International Journal of Pharmacy and Chemistry
2024, Vol. 10, No. 2, pp. 18-24
https://doi.org/10.11648/j.ijpc.20241002.11

SciencePG
Science Publishing Group

Research Article

Prodrugs: A Novel Approach of Drug Delivery

Rishabh Gaur*

Department of Pharmacology, Roorkee College of Pharmacy, Roorkee, India

Abstract

In the last one-decade numbers of review and research, articles have been published on prodrugs. This shows the interest of researchers in prodrugs because of the advantages offered by them over other drug delivery systems. Prodrug design is a method to focus many of the issues that trouble drug discovery and development, such as solidity, virulence, solubility, permeability, and drug targeting. Prodrug design is an effective method for targeting medications by altering their physiochemical, pharmacological, or pharmacokinetic properties. Prodrugs account for about 10% to 14% of all drugs sanctioned worldwide. Prodrugs can be created for a variety of administration methods, including transdermal, oral, intravenous, and more. However, the oral route of administration is the most popular and preferable approach; hence, oral prodrugs are highlighted in this article. Our main objectives are to explain the fundamental ideas behind the prodrug strategy, give a rundown of successfully registered oral prodrugs, and evaluate the therapeutic gains made in contrast to the parent drug. In this review article, we have made an attempt to incorporate all the basic details of prodrugs like Introductions, classification, applications of prodrug design in diverse fields of drug development, and basic functional categories that are amenable to prodrug design are all covered in this article. Using electronic databases such Web of Science, Google Scholar, PubMed, Sci Finder, Reaxys, and Cochrane, a literature search was conducted to locate information.

Keywords

Prodrugs, Development, Classification, Application, Functional Categories, Virulence

1. Introduction

The development of novel chemical entities with great pharmacological efficacy is made possible by potent contemporary drug discovery approaches, including combinatorial chemistry and high-throughput screening [1]. These methods have also brought about a new hurdle because many of the novel drug candidates still need to be chemically modified or use formulation technologies in order to attain adequate performance and effectively complete the demanding drug development process [2]. Chemical alterations can include adding salts for faster dissolution [3] or adding alkyl moieties to the drug's molecule to make it more lipophilic. However, these alterations may cause the drug to lose or have less pharmacological activity than the original compound [4]. To overcome physicochemical barriers, a variety of formulation strategies can be used [5-7], albeit they may or may not be successful in achieving adequate drug delivery. An strategy using prodrugs may be able to overcome these challenges [8], When describing chemicals that undergo biotransformation before having a pharmacological effect, Adrian Albert coined the word "prodrug" in 1958. He described these substances as "therapeutic agents that are inactive but can be converted into one or more active

*Corresponding author: rgaur7089@gmail.com (Rishabh Gaur)

Received: 23 May 2024; **Accepted:** 15 June 2024; **Published:** 29 June 2024

metabolites." Another name for the prodrug design approach is "drug latentiation".

Prodrugs are bioreversible, inactive drug derivatives that can change into their active parent drug inside of a person's body. The prodrug strategy is used to get around biopharmaceutical, pharmacokinetic, or pharmacodynamics barriers, such as poor chemical stability, solubility restrictions, a lack of site-specificity, extensive drug metabolism, passing through biological barriers, utilising endogenous metabolic pathways, toxicity, or compliance barriers (unacceptable taste/odor), all in favour of optimal oral bioavailability and a resulting therapeutic effect [9]. The prodrug technique is used to optimise recently discovered chemical entities as well as to enhance the qualities of medications that have already been put in to the market. In the last ten years, the Food and Drug Administration (FDA) of the United States has approved about 30 prodrugs (12% of all novel small-molecule entities). Prodrugs are thought to make up about 10% of all commercially marketed medications worldwide [10].

A prodrug is a pharmacologically inactive molecule that transforms into an active drug by metabolic biotransformation before, during, and after abstraction, or at specific target sites inside the body. When describing chemicals that undergo biotransformation before having a pharmacological effect, Adrian Albert coined the word "prodrug" in 1958. He described these substances as "therapeutic agents that are inactive but can be converted into one or more active metabolites." Another name for the prodrug design approach is "drug latentiation" [11, 12].

The prodrug technique used to be thought of as a last resort in the drug development process, but this is no longer the case, and now it is taken into consideration at the very beginning phases of drug research and development. In spite of the fact that creating a prodrug requires working with a novel chemical entity, the cost of producing a prodrug is lower than that of creating a novel drug. The quicker drug development process, which could ultimately result in time, money, and effort savings, is caused by the better performance (relative to the parent drug) [13-21].

Whatever the method or goal, after prodrug consumption, it must go through an activation process in which the free parent drug is released, allowing the pharmacological effect to be applied (Figure 1).

Prodrugs can be created for a variety of administration methods, including transdermal, oral, intravenous, and more [22]. However, the oral route of administration is the most popular and preferable approach; hence, oral prodrugs are highlighted in this article. Our main objectives are to explain the fundamental ideas behind the prodrug strategy, give a rundown of successfully registered oral prodrugs, and evaluate the therapeutic gains made in contrast to the parent drug. Additionally, effective prodrug examples that are already on the market or have undergone clinical trials are provided, highlighting their advantages over the parent drug in terms of pharmacological, therapeutic, and clinical outcomes.

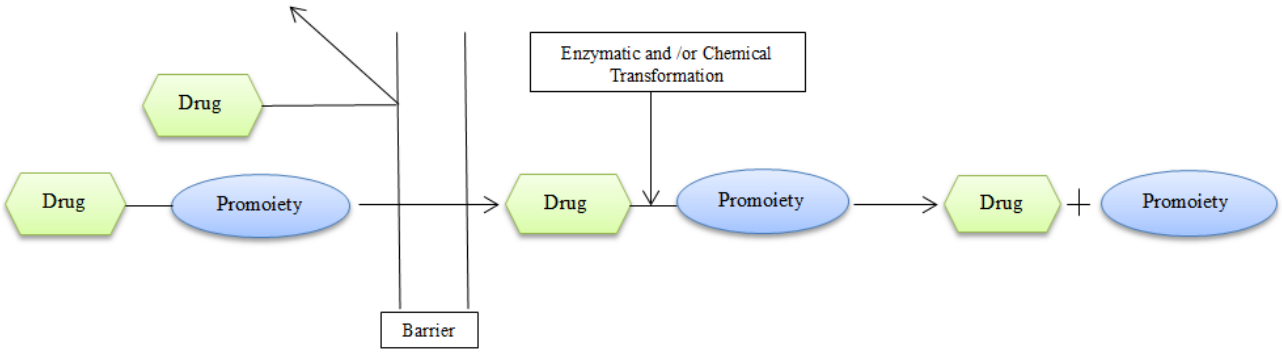

Figure 1. *Fate of prodrug approach.*

2. Classification of Prodrugs

Prodrugs can be categorized using a variety of different approaches. These might consist of those: (1) based on therapeutic categories, such as prodrugs for cardiovascular disease, anticancer, antiviral, antibacterial, and nonsteroidal anti-inflammatory conditions; (2) depending on the types of chemical linkages or moiety/carriers that bind to the active substance, such as esteric, glycoside, bipartite, and tripartite prodrugs, as well as enzymes that are driven by an antibody, gene, or virus; or (3) based on functional categories and employing deliberate strategies to overcome limitations of the active drug; for instance, prodrugs to enhance site specificity, prodrugs to avoid high first-pass metabolism, prodrugs to enhance absorption, and prodrugs to lessen side effects. [23-26]

Table 1. Classification of Prodrugs.

Prodrug type	Site of Conversion	Subtypes	Tissue location of conversion	Example
Type I	Intracellular	A	Therapeutics target tissues/cells	Type IA: Acyclovir, 5-Flurouracil, L-Dopa, Zidovudine etc.
		B	Metabolic Tissues (Liver, GI mucosal cell, lungs etc.)	Type IB: Cabamazepine, Carisoprodol, Heroin, Phenacetin, Sildinac, disulfide etc.
Type II	Extracellular	A	GI fluids	Type IIA: Lisdexamfetamine, Oxyphenisation, Sulfasalazine
		B	Systemic circulation and other Extracellular fluid comaprtments	Type IIB: Succinate, Divivefin, Bambuterol, Dihydropyridine etc.
		C	Therapeutic target tissues/cells	Type IIC: ADPEs, GDEPs, VDEPs

3. Prodrug Activation

Prodrug design is the activation process that, in order to achieve the therapeutic goal, efficiently and characterizedly releases the active parent drug from the prodrug. Prodrug activation can be based on chemical processes (such as oxido-reduction) or can occur through enzyme-mediated hydrolysis. Oxidoreductases, such as cytochrome P450, hydrolytic enzymes, such as carboxylesterases, phosphatases, and esterases, transferases, and lyases can all be used in prodrug activation [27].

The various absorption barriers and subsequent sites of possible metabolism on the path to the systemic blood circulation provide considerable obstacles for oral prodrug delivery. Whether the prodrug will be activated before or after absorption and systemic circulation is a major concern with oral prodrugs [28]. Prodrugs are medicines that, once ingested by the body, become active. Prodrugs increase a medication's efficacy. They could also be made to prevent specific negative effects or toxicities. Prodrugs are crucial for creating novel pharmaceuticals [29, 30].

Table 2. Prodrug formula and their therapeutic uses.

Prodrug	Chemical formula	Therapeutic Uses
Remdesivir	$C_{27}H_{35}N_6O_8P$	Coronavirus disease 2019 (COVID-19) in adults and adolescents with pneumonia requiring supplemental oxygen [31, 32]
OBI-3424	$C_{21}H_{25}N_4O_6P$	Relapsed/refractory T-cell acute lymphoblastic leukemia, hepatocellular carcinoma, and castrate-resistant prostate cancer [33-35]
Baloxavir marboxil	$C_{27}H_{23}F_2N_3O_7S$	Influenza [36, 37]
Selexipag	$C_{26}H_{32}N_4O_4S$	Pulmonary arterial hypertension [38]
Valacyclovir	$C_{13}H_{20}N_6O_4$	Herpesvirus [39, 40]
Gabapentin enacarbil	$C_{16}H_{27}NO_6$	Restless leg syndrome, postherpetic neuralgia [41, 42]
NUC-1031	$C_{25}H_{27}F_2N_4O_8P$	Advanced biliary tract cancer [43, 44]
Tenofovir alafenamide	$C_{21}H_{29}N_6O_5P$	HIV/AIDS and chronic hepatitis B [45, 46]

4. Objectives of Prodrug Design

4.1. Pharmaceutical Objectives

1) To ameliorate solvability (e.g., corticosteroids).
2) To ameliorate chemical constancy (e.g., dopamine).
3) To ameliorate organoleptic properties (e.g., chloramphenicol palmitate is a sparingly resolve prodrug of chloramphenicol, which is practically flavorless due to its low aqueous solubility as well as it is hydrolyzed to active chloramphenicol by the action of pancreatic lipase).
4) To decrease annoyance and ache.

4.2. Pharmacokinetic Objectives

1) To ameliorate articulate (oral) absorption or permeability and thus multiply bioavailability (ampicillin, epinephrine).
2) To decrease first pass metabolism (propanolol).
3) To improve saturation by non oral routes.
4) To provide organ or tissue selective delivery of active agent.

4.3. Pharmacodynamics Objectives

1) To avoid adverse effects or toxicities.
2) To mask reactive species to improve its corrective index.
3) To improve site specificity (i.e., that the site of action of an active drugs rather nonspecific such as anticancer agents) [47, 48].

5. Prodrugs Approved

Prodrugs are roughly 10% of all pharmaceuticals that are marketed worldwide. The FDA has approved at least 30 prodrugs since 2008. Seven prodrugs were authorized in 2015 after six were approved in 2017. Examples of recently approved prodrugs are such as dabigatran etexilate (approved in 2010), gabapentin enacarbil (2011), sofosbuvir (2013), tedizolid phosphate (2014), isavuconazonium (2015), aripiprazole lauroxil (2015), selexipag (2015), latanoprostene bunod (2017), benzhydrocodone (2018), and tozinameran (2020). Stdies are still going on are new prodrugs [49].

6. Liposome Encapsulated Prodrugs Development

Prodrugs (drugs conjugated to pro-carriers) are inactive substances that can be converted into biologically active drugs in vivo by chemical or enzymatic processes. Prodrugs are used to enhance the parent drug's pharmacological, physicochemical, and ADME (absorption, distribution, metabolism, and excretion) properties. Prodrug techniques can facilitate drug preparation and administration, boost medication effectiveness, increase site specificity, and/or lessen toxicity. Today, prodrug approaches are used in the early stages of drug research [50].

Liposomal prodrug formulations have a number of important benefits, such as high drug loading efficiency, increased drug availability, controllable drug release, and a reduced tendency to aggregate following encapsulation. Prodrug-based liposomes have an advantage over other kinds of liposomal medications in that they can intelligently react to specific stimuli and release the required medicines. After years of research and development, numerous prodrug-based liposomes with various chemical alterations have come into existence as corresponding stimuli, including those from the internal tumour microenvironment (TME) (such as pH, redox environment, enzyme and hypoxic, etc.) and the external environment (such as light, heat, ultrasound, magnetic field, etc.) [51, 52].

7. Merits and Demerits

Liposomes are exceptional drug delivery systems because they preserve the encapsulated materials from physiological deterioration [53], increase the drug's half-life, regulate drug molecule release [54], and have great biocompatibility and safety. Production cost is high liposomal products examples: Arikayce, Shingrix, Vyxeos, Onivyde, Marqibo, Doxil Caelyx etc.

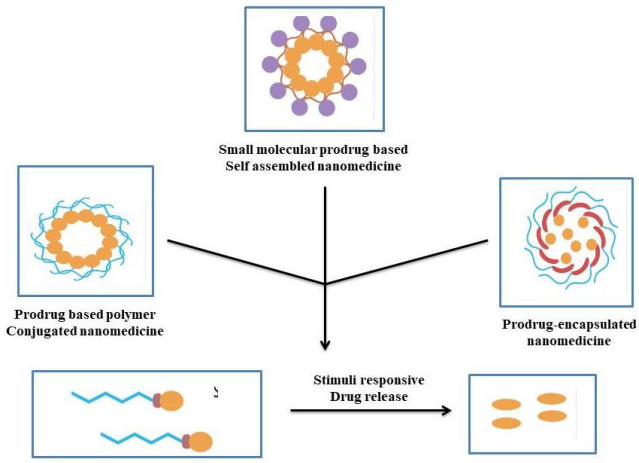

Figure 2. *Structure of prodrug-based nanocarriers.*

8. Limitations of Prodrug Design

Unexpectedly hazardous metabolite formation from the entire prodrug. The inert carrier formed after prodrug cleavage might also undergo a hazardous metabolite transformation. A essential cell component may be consumed by the prodrug during its activation stage, depleting it. Prodrugs are chemically altered forms of pharmacologically active agents

that have little to no biological activity. These prodrugs must be transformed in vivo to release the actual medication [55-58].

9. Conclusion

One of the most promising methods for boosting the therapeutic efficacy and/or mitigating the side effects of pharmacologically active agents is the prodrug strategy. This approach works through a variety of mechanisms, such as improved permeability and bioavailability, tissue-targeted delivery, increased solubility, and stability. As a result, prodrugs are emerging as a cutting-edge paradigm for drug discovery. Even with the amazing advancements in prodrug design, further research is obviously required, particularly in the early phases of drug development, to ensure that prodrugs reach the state of art and become a standard component of contemporary pharmacotherapy.

Abbreviations

IC	Intracellular
US	United States
FDA	Food and Drug Administration
EC	Extracellular
TME	Tumour Microenvironment

Author Contributions

Rishabh Gaur is the sole author. The author read and approved the final manuscript.

Conflicts of Interest

The authors declare no conflicts of interest.

References

[1] Sun, X.; Vilar, S.; Tatonetti, N. P. High-throughput methods for combinatorial drug discovery. *Sci. Transl. Med.,* 2013, 5, 205-201.

[2] Lipinski, C. A.; Lombardo, F.; Dominy, B. W.; Feeney, P. J. Experimental and computational approaches to estimate solubility and permeability in drug discovery and development settings. *Adv Drug Deliv Rev* 2001, 46, 3–26.

[3] Gupta, D.; Bhatia, D.; Dave, V.; Sutariya, V.; Varghese. Gupta. S. Salts of Therapeutic Agents: Chemical, Physicochemical, and Biological Considerations., 2018, 23, 1719.

[4] Knittel, J. J.; Zavod, R. M. Drug design and relationship of functional groups to pharmacologic activity. In: Lemke, T.; Williams, D. A.; Roche, V. F.; Zito, S. W. editors. Foye's Principles of Medicinal Chemistry. 7th ed. Wolters Kluwer Lippincott Williams and Wilkins; London, UK: 2013. p. 51.

[5] Beig, A.; Fine-Shamir, N.; Porat, D.; Lindley, D.; Miller, J. M.; Dahan, A. Concomitant solubility-permeability increase: Vitamin E TPGS vs. amorphous solid dispersion as oral delivery systems for etoposide. *Eur. J. Pharm. Biopharm. Off. J. Arb. Fur. Pharm. Verfahr. EV*., 2017, 121, 97–103.

[6] Beig, A.; Miller, J. M.; Lindley, D.; Carr, R. A.; Zocharski, P.; Agbaria, R.; Dahan, A. Head-to-Head comparison of different solubility-enabling formulations of etoposide and their consequent solubility-permeability interplay. *J. Pharm. Sci.*, 2015, 104, 2941–2947.

[7] Dahan, A.; Beig, A.; Lindley, D.; Miller, J. M. The solubility-permeability interplay and oral drug formulation design: Two heads are better than one. *Adv, Drug, Deliv, Rev*., 2016, 101, 99–107.

[8] Ettmayer, P.; Amidon, G. L.; Clement, B.; Testa, B. Lessons learned from marketed and investigational prodrugs. *J. Med. Chem.,* 2004, 47, 2393–2404.

[9] Stella, V. J. Prodrugs as therapeutics. *Expert, Opin, Ther, Pat.,* 2004, 14, 277–280.

[10] Rautio, J.; Meanwell, N. A.; Di, L.; Hageman, M. J. The expanding role of prodrugs in contemporary drug design and development. *Nat. Rev. Drug. Discov.,* 2018, 17, 559–587.

[11] Tripathi, K. D. Essentials of medical pharmacology, 6th edition, 2009, 23.

[12] Khade, M. M.; Salunkhe, A. M.; Doijad, R. C.; Patil, S. J. A Prodrug Design: Synthesis and Biological Screening of Cox II Inhibitor. *J. curr. Pharma. res.,* 2013, 3(2), 784.

[13] Dahan, A.; Khamis, M.; Agbaria, R.; Karaman, R. Targeted prodrugs in oral drug delivery: The modern molecular biopharmaceutical approach. *Expert. Opin. Drug. Deliv.*, 2012, 9, 1001–1013.

[14] Dahan, A.; Zimmermann, E. M.; Ben-Shabat, S. Modern prodrug design for targeted oral drug delivery. *Molecules*. 2014, 19, 16489–16505.

[15] Markovic, M.; Ben-Shabat, S.; Dahan, A. Lipidic prodrugs for drug delivery: Opportunities and challenges. In: Kamal Shah, D. N. C.; Chauhan, N. S.; Mishra, P. editors. Recent Advancement in Prodrugs. *Taylor & Francis Group*; *Abingdon-on-Thames*, UK: 2020.

[16] Stella, V. J.; Nti-Addae, K. W. Prodrug strategies to overcome poor water solubility. *Adv. Drug. Deliv. Rev.*, 2007, 59, 677–694.

[17] Stella, V. J. Prodrug approaches to enhancing the oral delivery of poorly permeable drugs. In: Stella, V. J.; Borchardt, R. T.; Hageman, M. J.; Oliyai, R.; Maag, H.; Tilley, J. W. editors. Prodrugs: Challenges and Rewards Part 1. Springer New York; New York, NY, USA: 2007. pp. 37–82.

[18] Markovic, M.; Ben-Shabat, S.; Keinan, S.; Aponick, A.; Zimmermann, E. M.; Dahan, A. Lipidic prodrug approach for improved oral drug delivery and therapy. *Med. Res. Rev.*, 2019, 39, 579–607.

[19] Linderoth, L.; Fristrup, P.; Hansen, M.; Melander, F.; Madsen, R.; Andresen, T. L.; Peters, G. H. Mechanistic study of the sPLA2-mediated hydrolysis of a thio-ester pro anticancer ether lipid. *J. Am. Chem. Soc*., 2009, 131, 12193–12200.

[20] Markovic, M.; Ben-Shabat, S.; Dahan, A. Computational simulations to guide enzyme-mediated prodrug activation. *Int. J. Mol. Sci.,* 2020, 21, 3621.

[21] Markovic, M.; Ben-Shabat, S.; Keinan, S.; Aponick, A.; Zimmermann, E. M.; Dahan, A. Molecular modeling-guided design of phospholipid-based prodrugs. *Int. J. Mol. Sci.,* 2019, 20, 2210.

[22] Stella, V. J. Prodrugs Challenges and Rewards. Springer; New York, NY, USA: 2007. A Case for prodrugs; p. 1464.

[23] Han, H. K.; Amidon, G. L. Targeted prodrug design to optimize drug delivery. *AAPS. Pharm. Sci.,* 2000, 2, 1–11.

[24] Hu, L.; The prodrug approach to better targeting; Meeting Report of Prodrugs: Effective Solutions for Solubility, Permeability, and Targeting Challenges; Philadelphia, PA, USA. 28-29 June 2004; [accessed on 10 October 2023]. Available online: www. currentdrugdiscovery. com. [Google Scholar] [Ref list].

[25] Liederer, B. M.; Borchardt, R. T. Enzymes involved in the bioconversion of ester-based prodrugs. *J. Pharm. Sci.,* 2006, 95, 1177–1195.

[26] Smith and Williams, Introduction to the Principles of Drug Design and Action, 4th Ed, Taylor and Francis Group, USA: 216-230.

[27] Yang, Y. h.; Aloysius, H.; Inoyama, D.; Chen, Y.; Hu, Lq. Enzyme-mediated hydrolytic activation of prodrugs. *Acta. Pharm. Sin. B.,* 2011, 1, 143–159.

[28] Sun, J.; Dahan, A.; Amidon, G. L. Enhancing the intestinal absorption of molecules containing the polar guanidino functionality: A double-targeted prodrug approach. *J. Med. Chem.,* 2010, 53, 624–632.

[29] Sun, J.; Dahan, A.; Walls, Z. F.; Lai, L.; Lee, K. D.; Amidon, G. L. Specificity of a prodrug-activating enzyme hVACVase: The leaving group effect. *Mol. Pharm.,* 2010, 7, 2362–2368.

[30] Sun, J.; Miller, J. M.; Beig, A.; Rozen, L.; Amidon, G. L.; Dahan, A. Mechanistic enhancement of the intestinal absorption of drugs containing the polar guanidino functionality. *Expert. Opin. Drug. Metab. Toxicol.,* 2011, 7, 313–323.

[31] US Food and Drug Administration, Emergency Use Authorization (EUA) for emergency use of remdesivir for the treatment of hospitalized 2019 coronavirus disease (COVID-19) patients. [(accessed on 11 October 2023)]; Available online: https://www. fda. gov/media/137564/download [Ref list].

[32] Lo, M. K.; Albariño, C. G.; Perry, J. K.; Chang, S.; Tchesnokov, E. P.; Guerrero, L.; Chakrabarti, A.; Shrivastava-Ranjan, P.; Chatterjee, P.; McMullan, L. K. Remdesivir targets a structurally analogous region of the Ebola virus and SARS-CoV-2 polymerases. *Proc. Natl. Acad. Sci.,* USA. 2020.

[33] Study to Test AKR1C3-Activated Prodrug OBI-3424 (OBI-3424) in Patients With Relapsed/Refractory T-Cell Acute Lymphoblastic Leukemia (T-ALL); ClinicalTrials. gov Identifier: NCT04315324. [(accessed on 11 October 2023)].

[34] This Study is to Evaluate OBI-3424 Safe and Effective Treatment Dose in Subjects With Hepatocellular Carcinoma or Castrate Resistant Prostate Cancer. [(accessed on 11 October 2023)]; ClinicalTrials. gov Identifier: NCT03592264.

[35] Evans, K.; Duan, J.; Pritchard, T.; Jones, C. D.; McDermott, L.; Gu, Z.; Toscan, C. E.; El-Zein, N.; Mayoh, C.; Erickson, S. W. OBI-3424, a Novel AKR1C3-Activated prodrug, exhibits potent efficacy against preclinical models of T-ALL. *Clin. Cancer. Res: Off. J. Am. Assoc. Cancer. Res.,* 2019, 25, 4493–4503.

[36] Hayden, F. G.; Sugaya, N.; Hirotsu, N.; Lee, N.; de Jong, M. D.; Hurt, A. C.; Ishida, T.; Sekino, H.; Yamada, K.; Portsmouth, S. *Baloxavir marboxil* for uncomplicated influenza in adults and adolescents. *New. Engl. J. Med.,* 2018, 379, 913–923.

[37] Mullard, A. 2018 FDA drug approvals. *Nat. Reviews. Drug. Discov.*, 2019, 18, 85–89.

[38] Simonneau, G.; Torbicki, A.; Hoeper, M. M.; Delcroix, M.; Karlócai, K.; Galiè, N.; Degano, B.; Bonderman, D.; Kurzyna, M.; Efficace, M. Selexipag: An oral, selective prostacyclin receptor agonist for the treatment of pulmonary arterial hypertension. *Eur. Respir. J.,* 2012, 40, 874.

[39] Soul-Lawton J, Seaber E, On N, Wootton R, Rolan P, Posner J. Absolute bioavailability and metabolic disposition of valaciclovir, the L-valyl ester of acyclovir, following oral administration to humans. