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Insights on Fatty Acids in Lipophilic Prodrug Strategy

Elżbieta Dąbrowska-Maś[1*]

[1]ICN Polfa Rzeszów S.A., Przemyslowa 2, 35-959 Rzeszów, Poland.

Author's contribution

The sole author designed, analyzed and interpreted and prepared the manuscript.

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Review Article

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ABSTRACT

Aim: This review is dedicated to fatty acids importance in prodrugs development strategy. Various strategies of fatty acid-linked prodrugs are discussed in the article.
Summary: The increased drug lipophilicity is of great significance in both blood and lymphatic delivery, as the most desirable physical factor for the specified drug forms. Increased lipophilicity can prolong the action of the drug and enhance drug passive diffusion thorough the biological barriers like skin, gastrointestinal epithelium and blood-brain barrier.
Fatty acids as lipids are present in the human body and occur in the nature, moreover as the esters with steroid hormones also exist naturally.
Thus, the implementation of fatty acids into the prodrug research strategy seems to be the most desirable, especially for the improvement of lipophilicity of the parent drug. The drugs may be linked to the fatty acids either thorough the carboxylate group or by the ω-position.

Keywords: Lipophilic prodrug; fatty acid; fatty acid ester; fatty acid amide; ω-position linkage.

1. INTRODUCTION

The modern pharmaceutical industry is focused on research in innovative therapeutic substances, especially in these areas where the current therapies are not sufficiently effective. Nevertheless, a broad spectrum of current research in the drug design is improvement of

**Corresponding author: E-mail: Elzbieta.DabrowskaMas@valeant.com;*

insufficient properties of already marketed drugs, depending on intended application, as well as improving stability, decreasing toxicity or modifying the release of the active substance from the drug form.

In the last field, various approaches are used, ranging from modifying the drug formulation, thorough combining the drug with transport protein inhibitors or metabolic enzymes, finally to the formation of chemical derivatives of active substances, including prodrugs (also produced *in situ* in the formulation), showing more appropriate properties in comparison to their precursors. The object of prodrug design is to improve bioavailability due to unfavourable physicochemical or pharmacokinetic properties of the parent drug and in some conditions to achieve modified release.

The first prodrug marketed in 1867 by Cahn and Hepp was acetanilide, which is *in vivo* hydroxylated to paracetamol. Phenacetine marketed in 1887 by von Mering was the second one, and it also undergoes biotransformation to paracetamol thorough O-dealkylation. The term prodrug, introduced by Albert in 1958 [1], means chemically modified version of a drug substance, which undergoes enzymatic [2] or physicochemical transformation, and releases *in vivo* the parent active ingredient. IUPAC definition states that the prodrug is a compound that undergoes biotransformation before exhibiting pharmacological effects [3]. Prodrugs can exist naturally as aspirin or codeine, or they can be obtained *via* synthetic or semisynthetic process as a part of drug design. Actually, it is estimated that about 10% of the drugs worldwide and about 15% of new drugs approved yearly can be classified as prodrugs [4].

The lipophilic drugs are intended for almost all routes of administration, especially topical, intramuscular of subcutaneous, but also oral as to avoid first-pass metabolism or hydrolysis of a drug in gastro internal track. Increased lipophilicity is the factor that causes targeting drug to lymphatic transport pathway. There are many examples of lipophilic prodrugs both marketed and under clinical trials or research [5].

This review concerns the fatty acids importance in the lipophilic prodrugs design, because of lack of the comprehensive scientific description focused especially on this area of the prodrug strategy. Most scientific review papers treat the use of fatty acids in prodrugs design in a marginal manner. This paper highlights in detail their significance in the modern medicine, based on various approaches and examples.

2. FATTY ACIDS IN PRODRUG STRATEGY

Fatty acids, as carboxylic acids with a long aliphatic chain, either saturated or unsaturated, naturally occurring, have an unbranched chain of the number of carbon atoms from 4 to 28. Fatty acids in a lipid conjugates and as the esters with steroid hormones exist naturally.

Free fatty acids or its derivatives are used *inter alia* in such formulations as emulsions, liposomes, micelles, lipid nanoparticles [6] to improve the specified factors of the drug. Additionally, sugar fatty acid esters can be used as penetration and absorption enhancers [7]. Moreover, the scientific research have shown that the skin permeation of drugs can be evidently increased using free fatty alcohols, fatty acids and fatty esters and their enhancing efficiency shows the relationship to the saturation and/or length of carbon chain [8-13]. The above mentioned attributes were the basis of implementation of fatty acids into the prodrug research strategy, which is especially connected with the improvement of lipophilicity of the parent drug, as a result of linking fatty acids to polar residues of a drug *via* appropriate chemical bonds.

The passive transport of a drug to the desirable action site usually requires passage through lipid membranes [14]. This is a reason, that the increased drug solubility in lipids is of great significance either in blood and lymphatic delivery systems. Moreover, the higher lipophilicity can prolong the action of the drug [15] and enhance drug passive diffusion thorough the biological barriers like skin, gastrointestinal epithelium and blood-brain barrier [16], furthermore the carbon chain length plays indisputable role in the power of lipophilicity increase [17].

Prodrugs can be classified into three basic groups by chemical criteria. The first one are carrier linked prodrugs and consist on the attachment of a carrier moiety and the active substance. The carrier linked prodrugs can be divided into bipartite where one carrier group is attached to the active substance; tripartite where the carrier group is attached *via* linker/spacer to the drug substance and mutual - bipartite or

tripartite prodrug, so called “codrug” which consists of two active substances coupled together. The next group are bioprecursor prodrugs, which have not temporary linkage between the active substance and a carrier moiety, but are chemically modified. The last group is drug delivery systems/Polymeric Prodrugs, where the drug substance is dispersed or incorporated into the polymer system without formation of covalent bonds, and this group contains drug-polymer conjugates and drug-antibody conjugates [18].

Fatty acids have the strong feedback from carrier linked prodrugs strategy. As regards the fatty acid-linked prodrugs, the drugs may be linked, from the chemical point of view, either through the carboxylate group or by the ω-position at the end of the carbon chain of an acid. In the conjugation to the carboxylate group, a drug containing hydroxylic group (alcoholic, phenolic) or amino group may be reacted with fatty acid, resulting in an ester or amide formation, respectively (see Fig. 1). Other chemical approaches are acceptable when leading to the same objective, as *e.g.* transesterification, alcoholysis of acyl chloride/anhydride or the reaction between carboxylate anion and alkyl halide in a case of esters, and various rearrangements, oxidation or hydrolysis in a case of amides.

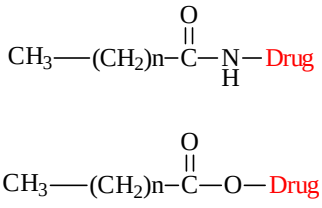

Fig. 1. Schematic presentation of prodrugs of fatty acids – conjugation *via* carboxylic group

In a case of the ω-modified fatty acid, the amino or thiol analogs of an acid must be employed to link the parent drug (see Fig. 2).

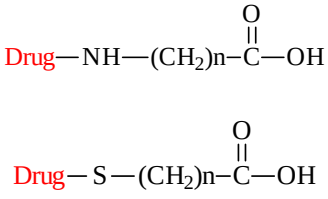

Fig. 2. Schematic presentation of prodrugs of fatty acids – conjugation *via* ω-position

The most important step in effective prodrug therapy is its activation to release the parent drug and the rationale for prodrug design must be based on the *in vivo* possibility for drug action. At the time when the term prodrug was introduced by Albert, mechanism of the prodrug activation was not known because of the lack of suitable tools for its determination, and liberation of a drug itself was considered as the success of the prodrug activation. But, in recent years, it is well recognized that basic knowledge of the activation mechanism can aid to design of new successful solutions.

3. FATTY ESTER PRODRUGS

Nearly half of all prodrugs undergoes biotransformation *via* hydrolysis process, and they are mainly in a form of an ester [19] of both mineral and carboxylic acids. The reason is that esters are simply obtained and readily hydrolysed *via* biochemical processes, depending on their chemical composition. Phosphate esters with increased aqueous solubility [20] are bioconverted to the parent drugs by alkaline phosphatases, whereas the human esterases are responsible for metabolism of many drugs, also carboxylic ester prodrugs [21-22].

Esterases found in the blood and human tissues, like carboxylesterases, butyrylcholinesterases, paraoxonases, acetylcholinesterases and arylesterases promotes hydrolyse of carboxylic esters *in vivo* [23-27]. This bioconversion is applicable also for diesters, as it was found for two apomorphine diester prodrugs which were degraded into monoesters and free apomorphine [26]. As regards the *in vivo* activation time of carboxylic esters, it depends on the chemical nature of an ester itself, the place of release and the route of administration. Carboxylic esters of simple carboxylic acids are not frequently used as lipophylic prodrugs since they can be readily hydrolysed at the time of absorption, but obtaining fatty ester prodrugs is the most suitable approach to increase lipophilicity of the parent active substance, what most often is equal to better passive transport through biological membranes [28-32].

