Mutual Prodrug Concept: Fundamentals and Applications

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A therapeutically significant drug may have limited utilization in clinical practice because of poor organoleptic properties, poor bioavailability, short duration of action, nonspecificity, incomplete absorption, poor aqueous solubility, high first-pass metabolism or other adverse effects. There is a great emphasis on research to discover methods aimed at improving their therapeutic efficacy by minimizing or eliminating these undesirable properties. Sometimes, an adequate pharmaceutical formulation can overcome these drawbacks, but often the galenic formulation is inoperant and a chemical modification of active molecule is necessary to correct its pharmacokinetic insufficiencies. This chemical formulation process, whose objective is to convert an interesting active molecule into a clinically acceptable drug, often involves the so-called 'Prodrug design.' Mutual prodrug is a type of carrier-linked prodrug, where the carrier used is another biologically active drug instead of some inert molecule. A mutual prodrug consists of two pharmacologically active agents coupled together so that each acts as a promoiety for the other agent and *vice versa*. Mutual prodrug design is really no different from the general drug discovery process, in which a unique substance is observed to have desirable pharmacological effects, and studies of its properties lead to the design of better drugs. It is a very fruitful area of research, and its introduction in human therapy has given successful results in improving the clinical and therapeutic effectiveness of drugs suffering from some undesirable properties that otherwise hinder their clinical usefulness. The present article takes a review of various applications of mutual prodrugs and the developments in this field during the last few decades.

Almost every drug is characterized by various physicochemical and biological properties, some of which are desirable while others are undesirable. There is a great emphasis on research to discover methods aimed at improving their therapeutic efficacy by minimizing or eliminating their undesirable properties. A drug molecule with optimal structural configuration and physicochemical properties for eliciting the desired therapeutic response may not necessarily possess the best molecular framework and properties for its delivery at the target site. Usually a small fraction of administered drug reaches the target area and the remaining fraction also interacts with non-targeted sites, resulting in an inefficient delivery and undesirable side effects[1].

A therapeutically significant drug may have limited utilization in clinical practice because of various shortcomings[2] like poor organoleptic properties (chloramphenicol), poor bioavailability (ampicillin), short duration of action (pilocarpine), nonspecificity (antineoplastic agents), incomplete absorption (epinephrine), poor aqueous solubility (corticosteroids), high first-pass metabolism (propranolol) or other adverse effects. Sometimes, an adequate pharmaceutical formulation can overcome these drawbacks, but often the galenic formulation is inoperant and a chemical modification of active molecule is necessary to correct its pharmacokinetic insufficiencies. This chemical formulation process, whose objective is to convert an interesting active molecule into a clinically acceptable drug, often involves the so-called 'prodrug design.'

Initially, the term prodrug was introduced by Albert to describe any compound that undergoes biotransformation prior to exhibiting its pharmacological effects[3]. Harper referred to this process as drug latentiation, that is, chemical modification of a biologically active compound to form a new compound that, upon *in vivo* enzymatic attack, will liberate the parent compound[4].

Classification of prodrugs:

Wermuth, after surveying the literature, has classified the prodrugs into two broad categories: the carrier-linked

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prodrugs and bioprecusors[5]. The carrier-linked prodrug consists of the attachment of a carrier group to the active drug to alter its physicochemical properties and then subsequent enzymatic or nonenzymatic mechanism to release the active drug moiety. Thus, the carrier-linked prodrugs[6] are drugs with major drawbacks that are linked through covalent linkage with specialised nontoxic protective groups or carriers or promoieties in a transient manner to alter or eliminate undesirable properties in the parent molecule (fig. 1)[7]. Depending upon the nature of carrier used, the carrier-linked prodrug may further be classified into:

1. Double prodrugs, pro-prodrugs or cascade-latentiated prodrugs, where a prodrug is further derivatized in a fashion such that only enzymatic conversion to prodrug is possible before the latter can cleave to release the active drug.
2. Macromolecular prodrugs, where macromolecules like polysaccharides, dextrans, cyclodextrins, proteins, peptides, and polymers are used as carriers.
3. Site-specific prodrugs where a carrier acts as a transporter of the active drug to a specific targeted site.
4. Mutual prodrug, where the carrier used is another biologically active drug instead of some inert molecule (fig. 1). A mutual prodrug consists of two pharmacologically active agents coupled together so that each acts as a promoiety for the other agent and *vice versa*. The carrier selected may have the same biological action as that of the parent drug and thus might give synergistic action, or the carrier may have some additional biological action that is lacking in the parent drug, thus ensuring some additional benefit. The carrier may also be a drug that might help to target the parent drug to a specific site or organ or cells or may improve site specificity of a drug. The carrier drug may be used to overcome some side effects of the parent drugs as well.

