World Journal of
Biological and Pharmaceutical Research

Journal homepage: https://zealjournals.com/wjbpr/

ISSN: 2799-0338 (Online)

(REVIEW ARTICLE)

Check for updates

'Mutual Prodrug' and approach to increase the effectiveness of Non-Steroidal Anti-inflammatory Drugs

Manish S. Junagade * and Anju Goyal

Faculty of Pharmacy, Bhupal Noble's University, Udaipur (Rajasthan) 313001, India.

World Journal of Biological and Pharmaceutical Research, 2021, 01(01), 035–045

Publication history: Received on 27 December 2020; revised on 20 May 2021; accepted on 24 May 2021

Article DOI: https://doi.org/10.53346/wjbpr.2021.1.1.0011

Abstract

A clinically useful drug may have limitations in practice because of undesirable side effects, poor solubility, and poor bioavailability, short duration of action, first-pass effect, poor absorption & adverse effects. There are increased efforts in research to increase the therapeutic efficacy of drugs by eliminating or minimizing the undesirable properties of drug molecules. Some of the problems can be solved using a formulation development approach but in some cases, chemical modification in the molecule is necessary to correct the pharmacokinetic parameters. One of the approaches to convert the existing molecule to a more efficient molecule is prodrug design. Mutual Prodrug is the molecule in which an active drug molecule is attached to a carrier molecule having pharmacological activity. So a mutual prodrug consists of two pharmacologically active molecules connected by a bio labile linkage. Both molecules in this act as a pro moiety of each other. The design of mutual prodrug is very fruitful in the area of research & has given successful results in increasing the clinical & therapeutic effectiveness of the drugs. The present article takes a review of various applications of mutual prodrugs & development in this field in the last few decades.

Keywords: NSAIDs; Side effects; Prodrug; Mutual prodrug

1. Introduction

A mutual prodrug is a form of the prodrug in which two pharmacologically active agents are attached in such a way that each drug acts as a pro moiety/carrier for each other and vice versa. The association may be "synergistic" if the carrier shows the same biological action as that of the parent drug or may provide "additional" benefit if it shows new pharmacological action which is lacking in the parent drug. [2]

A drug molecule is characterized by several properties. Some are desirable while some are undesirable. There are increased efforts in research to increase the therapeutic efficacy of drugs by eliminating or minimizing the undesirable properties of drug molecules. A drug molecule may not possess the best properties for 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 & undesirable side effects. A drug may have limited utilization because of various shortcomings like poor solubility (chloramphenicol), poor bioavailability (ampicillin), short duration of action pilocarpine, nonspecific action (anticancer drugs), incomplete absorption (epinephrine), and first-pass effect (propranolol). Some of the problems can be solved using a formulation development approach but in some cases, chemical modification in the molecule is necessary to correct the pharmacokinetic parameters. One of the approaches to convert the existing molecule to a more efficient molecule is prodrug design. Mutual Prodrug is the molecule in which an active drug molecule is attached to a carrier molecule having pharmacological activity. So a mutual prodrug consists of two pharmacologically active molecules connected by a bio labile linkage. Both molecules in this act as a pro-moiety

* Corresponding author: Mr. Manish S. Junagade
Faculty of Pharmacy, Bhupal Noble's University, Udaipur (Rajasthan) 313001.

of each other. The design of mutual prodrug is very fruitful in the area of research & has given successful results in increasing the clinical & therapeutic effectiveness of the drugs. [3].

2. Classification of Prodrugs

Wermuth, after surveying the literature, has classified the prodrugs as carrier-linked prodrugs & Bio precursors. Carrier linked prodrugs consist of a carrier moiety attached to the drug through a metabolically labile linkage. This carrier moiety imparts some physicochemical properties to the resulting molecule based on its structure & properties. Carrier linked prodrugs are further classified into 4 types.

- Double prodrug: Here prodrug is further converted to another molecule that can be easily converted to prodrug.
- Macromolecular prodrug: Here carrier moiety is a large molecular weight molecule like peptides, protein, polysaccharides, etc.
- Site-specific prodrugs: In this type promoiety acts as a carrier to a specific site.
- Mutual prodrugs: Here carrier moiety is not inert but is having some useful activity that is supportive to the activity of drug molecule.

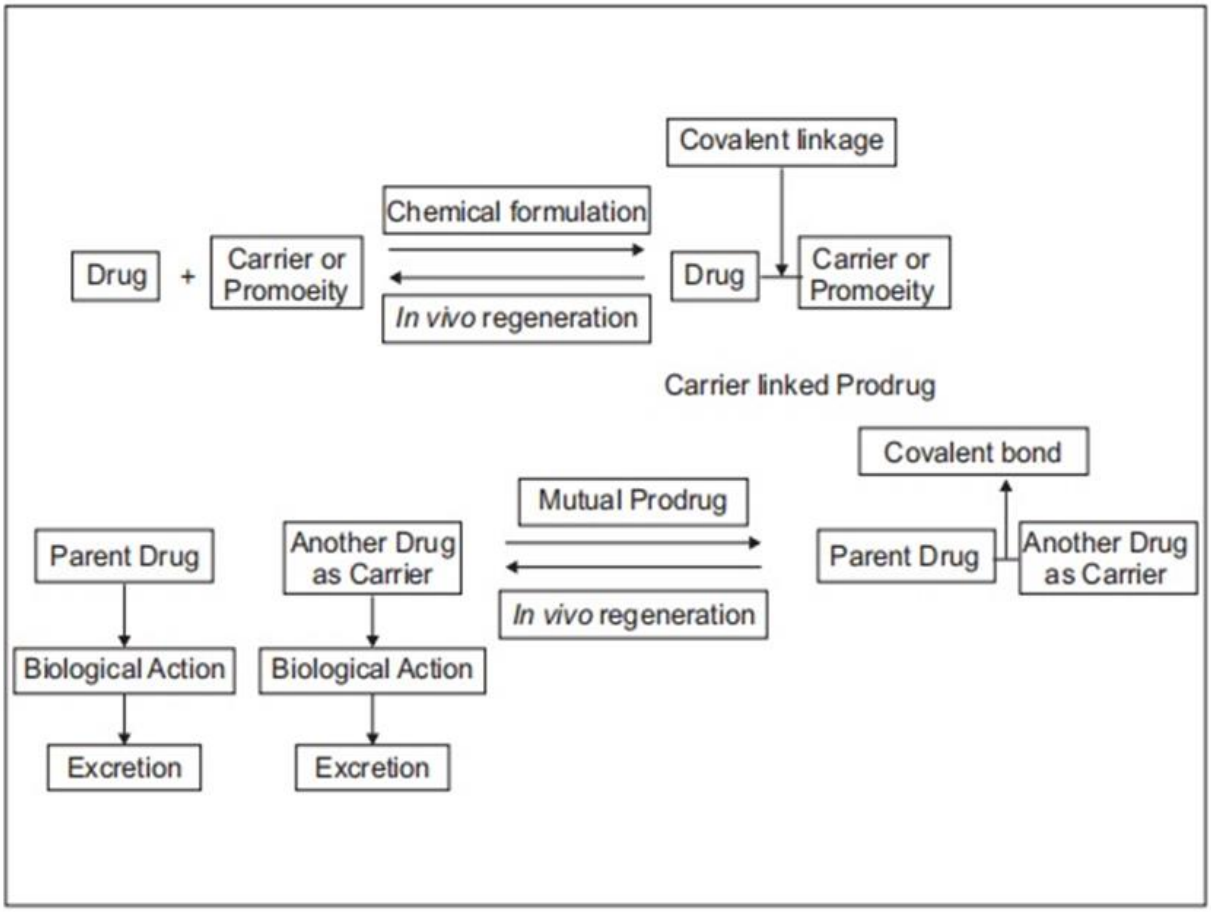


Figure 1 Schematic representation of carrier-linked prodrug and mutual prodrug concept

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 bio reversible.
- The prodrug and the carrier released after *in vivo* enzymatic or non-enzymatic attack should be nontoxic.
- The generation of the 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 the parent molecule. The bio activation process is exclusively hydrolytic and sometimes a redox system.