Esters of fatty acids C-17, C-19 and C-21 and steroids were strongly investigated at the end of the last century [33], but new fatty ester prodrugs are constantly developed and currently under research. Both marketed and researched prodrug, as well as their basic properties are described briefly below.

Esters of calcipotriol and poly-unsaturated-fatty-acids, partially and gradually hydrolyzed by skin esterases, releasing the active substance in the deep skin layers, lead to sustained drug delivery followed by prolonged activity [34]. A good deal of drugs is investigated also for prolonged intramuscular injections [35], which are dedicated for long acting treatment, but until now there are about twenty available on US and/or EU markets. These include oil based injections for schizophrenia and hormone therapy, based on prodrug esters as decanoate (Haloperidol, Flupenthixol, Fluphenazine, Zuclopenthixol), palmitate (Pipothiazine), valerate (Estradiol) or cypionate (Estriadiol, Testosterone). Prodrugs in an ester form are also available as injectable drug suspension, e.g. Palipideridone palmitate, Medroxyprogesterone acetate. Acetate of Lanreotide is available as supersaturated drug solution for deep subcutaneous injection, but the same is marketed as the intramuscular microsphere, as well as acetates of Leuprolide, Octreotide and Lanreotide [36]. When drug is released intramuscularly, their release is slow. Some ester prodrugs of few omega-3 fatty acids have been also described [37].

Fatty ester prodrugs with increased lipophilicity are designed mainly for topical administration [38], but as they are stable under gastric conditions and can cause lower gastrointestinal irritation than the parent drugs [39], their usage in oral forms may be also useful.

Other important factors may be improved with prodrug strategy and here fatty ester prodrugs of salicylic acid as octanoyl, nonanoyl, decanoyl, lauroyl, myristoyl and palmitoyl oxysalicylate were investigated for ultraviolet protection as regards their lipophilicity, chemical and enzymatic stability [40]. Another known example is hexanoyl ester prodrug of rohitukine [41].

It is very important, that fatty prodrug esters may be relatively stable in the skin and therefore useful for topical drug products delivery [42]. Some esters of ketoprofen and few fatty acids (stearic, linoleic, oleic) show low skin permeation allowing the drug to accumulate in the skin [43]. As regards chemical stability, the differences were observed in three lipophilic nalmefene esters injected intramuscularly: palmitate, octadecyl glutarate and decyl carbamate, where the smallest one – decyl carbamate was too stable to be used as a prodrug, but the other two delivered a constant level of nalmefene for one month and may be recognized for prolonged drug form [44]. Palmitoyl danshensu was investigated to improve its bioavailability and also prolong its half-life time [45].

The following examples include SN38-undecanoate for oral chemotherapy showing better availability in lipid-based formulation strategy [46]. Subsequently, the permeation of cycloserine *via* skin was increased up to 20-fold by the fatty acid esters [47]. Moreover, fatty acid conjugation has been developed to increase the stability of drug forms and some conjugates demonstrate also reduced toxicity [6]. Next, lipophilic oleate prodrug of docetaxel showed slower drug release [48].

Even though the synthesis procedure for esterification is well understood, from simple Fisher process to more advanced techniques, it requires the presence of chemical or biological catalyst or coupling agent, sometimes of specific use [49-66] and this is a reason in many cases for need the unique effective synthesis procedures for the ester prodrugs with fatty acids. And here, the microwave irradiation in ionic liquids was used for dihydrotestosterone heptanoate [67-69], but ionic liquid can be also useful medium in the lipase-catalyzed fatty acid ester process [70-71]. The next advantageous process is transestrification of non-fatty esters into fatty analogs. The other useful chemical procedure may be the reaction of a selected drug with an fatty acid chloride, what was successfully tested for glyceride prodrugs of naproxen [72].

4. FATTY AMIDE PRODRUGS

Amide prodrug approach, although chemically possible (see Fig. 1), is not widely researched because of lack of the selective biotransformation way for parent drug release, in many cases there is lack of active proteolytic enzyme which can break the amide linkage [73], due to its high *in vitro* stability and also other possible ways of biotransformation, which may cause formation of unexpected metabolites. Actually, there are only few drugs that undergo metabolic hydrolysis of an amide bond; these include *inter alia* valpromide derivatives or metopimazine.