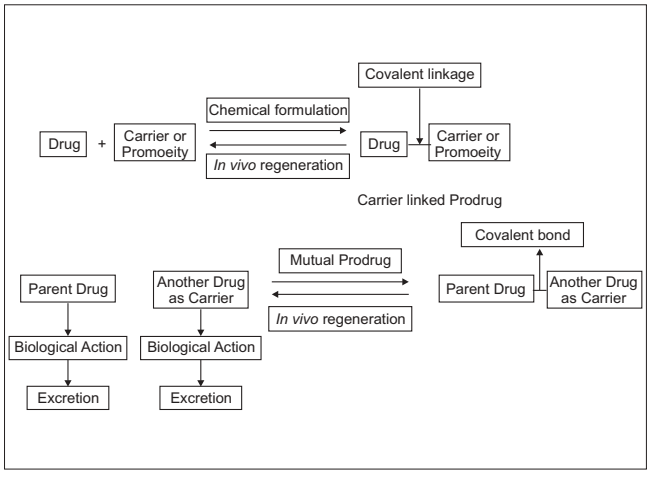


Fig. 1: Schematic representation of carrier-linked prodrug and mutual prodrug concept.

IDEAL CRITERIA FOR CARRIER–LINKED PRODRUGS

A well-designed carrier-linked prodrug should satisfy certain criteria[8]. The linkage between the drug and the carrier should usually be a covalent bond. As a rule, the prodrug itself should be inactive or less active than the parent drug. The linkage should be bioreversible. The prodrug and the carrier released after *in vivo* enzymatic or non-enzymatic attack should be nontoxic. The generation of active form must take place with rapid kinetics to ensure effective drug levels at the site of action.

The bioavailability of carrier-linked prodrug is modulated by using a transient moiety. The lipophilicity is generally the subject of profound alteration of parent molecule. Bioactivation process is exclusively hydrolytic and sometimes a redox system.

Ideal criteria for carriers:

An ideal carrier should be without intrinsic toxicity. It should be non-immunogenic and non-antigenic and should not accumulate in the body. It should possess a suitable number of functional groups for drug attachment and adequate loading capacity. It should be stable to chemical manipulation and autoclaving. It should be easy to characterize and should mask the liganded drug's activity until release of active agent at the desired site of action. In mutual prodrug approach, the carrier should have some biological activity of its own.

APPLICATIONS OF MUTUAL PRODRUG APPROACH

Reduction of gastrointestinal (GI) side effects and ulcerogenicity of nonsteroidal antiinflammatory drugs (NSAIDs):

Despite the intensive research that has been aimed at the development of NSAIDs, their clinical usefulness is still restricted by their GI side effects like gastric irritation, ulceration, bleeding, perforation and in some cases may develop into life threatening conditions[9]. GI lesions produced by NSAIDs are generally attributed to either direct and/or indirect mechanisms. The direct contact

effects result usually from local irritation produced by free acidic group of NSAIDs and local inhibition of prostaglandin synthesis in GIT. Indirect mechanism is due to generalized systemic action occurring after absorption and is demonstrated on intravenous dosing[10]. This problem has been solved by derivatization of carboxylic function of NSAIDs into ester and amide mutual prodrugs using amino acids like L-tryptophan, L-histidine, L-glycine as carriers that have marked antiinflammatory activity of their own[11]. Other analgesic, antiinflammatory drugs like paracetamol and salicylamide have also been used as carriers to synthesize mutual prodrugs of NSAIDs, the examples of which are cited below. Benorylate (1) is a mutual prodrug of aspirin and paracetamol, linked through ester linkage, which claims to have decreased gastric irritancy with synergistic analgesic action[12]. Glycine methyl ester conjugate of ketoprofen (2)[13], histidine methyl ester conjugate of diclofenac (3)[14], and various conjugates of flurbiprofen with amino acid like L-tryptophan (4a), L-histidine (4b), phenylalanine (4c) and alanine (4d) as mutual prodrugs[15] were reported to have less ulcerogenicity with better antiinflammatory/analgesic action than their parent drugs. Mutual prodrugs of ibuprofen with paracetamol (5) and salicylamide (6) have been reported with better lipophilicity and reduced gastric irritancy than the parent drug[16]. Naproxen-propyphenazone mutual prodrugs (7) were synthesised with an aim to improve therapeutic index through prevention of GI irritation and bleeding. Esterification of naproxen with different alkyl esters and thioesters led to prodrugs with retained antiinflammatory activity but exhibited greatly reduced GI erosive properties and analgesic potency, but esterification with ethyl piperazine showed that analgesic activity was preserved whereas antiinflammatory activity was generally reduced. Propyphenazone, a nonacidic pyrazole with good analgesic and antipyretic activity, was coupled with naproxen to achieve many advantages related to the synergistic analgesic effect with reduced gastric irritation. Propyphenazone is converted to its active metabolite, 3-hydroxy methyl propyphenazone, which actually gives the analgesic effect. Coupling of these two compounds as a hybrid drug or through a spacer as a mutual prodrug resulted in potent analgesic/antiinflammatory compound with reduced adverse local effects related to NSAID[17].

