Figure 5 shows ampicillin plasma concentrations *versus* time in human volunteers given equimolar amounts of bacampicillin and ampicillin (Magni et al., 1976). There is an approximate 2- to 5-fold increase in relative oral bioavailability when bacampicillin is administered. Bacterial infections treated with drugs like ampicillin often require the drug to reach other tissues and organs, besides the plasma. Simon et al. (1978) demonstrated that ampicillin tissue concentrations following bacampicillin administration correlated with the increased blood concentrations of ampicillin.

For other examples where prodrugs have been developed to improve the gastrointestinal absorption of polar drugs, see Bodor (1977), Vickers et al. (1978), Roche (1977b) and Saari et al. (1978).

4.2 Prevention of Presystemic Metabolism

Many drugs are efficiently absorbed from the gastrointestinal tract but undergo presystemic me-

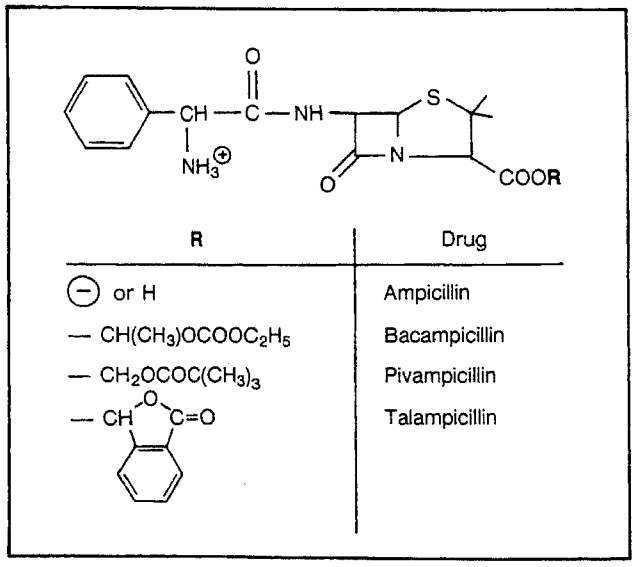


Fig. 4. The ester prodrugs of ampicillin: bacampicillin, pivampicillin and talampicillin.

tabolism or inactivation before reaching the systemic circulation. This inactivation may be chemically or enzymatically based. The acid in the stomach, for example, partially degrades a number of drugs before they can be efficiently absorbed. The major problem associated with enzymatic metabolism is that orally administered drugs are exposed to the enzymes of the gastrointestinal lumen, the brush border, the mucosal cell and the liver, prior to reaching the systemic circulation.

A major class of drugs that undergo marked presystemic metabolism are those containing phenolic moieties. Sulphation, glucuronidation and, to a minor extent, methylation all contribute to rapid inactivation of many of these drugs. For example, only 4% of orally administered isoprenaline (isoproterenol) reaches the systemic circulation intact as compared with an equivalent intravenous dose (Redwood, 1969). Similarly, conjugation of other phenolic molecules such as salicylamide, α-methyldopa, terbutaline and salbutamol also limits their systemic availability. Presystemic metabolism is not just limited to drugs with phenolic moieties. Oxidative N- and O-dealkylation, ester cleavage and peptide degradation are other major cleavage routes. However, the phenols, as a class of presystemically metabolised drugs, have been the most extensively studied with respect to developing suitable prodrugs for preventing their presystemic clearance.

4.2.1 Traditional Prodrug Approaches with Phenolic Compounds (e.g. paracetamol)

The traditional approach has been to 'mask the metabolisable moiety', i.e. to derivatise the phenolic group with either an ester or ether type group. These approaches have met with only marginal success in preventing presystemic clearance of the parent drug.

The basis for this poor performance can be seen in the work of Pang and Gillette (1978) who studied the liver metabolism of paracetamol (acetaminophen) and its prodrug, phenacetin (acetophenetidin), in an *in vitro* perfused liver study. The steady-state hepatic extraction ratio is the fraction of drug eliminated during its passage through the liver, and this was measured for both paracetamol and phenacetin. It was found that the extraction ratio of paracetamol perfused as paracetamol was less than the extraction ratio of paracetamol perfused through the liver as phenacetin; i.e. paracetamol produced from phenacetin by the liver was more efficiently metabolised. This process was referred to by Pang and Gillette (1978) as sequential metabolism. Qualitatively, in this case the O-dealkylation of phenacetin to paracetamol occurs in the liver, and since the active drug (paracetamol) is metabolised by the same organ (the liver), it is rapidly inactivated by conjugation. Thus paracetamol is more efficiently metabolised when administered as the phenacetin prodrug. Therefore, designing prodrugs to mask phenolic groups will not be successful in preventing presystemic metabolism unless the 'demasking' occurs in an organ other than where the presystemic metabolism of the parent drug occurs. This concept of sequential organ metabolism may explain the apparent failures seen with most postulated ester and ether prodrugs of phenols, since the liver and intestinal mucosal cells are rich in esterase and oxidative O-dealkylation (P-450) enzymes.