Although both esters and amides can undergo hydrolysis process by the same hydrolases, the amides are generally hydrolyzed slowly. For simple primary aliphatic amides, the degree of *in vivo* hydrolysis depends parabolically on the length of carbon chain, and it is the fastest for

carbon amount from 6 to 7, but depends also on branching (branched analogues are hydrolyzed less readily) [74]. The other factor to be taken into consideration in the amide prodrug design, is the place of biotransformation, and here some amides may be resistant in blood and hydrolyze only in the liver. Finally, some amides are completely resistant to *in vivo* hydrolysis and undergo biotransformation *via* oxidative pathways. All these adverse factors cause that the amide prodrug design is less favorable than the ester approach.

5. MODIFIED FATTY ACIDS IN PRODRUG DESIGN

Fatty acids play the role of a high importance in mammalian energy metabolism. Long chain fatty acids (LCFA, from C-16 to C-20) are insoluble in body fluids, and their high lipophilicity and low solubility in blood plasma and interstitial fluid causes that they bind to specified proteins to increase their concentration in the compartments. The main fatty acid binding protein in extracellular fluids is albumin [75]. Both the long chain and the carboxylate group are essential for association affinity of fatty acids with albumin. Long chain fatty acids association with albumin is possible only if their carboxylate moiety is not chemically linked [76]. The above *in vivo* phenomenon was the basis of research on prolonged forms, especially of short-lived peptide or protein drugs, which are linked to ω-position of LCFA.

Long chain fatty acid, ω-modified, are useful for the synthesis of binding ligands, having an enhanced associating affinity with human serum albumin, and after conjugation of this fatty acid with the parent drug, *in vivo* action is prolonged due to the elevated hydrophobic character [77], but in some cases elevating hydrophobicity may in parallel reduce their bioavailability in an undesirable fashion [78].

The ω-modified fatty acids are used in albumin-binding probes [79-80], capable of converting amino- or mercapto- drugs into prolonged-action prodrugs. The insulins acylated by saturated fatty acids (C-10 to C-16) on the ε-amino group of Lys^{B29} were established [81], whereas the long-acting derivative – insulin-detemir, where LCFA-like probe is linked into the insulin molecule, was marketed [82]. Besides, also ω-carboxylic acid isosters, such as tetrazol or —SO_3H, are used in conjugates comprising a protein/glycoprotein, linked to the albumin binding residue [83].

Glucagon-like-peptide-1 (GLP-1) analogs, mono- or double acylated, linked to albumin binding residues, comprising *inter alia* —COOH, with prolonged profile of action *in vivo*, are also known [84-86]. Apart from GLP-1 therapies, based on parenteral drug administration, the recent research is also focused on obtaining oral delivery forms of GLP-1 peptides, and it is accomplished with the specific pharmaceutical composition, comprising at least one fatty acid amino acid (FF-aa), where an amino acid is acylated with a fatty acid (C-5 to C-19) [87].

LCFA-like albumin-binding probes containing HOOC—$(CH_2)_{15}$—S-MAL-FMS-OSu bond, which are readily hydrolysable and, when associate with albumin, capable of converting short-lived peptides and proteins to prodrugs with prolonged *in vivo* action are known [88]. This new derivatives undergo slow hydrolysis process and release the parent drug [80]. LCFA-like albumin-binding ligands can also contain no-hydrolysable bonds, but these also possess an enhanced associating affinity with albumin, and subsequently, upon conjugation with short-lived drugs, prolong its pharmacological activity [78].

6. CONCLUSION

The scientific research have shown that fatty acids employed in prodrug design can change the properties as lipophilicity/hydrophobicity. This phenomenon is mainly the result of the properties of fatty acids itself, as recent works indicated that many factors are connected with the structure of fatty acid, and here the permeation of drugs can be evidently increased using free fatty alcohols, fatty acids and fatty esters and their enhancing efficiency shows the relationship to the saturation and/or length of carbon chain [8-9]. The tendency was that as the level of unsaturation increased, there was an increase in the permeation of a drug [8].

Prodrug design, as the competitive strategy to new entities research, is nowadays the most growing strategy for drug improvement. From many factors and properties of a drug to be improved and increased, lipophilicity plays the crucual role, as accompanied with passive transport thorough mammalian membranes, both for blood and lymphatic transport. And here, fatty acids conjugates with drugs in a prodrug design seems to be the most effective strategy for lipophilicity refinement.

COMPETING INTERESTS

Author has declared that no competing interests exist.

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