A more recent strategy for devising a gastric-sparing NSAID involves chemically coupling a nitric oxide (NO) releasing moiety to the parent NSAID. Studies have shown that the use of NSAIDs with NO-releasing properties has an improved GI safety. Along with prostaglandins, NO plays an important cytoprotective role in GI homeostasis and defence by helping to maintain mucosal blood flow, optimizing mucus gel secretion and inhibiting activation of pro-inflammatory cells[18-22]. Thus NO may counteract the detrimental effects of COX inhibition. Synthesis of NO-releasing organic nitrate esters of several NSAIDs like aspirin, diclofenac, naproxen, ketoprofen, flurbiprofen has been reported with comparable antiinflammatory activity and reduced GI toxicity as compared to their parent counterparts. In contrast to COX-2 inhibitors and standard NSAIDs, NO-releasing NSAID mutual prodrugs and NO donors have shown existing ulcer-healing properties in rats. NO-releasing diclofenac ester prodrugs with tertiary nitrosothiols as NO donors (8)[23], NO-releasing furoxan esters of ibuprofen (9) and NO-releasing furazan esters of naproxen (10) have been reported with reduced gastrotoxicity[24]. NO-aspirin and NO-flurbiprofen are in clinical trials at present[25]. 4-Biphenyl acetic acid (4-BPA) is the active metabolite of fenbufen and is twice active as the parent drug. 4-BPA suffers severe GI side effects on oral administration and hence is not used for therapeutic purpose. Mutual prodrugs of 4-BPA (11) have been synthesized using naturally occurring phenolic antioxidants like thymol, guaiacol, eugenol, and other alcoholic compounds[26]. The antioxidant activity of phytophenols is likely to enhance the effectiveness of 4-BPA by lowering its ulcerogenic potential. Probenecid and diclofenac were converted to hydrazide derivatives via their methyl ester by reacting with hydrazine hydrate. The hydrazide derivatives were further reacted with biphenyl acetic acid. The hydrazide derivative of naproxen was reacted with p-chlorobenzoic acid to synthesize their oxadiazole analogue in order to produce mutual prodrug with lower ulcerogenicity and synergistic action[27]. Mutual prodrug conjugates of flurbiprofen have been reported with histamine H_2 antagonist in order to reduce gastric damage by NSAID. A new term has been introduced for mutual prodrug called chimera drug[28].

Mutual prodrug of NSAIDs with additional antiarthritic activity:

Mutual prodrugs of ketoprofen (12a)[29], ibuprofen (12b)[30], diclofenac (12c)[30] and flurbiprofen (12d)[31] with an antiarthritic nutraceutical D-glucosamine have been reported with reduced gastrointestinal ulcerogenicity, better analgesic/antiinflammatory effects and additional antiarthritic activity. Glucosamine is used as an antiarthritic drug and nutritional supplement in conditions like joint ache, stiffness, severely restricted movements and serious pain[32-33]. It acts as an essential substrate for the

biosynthesis of glucosaminoglycans and the hyaluronic acid backbone needed for formation of proteoglycans found in the structural matrix of joints[34]. NSAIDs are used for the symptomatic treatment of inflammation associated with arthritis but are unable to remove the underlying cause of the disease. Their prolonged use results in GI side effects. When tested in Fruend's adjuvant-induced arthritis assay, these mutual prodrugs have shown antiarthritic activity, which was lacking in the parent drugs with comparable antiinflammatory activity and lowered ulcerogenicity[29-31].

Site-specific drug delivery:

A drug, after its absorption into systemic circulation, gets distributed to target site as well as non-targeted tissues. The distribution of drug to non-targeted tissues may lead to undesirable toxic effects in those tissues and insufficient concentration in the target site to evoke any therapeutic response. If the target site has a longer distribution time, the drug may get eliminated without reaching such a site; and even if the drug reaches the targeted area in sufficient concentrations, it may have such a low penetration power that it may not penetrate the target cells at all. Targeting the drug to its site of action through prodrug concept has been utilized to overcome these problems. While designing the prodrug, utilization of the enzymes that are specifically present in that organ or tissue or specific constant pH of that area which is different from body pH should be made so that the prodrug releases the drug only in the targeted organ. Some of the important examples of the site-specific drug delivery through mutual prodrug concept are discussed below.