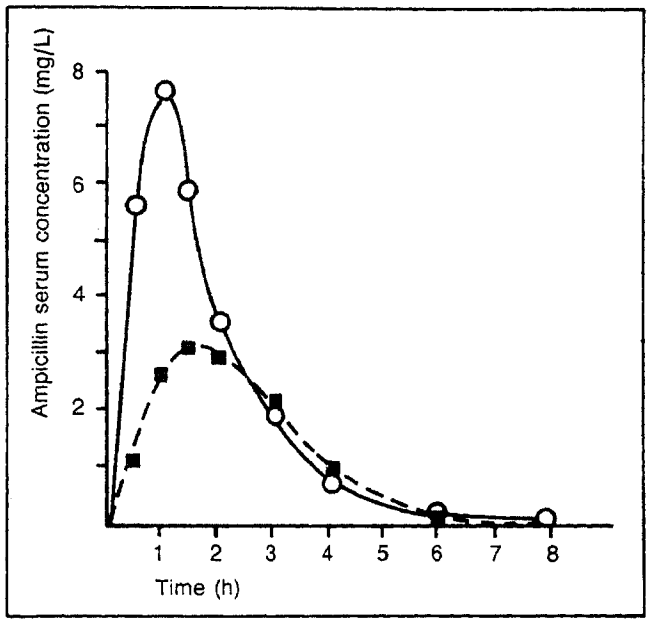


Fig. 5. Mean serum concentration (mg/L) of ampicillin in human volunteers following oral administration of equimolar amounts of bacampicillin (400mg) [O——O] and ampicillin (278mg) [■----■] (after Magni et al., 1976).

4.2.2 New Prodrug Approaches

Future prodrug research for the prevention of presystemic metabolism of phenols may well follow the outline shown in figure 6. This involves the design of firstly 'masking' promoieties which are not cleaved in the intestinal lumen, mucosal cell or liver, but by a systemic enzyme; thus, the functional group which is the source of the problem is protected. A second approach which we have been pursuing involves a biochemical technique (Williams, Pitman and Stella, unpublished data). Knowledge of the structure-reactivity requirements of a particular enzyme system (e.g. phenol sulphotransferase) allows one to recognise that the promoiety could be placed at some other position in the drug molecule (fig. 6) such that the prodrug is no longer a substrate – due to either steric, electronic or other effects – for the presystemic metabolising enzyme; i.e. even though the functional group originally attacked is not directly 'masked', the physicochemical properties of the prodrug are such that it is not recognised as a substrate. The advantage of this approach may well be the use of promoieties attached to other parts of the molecule that could not be easily placed on the phenolic group directly. However, the cleavage of the promoiety should still be triggered after passage through the liver, otherwise sequential metabolism will occur. This approach will require input from biochemists and enzymologists to be successful.