2.1. 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 activity until the release of the active agent at the desired site of action.

In a mutual prodrug approach, the carrier should have some biological activity of its own.

2.2. Objectives behind designing of mutual prodrugs

- To bring both active drugs to their respective active sites.
- To provide the desired pharmacological effects while minimizing adverse metabolic and/or toxicological events.
- To improve the clinical and therapeutic effectiveness of those drugs which suffer from some undesirable properties that otherwise hinder their clinical usefulness
- To avoid the practice of clinically co-administering two drugs to enhance pharmacological activity or prevent clinical side effects. Simultaneous administration does not guarantee equivalent absorption or transportation to the site of action. So, the mutual prodrug concept is useful when two synergistic drugs need to be administered at the same site at the same time. Mutual prodrugs are synthesized toward a pharmacological objective of improving each drug's efficacy, optimizing delivery, and lowering toxicities.[2]

2.3. Selection criteria

For a Mutual Prodrug synthesis includes some important factors such as therapeutic combinations of candidate drugs and probable linkage between drugs that may form the basis of selection criteria for mutual prodrug synthesis. The significant parameters which are to be considered before the synthesis of mutual prodrug are summarized below [4];

- The candidate drugs selected for mutual prodrug synthesis can be from one therapeutic category or different therapeutic categories. Similarly, the constituent drugs of a mutual prodrug can act on the same biological target with a similar mechanism of action or act on different biological targets with different mechanisms of action.
- The candidates for making mutual prodrugs can be the pairs of drugs that are currently used in combination therapy (including those combination studies at the investigational stage) in various therapeutic areas provided each of those drugs possesses the requisite functional group(s). There are several therapeutic areas where such combination therapy is applied routinely and successfully.
- The linkage between the first and second components should be cleavable. For example, the linkage may be hydrolysable and/or maybe enzymatically cleavable. Preferably, the linkage should be cleavable under physiological conditions, such as those present in a mammalian body, particularly a human body.[2]

2.4. Mechanism of activation

Like a prodrug, a mutual prodrug is converted into the component active drugs within the body through enzymatic and/or non-enzymatic reactions [4].

2.4.1. In vivo metabolic activations of bio precursor mutual prodrugs:

Oxidative Activation

- N- and O-Dealkylation
- Oxidative Deamination
- Oxidation
- Epoxidation

Reductive Activation

- Azo- Reduction
- Sulfoxide Reduction
- Disulfide Reduction
- Bioreductive Alkylation
- Nitro Reduction

Nucleotide Activation

- Phosphorylation Activation
- Decarboxylation Activation

2.4.2. Intramolecular activation

Active Drug as the cyclic product of intramolecular activation is one of the important approaches proposed to explain the activation of some mutual prodrugs. This approach found application in explaining the release of the parent drugs from carbamate mutual prodrugs in aqueous buffer (pH 6-11) and plasma (pH 7.4) through intramolecular reactions due to a hydroxyl nucleophile [2].

2.5. Methodologies used for Mutual prodrug Synthesis

Synthesis of Mutual prodrug is a concept of designing a drug through the conjunction of two different pharmacophores having similar or different pharmacological activities [4].

Before synthesizing mutual prodrugs, the following queries arise regarding the linkage between two pharmacologically active drugs:

- What types of groups are the easiest to link to a carrier drug?
- What types of groups are the easiest to cleave from a carrier drug?

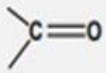
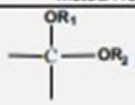
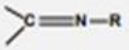
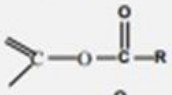
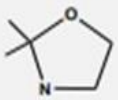
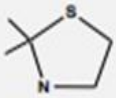
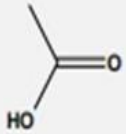
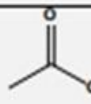
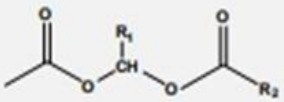
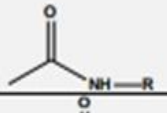
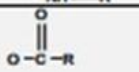
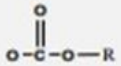
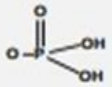
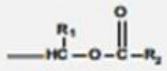
These are suitably answered by the study of the nature of functional groups forming a suitable linkage or bond between two drugs which get easily hydrolyzed by suitable enzymes.

Mutual Prodrug forms of various functional groups are shown in table 1.

There are so many methodologies followed to synthesize mutual prodrug depending upon the functional group attached to the parent drug or carrier drug. Among them some are given below:

- Esterification
- Amidation
- Using the spacer technique
- Azo linkage for example Sulfasalazine
- Enzymatic Regioselective methodology
- Elaborate protection/deprotection and separation strategies
- Multistep synthesis

Table 1 Mutual Prodrug Forms of Various functional groups

Functional Group	Mutual Prodrug Form
	 Ketals  Imines  Enol esters  Oxazolidines  Thiazolidines
	 Ester  α-acycloxyalkyl ester  Amides
	 Esters  Carbonate ester  Phosphate esters Ethers  α- acyloxyalkyl ethers

—SH	Thioester α- acyloxyalkyl ethers Disulphides
—NH_2	Amides Carbamates Imines Enamines N-Mannich bases N-acyloxy alkoxy carbonyl derivatives
>N	N-acyoxyalkyl derivatives
R_1—C(=O)—O—R_2	N-sulfonyl imidates
—SO_2NH_2	N-sulfonyl imidates
NH-Acidic group	N-mannich bases
Hetrocydic amine	N-acyloxyalkyl derivatives

3. Applications of Mutual pro drugs in Nonsteroidal anti-inflammatory drugs

3.1. Reduction of gastrointestinal (GI) side effects and ulcerogenicity of nonsteroidal anti-inflammatory 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.GI effects of NSAIDs result usually from local irritation produced by the free acidic group and local inhibition of prostaglandin synthesis in GIT. The 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 the 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 anti-inflammatory activity of their own [11]. Other analgesics, anti-inflammatory 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 an 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]. 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 ulcerogenic with better antiinflammatory/analgesic action than their parent drugs. Mutual prodrugs of ibuprofen with and salicylamide (6) have been reported with better lipophilicity and reduced gastric irritancy than the parent drug [16]. Naproxenpropyphenazone mutual prodrugs (7) were synthesized to improve therapeutic index through the prevention of GI irritation and bleeding. Esterification of naproxen with different alkyl esters and thioesters led to prodrugs with retained anti-inflammatory activity but exhibited greatly reduced GI erosive properties and analgesic potency, but esterification with ethyl piperazine showed that analgesic activity was preserved whereas anti-inflammatory 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 hydroxymethyl propyphenazone, which gives the analgesic effect. Coupling of these two compounds as a hybrid drug or through a spacer as a mutual prodrug resulted in a 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 improved GI safety. Along with prostaglandins, NO plays an important cytoprotective role in GI homeostasis and defense 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 anti-inflammatory 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 gastrotoxicity24 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 purposes. 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 to produce mutual prodrug with lower ulcerogenicity and synergistic action [27].