Sulfasalazine (fig. 2) is the classic example of colon-specific mutual prodrug of 5-aminosalicylic acid (5-ASA) and sulfapyridine, used in the treatment of ulcerative colitis[35]. 5-ASA and sulfapyridine are linked together by azo linkage, which is reduced only in the colon by azo reductases secreted by colonic microflora. This releases the active agent 5-ASA in the colon, having antiinflammatory effect on the colon along with sulfapyridine. The advantage of this approach is that the cleavage of azo linkage and generation of 5-ASA prior to the absorption prevents its systemic absorption and helps it to concentrate at the active site. Sulfapyridine was selected as a carrier in this mutual prodrug design by taking into account its antibacterial activity, but even though sulfapyridine proved to be a good carrier for targeting 5-ASA to colon, it gave rise to many side effects resulting from its systemic toxicity. Therefore, even if according to definition, sulfasalazine is a mutual prodrug, due to disadvantages of its carrier, it cannot be referred to as a true mutual prodrug. This led to the development of interesting mutual prodrug of 5-ASA called olsalazine (fig. 2), which is actually a diamer of 5-ASA, where 5-ASA is linked through azo linkage to one more molecule of 5-ASA[36]. When it reaches the large intestine, it is cleaved, releasing two molecules of 5-ASA for every molecule of olsalazine administered. This design overcomes the drawbacks of sulfasalazine, targets 5-ASA to colon, and fulfils all requirements of mutual prodrug too. Improvement in the bioavailability of 5-ASA is also achieved by this design. Clinical trials have been encouraging, although watery diarrhoea has emerged as a new and troublesome side effect, affecting 15% of patients. It appears to be related to a combination of GIT transit and stimulation of small intestinal secretion. Estramustine (fig. 3) is an antineoplastic mutual prodrug used in the treatment of prostate cancer[37]. It is composed

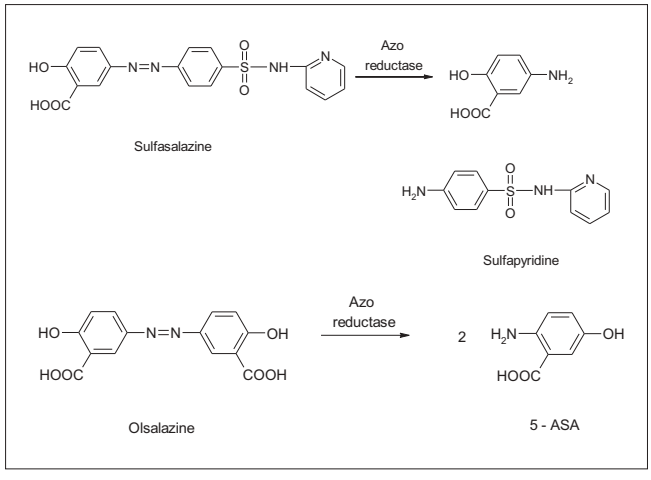


Fig. 2: Release of a) 5-ASA and sulfapyridine from sulfasalazine b) two molecules of 5-ASA from olsalazine.

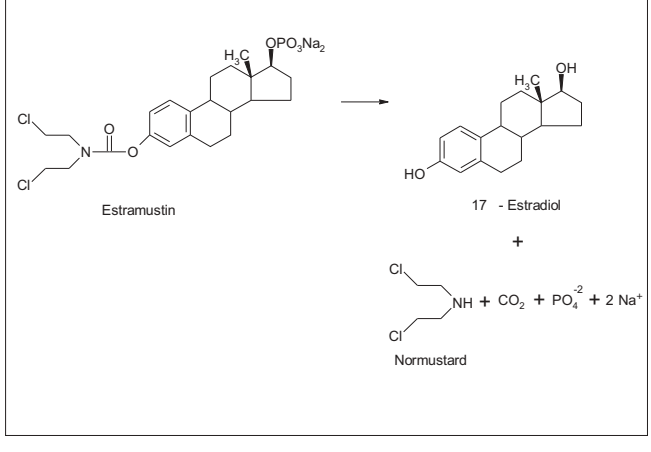


Fig. 3: Release of 17 α-estradiol and normustard from estramustine.

of a phosphorylated steroid, 17 α-estradiol linked to a normustard [HN ($CH_2CH_2Cl)_2$] through a carbamate linkage. The steroid portion of the molecule helps to concentrate the drug in prostate gland, where hydrolysis occurs to give normustard and CO_2. The normustard then acts as an alkylating agent and exerts a cytotoxic effect. The 17 α-estradiol also has antiandrogenic effect on the prostate and thereby slows the growth of cancer cell. Since both the steroid and the normustard possess activity, estramustine is termed as a mutual prodrug. Phosphorylation of estradiol can be utilized to increase the water solubility, which also constitutes a prodrug modification. Both types of esters, viz., phosphates or carbamates, are hydrolyzed by chemical or enzymatic means. When histone deacetylase inhibitor like sodium butyrate is combined with retinoic acid, some success in overcoming retinoic acid (RA) resistance has been reported for acute promyelocytic leukaemia in cell lines and clinic. This therapy counteracts effects of nuclear co-repressors, causing a DNA conformation that facilitates RA-induced gene transcription and cell differentiation. In an effort to improve delivery of each drug, a mutual prodrug of RA and butyric acid (13) called retinoyloxymethyl butyrate (RN_1) has been synthesised. RN_1 targets both drugs to the same cell or cellular compartments to achieve differentiation at lower concentrations than using RA and butyric acid alone. RN_1 overcomes retinoic acid resistance in leukaemias by induction of apoptosis, so it may be more widely active in haematologic malignancies than RA alone[38].

Nitrous oxide (NO) plays a critical role in a variety of bioregulatory processes, including normal physiological control of blood pressure, neurotransmission, and microphage-induced cytostatics and cytotoxicity[39]. NO can inhibit metastasis, enhance cancer cell apoptosis, and assist macrophages to kill tumour cells[40]. Diazenium diolates (NONOates) are compounds containing the [N (O) NO]$^-$ structural unit. It is known to be an excellent source for controlled release of NO, both *in vitro* and *in vivo*[41]. 5-Fluorouracil (5-FU) is one antitumour agent most frequently used for treating solid tumours like breast, colorectal, and gastric cancers. It is poorly tumour-selective, so its therapy causes high incidences of toxicity in the bone marrow, GIT, CNS and skin, which has promoted the efforts in the development of derivatives aiming at reducing the adverse effects of 5-FU. Therefore, search for novel prodrug of 5-FU possessing a broad spectrum of antitumour activity and less toxicity has led to the design of mutual prodrug of 5-FU (fig. 4) and diazenium diolate with methylene or acyloxymethylene as spacers. The prodrug has been synthesised with an aim to improve tumour selectivity, efficiency and safety[25].

One more way to direct 5-ASA to colon using mutual prodrug concept has been reported, where 5-ASA is conjugated with ursodeoxycholic acid (UDCA)[42]. UDCA is the bacterial product of chenodeoxycholic acid and has application in gallstone dissolution and treatment of cholestatic liver diseases. Recent studies have also shown that UDCA may be beneficial in colonic polyp reduction. It has been shown that UDCA-5ASA (14) is poorly absorbed from intestine and is targeted to colon, where it is partially hydrolyzed to UDCA and 5-ASA. While a portion of UDCA-5-ASA escapes bacterial cleavage, part of the UDCA is absorbed from the colon, enters enterohepatic circulation, is converted into taurine conjugate by hepatic enzymes and is secreted into the bile. It is postulated that both 5-ASA and UDCA may exhibit their antiinflammatory and cytoprotective effects in colon as well as liver. UDCA has also shown to inhibit polyp formation in experimental rats. As patients with ulcerative colitis are at a greater risk of primary sclerosing cholangitis (PSC) and as UDCA has been reported to be beneficial in PSC, the enterohepatic circulation of UDCA generated in colon may be cytoprotective to the hepatocyte in these patients.

Synergistic action with or without some additional benefit:

Chlorzoxazone [5-chloro-2 (3H)-benzoxazolone] is a centrally active muscle relaxant, while acetaminophen (N-acetyl-p-aminophenol) exhibits analgesic properties. Owing to their synergistic effects, these two drugs can be prescribed together[43,44]. Using this rationale, a mutual prodrug of chlorzoxazone and acetaminophen (fig. 5) has

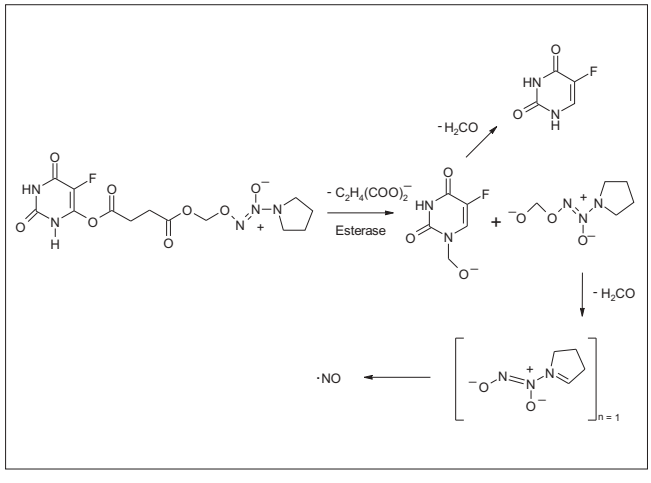


Fig. 4: Mutual prodrug of 5-FU and diazenium diolate.

been designed, and its synthesis and kinetics have been reported[45].