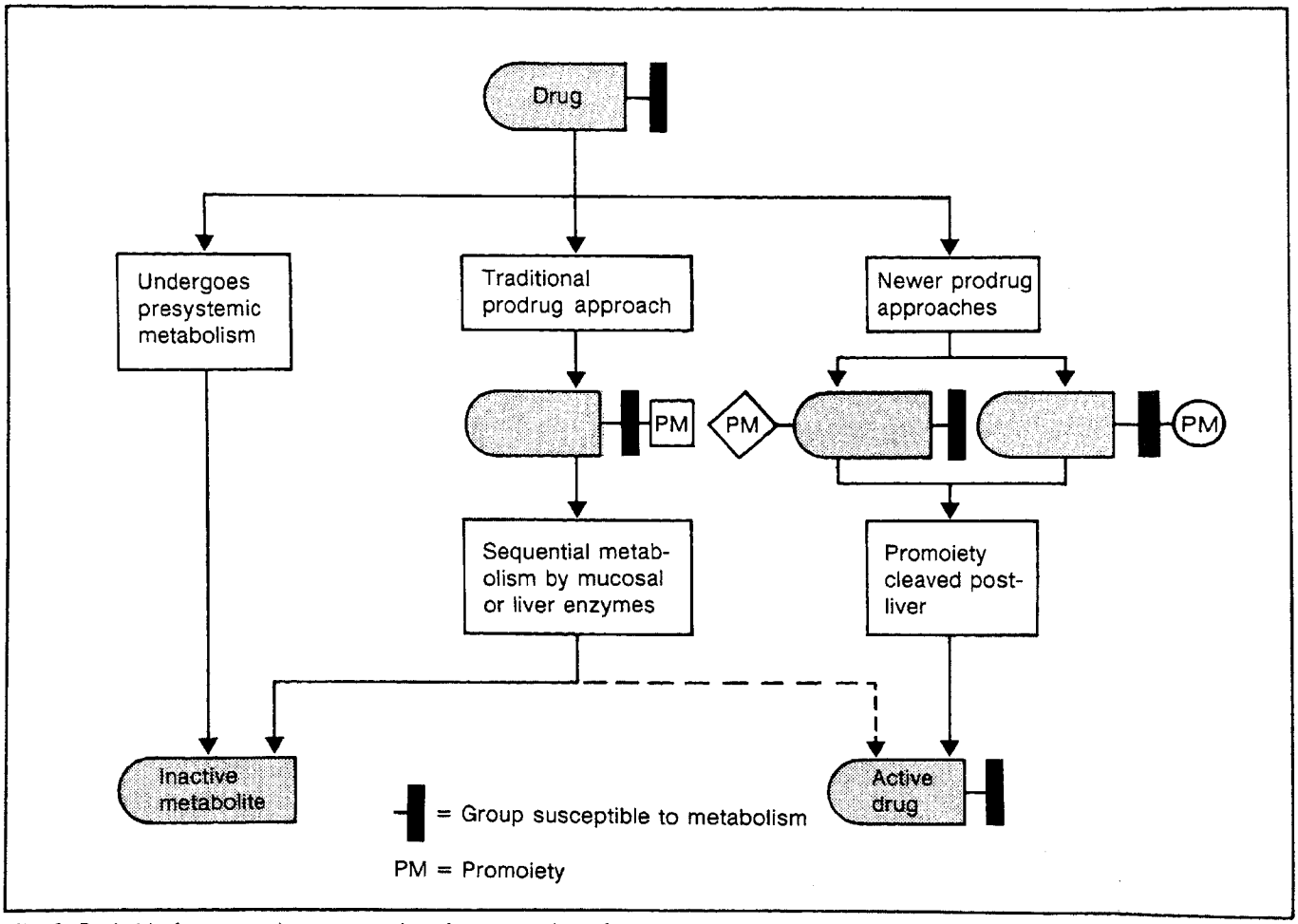


Fig. 6. Probable future prodrug approaches for prevention of presystemic metabolism of phenolic compounds. These involve the design of either 'masking' promoieties [-(PM)] which are cleared by a systemic enzyme rather than in the intestinal lumen, mucosal cell or liver, *or* a promoiety that is placed at some other position in the drug molecule[<PM>] such that the prodrug is no longer a substrate for the presystemic metabolising enzyme (even though the functional group originally attacked is not directly 'masked').

4.3 Prolongation of Drug Action

For drugs rapidly cleared from the body, frequent dosing with conventional dosage forms is required to maintain adequate plasma concentrations of the particular drug. This frequent dosing of short half-life drugs results in sharp peak-valley plasma concentration-time profiles, and consequently patient compliance is often poor. Sustained or prolonged release drug products will often overcome such problems. Traditional formulation approaches are often quite successful but the combination of a prodrug and a suitable delivery system may allow for the sustained release of drugs for which a pure formulation approach may not work.

Sinkula (1978) has summarised the ways in which alterations in the physicochemical properties of a drug, in the form of a prodrug, can be used to prolong or control drug action. They include alterations in:

1. The degree and rate of absorption
2. The rate and extent of conversion of the prodrug to the active species
3. The rate and extent of protein or tissue binding
4. The degree of tissue or organ localisation, distribution and subsequent release from such sites.