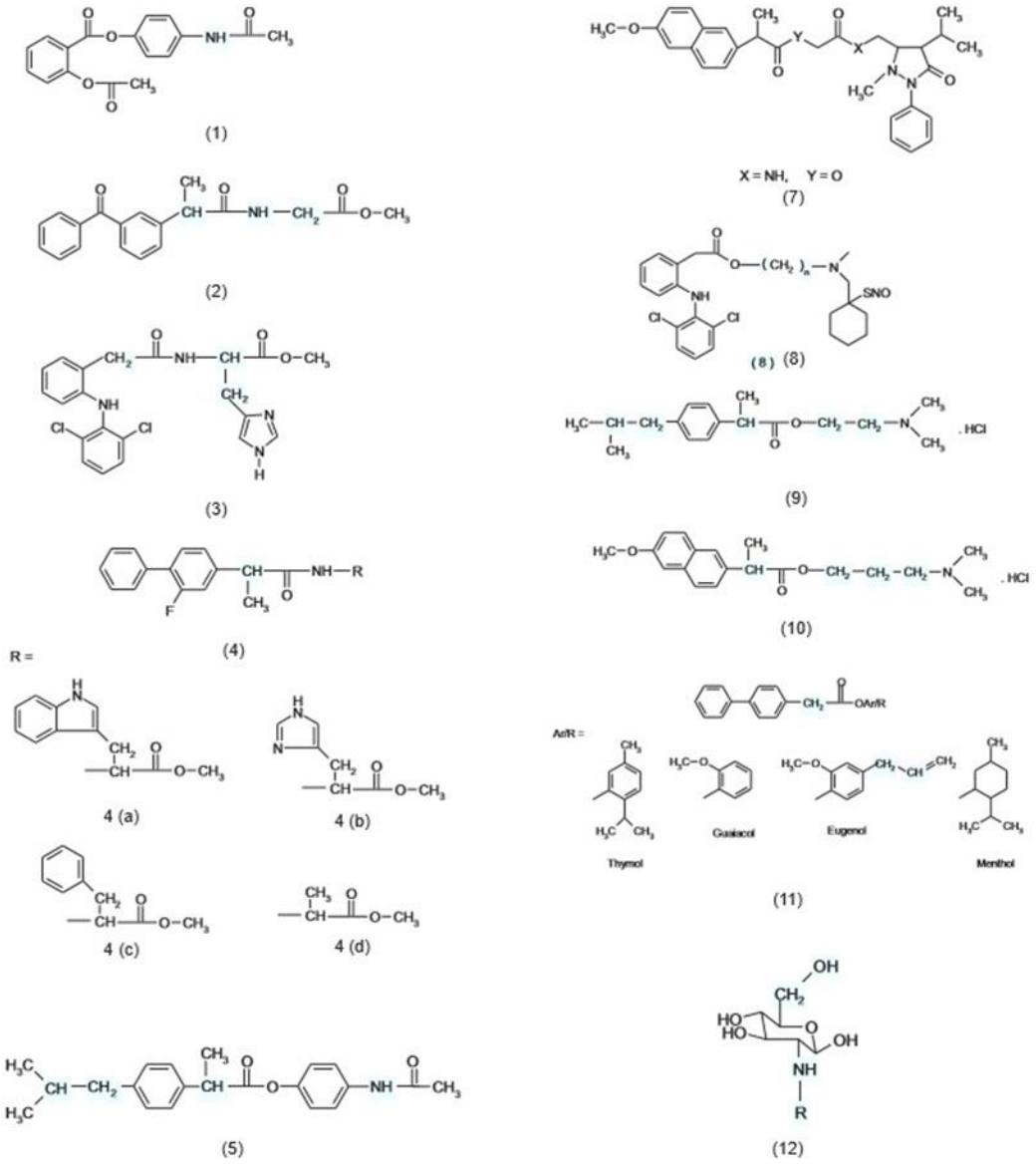
Mutual prodrug conjugates of flurbiprofen have been reported with histamine H2 antagonists in order to reduce gastric damage by NSAID. A new term has been introduced for a mutual prodrug called chimera drug [28].

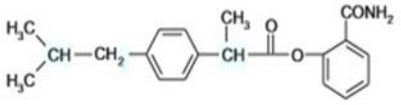
The mutual prodrugs of ibuprofen and indomethacin employing vanillin and chalcone were successfully synthesized and characterized by spectral (UV, IR, NMR) data. Calculated logP values indicated that the prodrugs are more lipophilic than the parent drugs. The mutual prodrugs were hydrolyzed at pH 7.4 and pH 9.5 but were resistant at pH 1.2 indicating that the conjugates are resistant to acidic conditions and both were found to be showing enhanced anti-inflammatory activity than the parent drug. Hence vanillin and chalcone could be used as promoities for ibuprofen and indomethacin. [33].

The therapeutic efficacy of piroxicam can be improved by retarding gastrointestinal side effects using a temporary modification of enolic hydroxyl group chemically. The NSAIDs such as aceclofenac, ibuprofen, mefenamic acid, and naproxen were selected as promoities to get synergistic (13) effect through these well-known pharmaco-counter parts. The targeted prodrugs are synthesized successfully and confirmed by characterization [34].

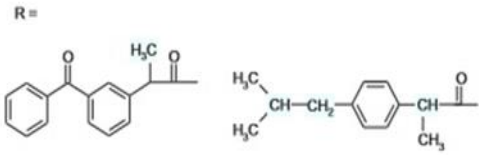
3.2. The mutual prodrug of NSAIDs with additional ant arthritic activity

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 ulcerogenic, better analgesic/anti-inflammatory 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 the 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 anti-inflammatory activity and lower ulcerogenicity.[29-31].

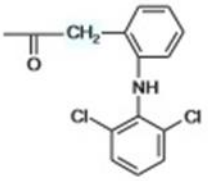




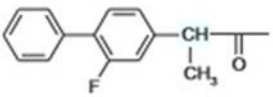
(6)



(12a) (12b)

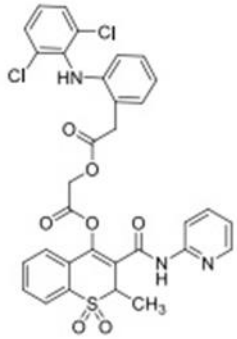


(12c)

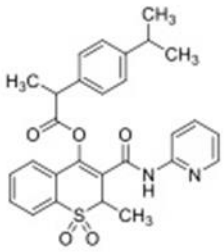


(12d)

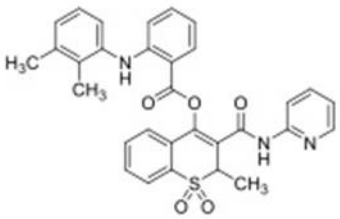
Mutual Prodrugs of Piroxicam (14)



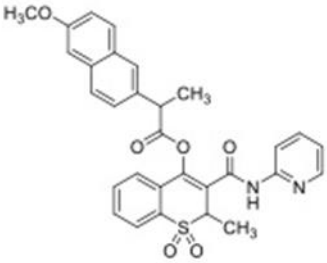
Piroxicam + Aceclofenac (PA)



Piroxicam + Ibuprofen (PI)



Piroxicam + Mephenamic acid (PM)



Piroxicam + Naproxene (PN)

Limitations and Drawbacks

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 the neurotransmitter, and enzyme inhibition measurement because bio activation 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.[4]certain toxicity mechanisms may work like the formation of a toxic metabolite of total prodrug which is not produced by the parent drug, consumption of vital constituent during the prodrug activation process, generation of a toxic derivative from a supposedly inert transport moiety, the 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 the area under the curve should be compared as it presents a better criterion for comparison. At the clinical stage, the predictive value of animal experiments is also questionable. The doses of two prodrugs of the same parent drug may appear to be the same in rats but may be quite different in clinical investigations [3]

4. Conclusion

The introduction of the mutual prodrug in human therapy has given successful results in overcoming undesirable properties like absorption, no specificity, poor bioavailability, and GI toxicity. Mutual prodrug design is 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 the 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, the 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 affecting its clinical use.

Compliance with ethical standards

Disclosure of conflict of interest

Both authors declare that they have no conflict of interest.

References

[1] Sharma PD, J. Sci. Ind. Res.1986; 45: 534.

[2] Brahmankar DM, Jaiswal SB. In; Biopharmaceutics and Pharmacokinetics a Treatise, Vallabh Prakashan, New Delhi. 1995; 162.

[3] Bhosale D, Bharambe S, Gairola N, Dhaneshwar S. Mutual product concept: fundamentals & applications, IJPS. 2006; 68(3): 286-294.

[4] Olhan S, Nanda S, Pathak DP, Jagia M. Mutual prodrugs-A SWOT analysis, IJSPR. 2011; 2(4): 719-729.

[5] Wermuth CG. In; Drug Design: Fact or Fantasy? Academic Press, London. 1984; 47.

[6] Sinkula AA. In; Medicinal Chemistry, Elsevier, Amsterdam. 1977; 125.

[7] Wermuth CG. In; Natural Prodrugs as Medicinal Agents, Hippokrates Verlag, Stuttgart. 1981; 185.

[8] Stella V. In; Prodrugs as a Novel Drug Delivery System, American Chemical Society, Washington DC. 1975; 115.

[9] Robert TS, Ronald JV, Amer J. Med. 1989; 86: 449.

[10] Cioli V, Putzolu S, Rossi V, Corrandino C. Toxicol. Appl. Pharmacol. 1979; 50: 283.

[11] Meyers J, Braine E, Monika DK, Davis RH. Inflammation. 1979; 3: 225.

[12] Croft DN, Cuddigan JHP, Sweetland C. Brit. Med. J. 1972; 3: 545.

[13] Dhaneshwar SS, Chaturvedi SC. Indian Drugs. 1994; 31: 374.

[14] Dhaneshwar SS, Dhaneshwar SR, Chaturvedi SC. Eastern Pharmacist. 1996; 119.

[15] Gairola N, Nagpal D, Dhaneshwar SR, Dhaneshwar SS, Chaturvedi SC, Indian J. Pharm. Sci. 2005; 67: 369.

[16] Bhosale AV, Agarwal GP, Mishra P. Indian J. Pharm. Sci. 2004; 66: 158.

[17] Sheha M, Khedr A, Elsherief H. Eur. J. Pharm. Sci. 2002; 17: 121.

[18] Wallace JL, Reuter B, Cicala C, McKnight W, Cirino G. Gastroenterology. 1994; 107: 173.

[19] Wallace JL, Reuter B, Cicala C, McKnight W, Grisham MB, Cirino G. Eur J. Pharmacol. 1994; 255.

[20] Elliot SN, McKnight W, Cirino G, Wallace JL. Gastroenterology. 1995; 109: 524.

[21] Muscara MN, McKnight W, Del Soldato P. Pharmacol. Lett. 1998; 62: 235.

[22] Wallace JL, Reuter B, Cirino G, J. Gastroenterol. 1994; 9: S 40.

[23] Burgaud JC, Riffaud JP, Del Soldato P, Curr. Pharm. Des. 2002; 8: 206.

[24] Shanbhag VR, Crider M. J. Pharma. Sci. 1992; 81: 149.

[25] Cai TB, Tang X, Nagorski J, Brauschweiger PG, Wang PG, Bioorg. Med. Chem. 2003; 11: 4971.

[26] Sharma PD, Kaur G, Kansal S, Chandiran SK. Indian J. Chem. 2004; 43B: 2159.

[27] Sharma V, Khan MS. Pharmazie. 2003; 58: 99.

[28] Otagiri M, Imai T, Fukuhara A. J. Control. Release. 1999; 62: 223.

[29] Pophalikar RN, Nagpal D, Dhaneshwar SS, Indian Drugs. 2004; 41: 458.

[30] Ghodeswar BC, Pophalikar RN, Bhojani MR, Nagpal D, Dhaneshwar SS. Indian J. Pharm. Sci. 2004; 66: 773.

[31] Ghodeswar BC, Bhojani MR, Dhaneshwar SS. Indian Drugs. 2003; 40: 156.

[32] Mc Alindon T, Lancet. 2001; 247: 357.

[33] Datar P, Shendage T. Design synthesis and stability studies of mutual prodrugs of NSAIDs, Chemical informatics, I Med Pub Journal. 2016; 1(1:1): 1-8.

[34] Redasni VK, Bhalerao OC, Kalaskar MG, Suarana SJ. Synthesis & evaluation of novel mutual prodrugs of piroxicam, Journal of Pharm Chem. 2017; 1(1): 1-4.