Another example of a mutual prodrug with synergistic action is sultamicillin (15). In the design of sultamicillin, the irreversible β-lactamase inhibitor sulbactam has been combined chemically via ester linkage with ampicillin. This design is based on the rationale that as sulbactam, a β-lactamase inhibitor with very limited antibacterial activity in a physical mixture with ampicillin, clearly enhances the activity of the latter against certain β-lactamase-producing bacteria, both *in vitro* and *in vivo,* the same phenomenon might hold true when these two drugs are linked chemically[46]. Upon oral administration, sultamicillin is completely hydrolyzed to equimolar proportions of sulbactam and ampicillin, thereby acting as an efficient mutual prodrug[47]. The mutual prodrug effect produced by sultamicillin results from its having a more efficient oral absorption than the single agent does. Peak serum concentrations of ampicillin are achieved that are approximately 3.5-fold those obtained with an equivalent amount of oral ampicillin. Equimolar concentrations of sulbactam are also provided with both ampicillin and sulbactum, being widely distributed among various body fluids and tissues. The pharmacokinetic parameters of the two components are similar, both being eliminated primarily by renal excretion. Although the elimination half-lives of ampicillin and sulbactam are each approximately 1 h, the high serum concentration achieved, coupled with their synergistic activity permit twice-daily dosing. One more important advantage presented by sultamicillin is that even though most β-lactamase-resistant antimicrobials must be given parenterally, sultamicillin is given by mouth. It has been found to be effective against skeletal infections in children, urinary infections in geriatric patients and uncomplicated gonorrhoea[48-51].

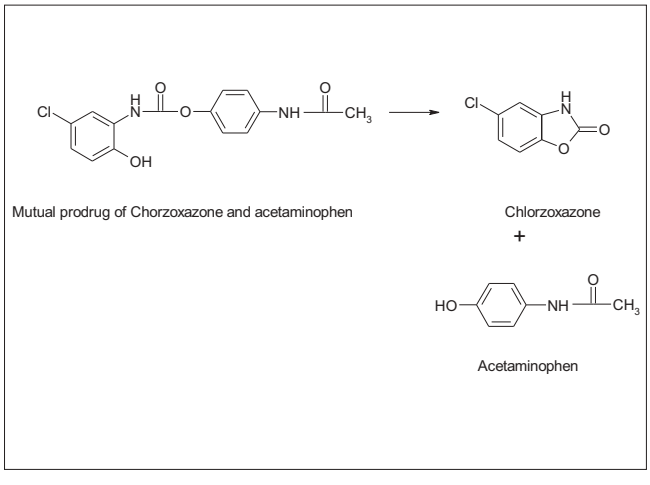
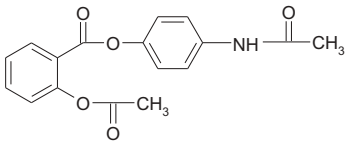


Fig. 5: Release of chlorzoxazone and acetaminophen from its prodrug.

A U.S. Patent of mutual prodrug of amlodipine and atorvastatin (16) has been issued on May 18, 2004 [U.S. Patent No. 6,737,430] for the treatment of atherosclerosis, angina pectoris, combined hypertension, hyperlipidaemia and management of cardiac risk[52]. Amlodipine is 1,4-dihydropyridine derivative of nifedipine. It is a second-generation calcium channel blocker, which has greater selectivity for vascular smooth muscle than myocardial tissue when compared to nifedipine. It is used in the treatment of chronic stable angina and management of mild to moderate essential hypertension, but it lacks the antihyperlipidaemic effect. On the other hand, atorvastatin is a selective, competitive inhibitor of HMG-CoA reductase, an enzyme that catalyzes conversion of HMG-CoA to mevalonate, an early rate-limiting step in cholesterol biosynthesis. Its mechanism of LDL-lowering effect involves both reduction of VLDL concentration and induction of LDL receptor, leading to reduction in production of LDL or increased catabolism of LDL. This lipid-lowering effect of atorvastatin indirectly helps to make the treatment and management of atherosclerosis, angina pectoris, hypertension and cardiac risk much easier than is possible independently by either amlodipine or atorvastatin. These two drugs are linked together by amide bond. Hydrolytic cleavage of this bond *in vivo*, releases the free drugs in the body. Ursodeoxycholic acid (UDCA) has been shown to dissolve gallstones by making bile unsaturated with cholesterol. N-acetylcysteine (NAC) and 2-mercaptopropionylglycine (MPG), on the other hand, lower the viscosity of bronchial and biliary mucus by reducing disulfide bonds in protein and dissolve macromolecular complex of mucine and bilirubine in the gallstone matrix. Using this rationale, mutual prodrugs of UDCA with NAC and MGP[53] have been synthesized, which may potentially increase the efficacy of gallstone dissolution by combining both the mechanisms of action. Unsymmetrical polar disulfide prodrug of paclitaxel with captopril[54] has been designed and synthesized as reductively activated mutual prodrug. It has been tested on L2987 lung carcinoma cells, and *in vivo* evaluation in mice has exhibited significant regressions and cures.