The development of prodrugs for the prolongation of therapeutic action has generally been avoided due to the inability to rationally predict the effect of the prodrug structural modification on the resulting pharmacokinetics. Future research will no doubt attempt to 'match' the delivery system with the drug or, if not possible, a prodrug to prolong drug action. The one area that has had some qualitative and predictive successes has been in the area of hormonal steroid and depot antipsychotic drug injections.

4.3.1 Testosterone

Lipophilic prodrugs of testosterone such as its 17-propionate, 17-phenylacetate, and 17-cypionate esters are administered in an oil vehicle by deep intramuscular injection.

It is generally accepted that these esters are slowly released from the intramuscular site after which they are stored in fat depots and ultimately cleaved to testosterone. For a detailed discussion of the release mechanisms, see Alibrandi et al. (1960), James et al. (1969), Tanaka et al. (1974) and Sinkula (1977).

4.3.2 Depot Antipsychotic Drugs

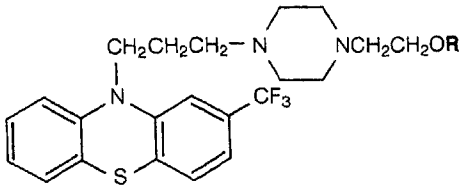
This same technology has been applied to various antipsychotic drugs. Prolongation of antipsychotic action is particularly desirable with drugs used for the long term control of schizophrenic patients. The depot forms of fluphenazine are its enanthate (heptanoate) and decanoate esters. These esters have greater lipophilicity than the parent compound, and when administered in sterile sesame oil, intramuscular injections exhibit a much longer duration of action than fluphenazine hydrochloride (fig. 7). It is worth mentioning that this type of prodrug approach has its clinical dangers. Once injected it is difficult to halt therapy if the patient experiences an adverse reaction to the drug. Unlike an implant that can be surgically removed or a transdermal patch that can be easily peeled off, once a deep intramuscular injection is given, if an adverse reaction occurs it probably can only be treated symptomatically.

Other examples of prolonged prodrug forms of antipsychotic agents have been reviewed by Villeneuve et al. (1972), Yale (1977, 1978), and Jorgensen (1978).

4.3.3 Other Drugs

Drug classes as different and diverse as β-lactam antibiotics, antimalarials and hypoglycaemic agents have been studied with a view to increasing their duration of action. Success is not always forthcoming because of the lack of predictive relationships between the structural modifications and the duration of action.

Realistically, neither the prodrug nor delivery system approach may be sufficient on their own to prolong the action of a drug, e.g. systems like the Orose® osmotic delivery system are ideally suited to the delivery of water-soluble salts (Theeuwes, 1975); therefore, a drug without sufficient aqueous solubility could not be used, or is less likely to be



Fluphenazine

R	Duration of action after IM injection
– H (as hydrochloride)	6-8 hours
– COC_6H_{13} F-enanthate	2 weeks
– COC_9H_{19} F-decanoate	4 weeks

Fig. 7. Fluphenazine hydrochloride and its esters used for depot injections.

used in such a system. The preparation of a prodrug with the ideal solubility properties may allow the use of such a sophisticated delivery system. It is thus likely that future drug products designed for prolonged action may well be suitably matched prodrug/delivery system combinations.

4.4 Reduction in Toxicity

One of the desired properties of all therapeutically active agents is that they have negligible or no toxicity associated with their clinical use. While it would be indeed naive to believe that toxicological problems could be solved by prodrug formulations, sufficient examples of a reduction in toxicity due to prodrug administration exist so as to provide an impetus for this exciting, albeit difficult, area of prodrug research.

4.4.1 Aspirin and Sulindac

As discussed earlier, aspirin can be considered a less corrosive prodrug form of salicylic acid. Similarly, sulindac, also mentioned earlier, is a prodrug of the corresponding sulphide. Sulindac itself, as the sulphoxide form of the active sulphide moiety, has little or no pharmacological activity but is much more water soluble. The advantages of the higher water solubility as it relates to more efficient gastrointestinal absorption are discussed in section 3.3.3. Following its absorption as the inactive sulphoxide, sulindac is reversibly reduced to the sulphide and a sulphoxide/sulphide equilibrium is established (fig. 3); the drug is also irreversibly oxidised to the inactive sulphone. The overall disposition of sulindac is complex and the subject of extensive research (Duggan, 1981; Duggan et al., 1977, 1980; Dobrinska et al., 1983; Shen and Winter, 1977). Since the anti-inflammatory activity and gastrointestinal intolerance of many anti-inflammatory drugs seem to be mediated by their inhibition of prostaglandin synthetase (Vane, 1974) and the ingested sulphoxide has little or no such activity, exposure of the gastrointestinal mucosa to the active substance is minimised. This may account for the reduced local gastrointestinal irritation caused by sulindac in comparison with certain other anti-inflammatory drugs such as aspirin, though such side effects are by no means absent.

In addition, the active sulphide metabolite of sulindac has a longer elimination half-life than sulindac (16 *vs* 7 hours) and due to the bioequilibrium between the two, a prolonged duration of action enabling twice daily dosing is seen. Moreover, sulindac, like many large molecular weight anionic drugs, undergoes enterohepatic recirculation mainly as either the unchanged prodrug or as a glucuronide conjugate. The latter may be cleaved in the intestine to liberate free sulindac, which can again be absorbed into the general circulation.

Sulindac is an excellent example of a clinically relevant prodrug with decreased toxicity and better absorption characteristics than its active drug, and

with a longer duration of action due to the conversion kinetics between the sulphoxide and sulphide as well as the enterohepatic recycling.

4.5 Achieving Site-Specific Drug Delivery

The targeting of drugs for certain tissues, sites, enzymes, etc., represents a major portion of drug-related research throughout the world. The use of prodrugs to achieve site specificity is one approach being actively pursued. This approach, along with others (Bundgaard et al., 1982; Gregoriadis, 1977, 1979; Juliano, 1980), holds the hope for achieving very precise and direct effects at the 'site of action' without subjecting the rest of the body to significant levels of the active agent. The hope is that effective therapy with minimal toxicity will be achieved.

Recently, Stella and Himmelstein (1980, 1982) realistically evaluated the potential of achieving site-specific delivery of drugs by using the prodrug approach. Using a hybrid physiological/classic pharmacokinetic model, they tested various hypotheses which had been proposed to achieve site-specific delivery of drugs via prodrugs. They concluded that at least 3 factors had to be optimised:

1. The prodrug must be readily transported to the site of action and uptake to the site must be rapid, and essentially perfusion rate-limited
2. Once at the site, the prodrug must be selectively cleaved to the active drug relative to its conversion at other sites. Perhaps as important, it must be selectively cleaved relative to cleavage in more highly perfused tissues such as the liver, kidney, etc.
3. The active drug once selectively generated at the site of action must be somewhat retained by the tissue.

Prior to 1980, only the first two points had generally been addressed. For example, selective uptake into tumour cells had generally been unsuccessful via prodrugs because they are relatively poorly perfused tissues compared with other organs (Gray et al., 1953) like the liver, and many of the enzymes such as phosphatases that are elevated in tumours are not accessible to phosphate prodrugs, i.e. the phosphate prodrugs are too polar to enter the tumour cells. The last point (site retention) has not generally been recognised as being important, but is probably the basis for most of the failures, considering that most researchers have tried to selectively deliver currently known active drugs. For these drugs to be active they must be readily accessible to the site of action. Therefore, if they can reach the site of action, they will also readily equilibrate with other tissues. If these drugs, as prodrugs, are selectively delivered to the site of action, chances are that only a momentary burst of drug activity at the site will be seen (Stella and Himmelstein, 1980) before the drug rapidly equilibrates with the rest of the body. Therefore the drugs which are most likely to be selectively delivered to target sites via prodrugs are likely to be agents that are as yet still under development, and for which the prodrug approach to selective delivery will be an integral part of a basic drug design programme.

This is not to say that site-specific delivery is not desirable or attainable with all current drugs. There are some very important recent examples in the literature where the efficacy of a drug has been improved due to selective delivery. Some of the better examples involve the local delivery of drugs. Drugs destined for delivery to the skin, eye or external tissue can be substantially improved if a prodrug is designed which readily penetrates the rate-limiting barrier to the tissue and is rapidly cleaved to the active drug. Site retention here is not quite as important because many of these tissues are not highly perfused such that drug turnover from these tissues is reasonably slow.

4.5.1 Dipivefrin

Locally administered solutions of adrenaline (epinephrine) have long been used for the treatment of glaucoma, although both local ocular and systemically based side effects often occur. The pivalic acid ester prodrug of adrenaline, dipivefrin (dipivaloyladrenaline), is a therapeutically more efficacious agent than adrenaline itself (Anderson et al., 1980; Mandell et al., 1978; McClure, 1975) [fig. 8]. This ester is approximately 100 times more ac-

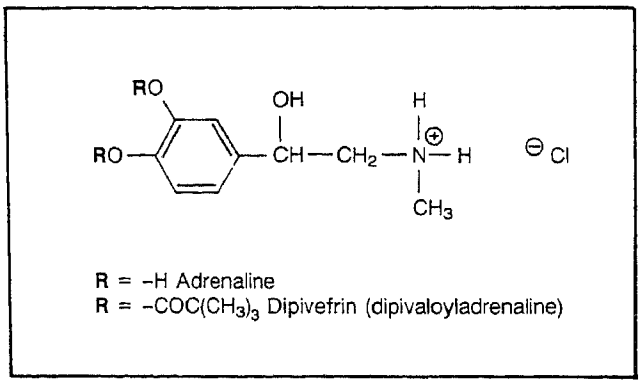


Fig. 8. Structural formulae of adrenaline (epinephrine) and its pivalic acid ester prodrug, dipivefrin (dipivaloyladrenaline).

tive than adrenaline in lowering intraocular pressure due to glaucoma. The greater potency results from more efficient corneal transport, followed by rapid cleavage of the ester in its passage through the corneal tissue releasing adrenaline to the aqueous humour fluid (Anderson et al., 1980). In addition, because lower doses of the ester can be used, untoward cardiac side effects due to adrenaline absorption from the tear duct overflow are diminished and the accumulation of melanin deposits in the eye are not seen.

4.5.2 Pro-2-PAM

Systemic site-specific delivery is probably one of the ultimate goals in drug delivery. This process is infinitely more complex than local site-specific delivery because the drug (or prodrug) must be transported into and via the blood through a variety of complex barriers before reaching the target organ. There have been a number of recent attempts at promoting systemic site specificity via increased permeability of a drug to a particular organ by prodrug modifications. Bodor et al. (1975, 1976) and Shek et al. (1976a,b) were able to increase the brain concentrations of the highly polar quaternary ammonium anticholinesterase inhibitor, 2-PAM (pralidoxime), by administering its dihydro-prodrug, pro-2-PAM. Pro-2-PAM rapidly reverts to 2-PAM by an *in vivo* oxidative mechanism. The success of pro-2-PAM is due to its increased permeability through the blood-brain barrier and to the presence of enzymes in the brain capable of converting pro-2-PAM to 2-PAM. Although brain concentrations of 2-PAM were significantly increased by pro-2-PAM administration relative to 2-PAM itself, the majority of the administered dose of pro-2-PAM was converted to 2-PAM in tissues and organs other than the brain. If the brain was selectively able to convert pro-2-PAM to 2-PAM, true site-selective delivery may have been achievable in this case.

Similar studies for the delivery of other aromatic quaternary ammonium compounds have recently been published (Bodor and Brewster, 1983; Repta et al., 1982).

4.5.3 γ-Glutamyl-Dopamine and γ-Glutamyl-L-Dopa

A number of studies that have attempted to utilise the high levels of γ-glutamyl transpeptidase in the kidney have arrived at some interesting findings. The selective delivery of dopamine, useful in the treatment of shock (due to its vasodilatory action on the kidney), has been achieved by the prodrug γ-glutamyl-dopamine (Kyncl et al., 1979) and γ-glutamyl-L-dopa (Wilk et al., 1978). Here the polar prodrugs were able to reach the highly perfused kidney where selective cleavage by γ-glutamyl transpeptidase released the polar dopamine, resulting in its selective delivery to the kidney.

At present, systemic site-specific delivery by prodrugs is applicable to a small number of currently useful therapeutic agents. However, it is envisaged that this approach will become more successful as it is applied to new chemical entities whose potential activity is determined by their action in an *in vitro* biochemical screen, but whose physicochemical properties are such that delivery to the *in vivo* target site is seen as a problem. Here the statement by Higuchi (personal communication) that 'drugs will have to be designed with delivery components in mind' is most pertinent.

In the next decade the term prodrug may disappear from common usage as the approach will become an integral part of basic drug design and not necessarily as a hindsighted approach to the solution of problems associated with older drugs.

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