A mutual prodrug approach has been applied for the synthesis of dual-acting thromboxane receptor antagonist – thromboxane synthatase inhibitor compounds in which TXA_2 antagonist and inhibitory 1,3-dioxanes with hexenoic acid side chains are linked by diester and



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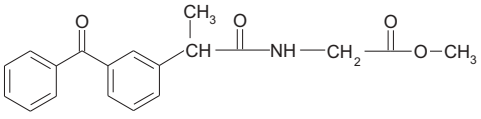

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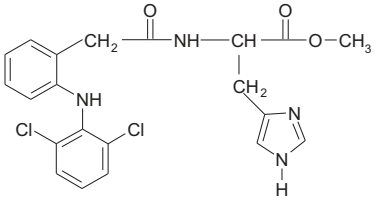

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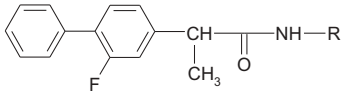

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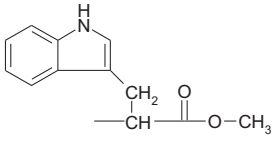

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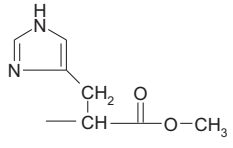

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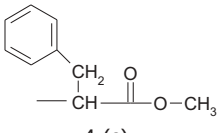

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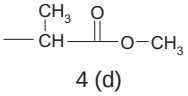

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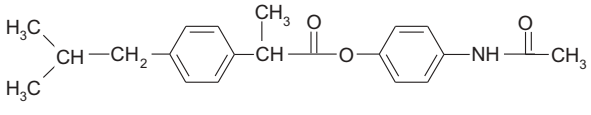

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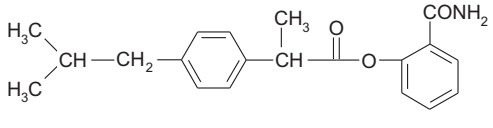

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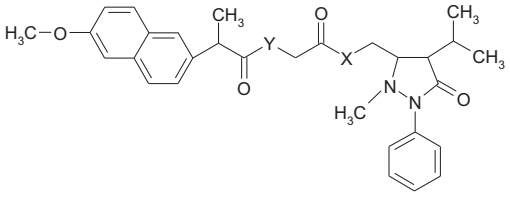
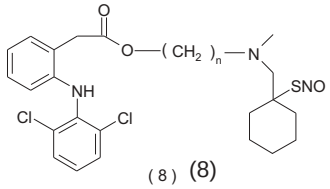
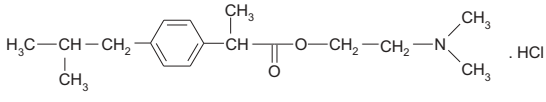


X = NH, Y = O

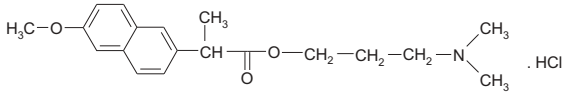
(7)



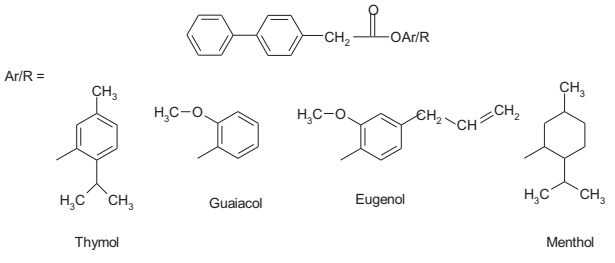
(8)



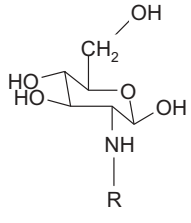
(9)



(10)

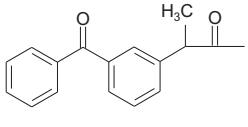


(11)

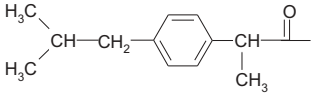


(12)

R =



(12a)



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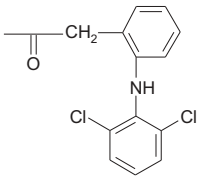

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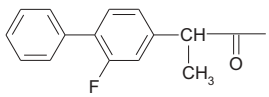

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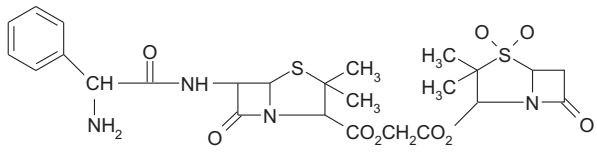

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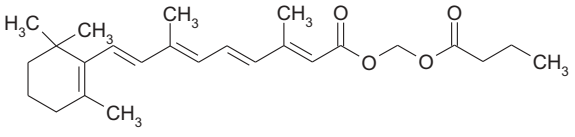

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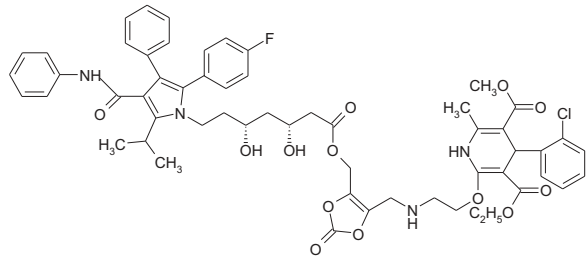

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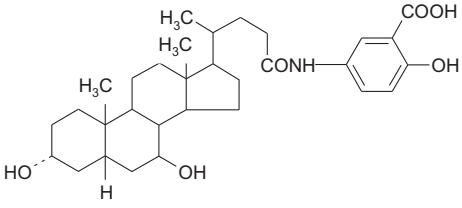

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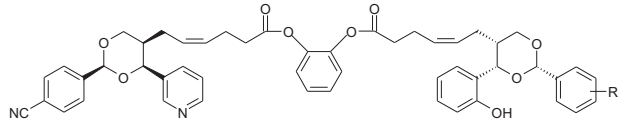

(17)

diamide groups[55]. Both TXA_2 receptor antagonist activity and TXA_2 synthatase inhibition were observed for the enantiomer (17) in *ex vivo* tests following oral dosing to dogs at 5 mg/kg. Synthesis of mutual prodrugs, viz., 3-acyloxymethoxycarbonyl-1-aryl-3-methyltriazenes associating the antitumour monoethyltriazenes with antiinflammatory NSAIDs as well as with the anticancer agent butyric acid has been reported[56].

LIMITATIONS AND DRAWBACKS

Even if mutual prodrug design has proven highly beneficial in overcoming various undesirable properties of drugs, it can also give rise to a large number of newer difficulties, especially in the assessment of pharmacological, pharmacokinetic, toxicological, and clinical properties.

At the pharmacological level, these compounds cannot be submitted to preliminary *in vitro* screening tests like binding studies, reuptake of neurotransmitter and enzyme inhibition measurement because bioactivation to their active species is necessary. At the toxicological level, even though prodrugs are derived from well-known active principles, they have to be regarded as new entities. In a review by Gorrod[57], he has cited certain toxicity mechanisms like formation of toxic metabolite of total prodrug which is not produced by the parent drug, consumption of vital constituent during prodrug activation process, generation of a toxic derivative from a supposedly inert transport moiety, release of a pharmacokinetic modifier which may cause enzyme induction or alter drug excretion. The pharmacokinetic studies may lead to numerous misinterpretations. When a prodrug and parent molecule are being compared, one must take into account the differences in their respective time courses of action. The maximum activity may appear later for prodrug than for parent compound, so area under the curve should be compared as it presents a better criterion for comparison. At clinical stage, the predictive value of animal experiments is also questionable. The active doses of two prodrugs of the same parent drug may appear to be same in rats but may be quite different in clinical investigations.

CONCLUSIONS

The introduction of mutual prodrug in human therapy has given successful results in overcoming undesirable properties like absorption, nonspecificity, poor bioavailability and GIT toxicity. Mutual prodrug design is really no different from the general drug discovery

process, in which a unique substance is observed to have desirable pharmacological effects, and studies of its properties lead to the design of better drugs. The review of application of mutual prodrug design suggests that the gain in therapeutic benefit from such an approach may either be modest or marked. For well-accepted and useful drugs with minor undesirable properties, which can be ameliorated through prodrug design, the gain is usually modest. On the other hand, for the active compounds that suffer from severe limitations, like lack of site specificity, poor bioavailability or lack of particular activity, mutual prodrug design leads to a marked therapeutic gain. Thus, mutual prodrug approach offers a very fruitful area of research and an efficient tool for improving the clinical and therapeutic effectiveness of a drug that is suffering from some undesirable properties hindering its clinical usefulness otherwise.

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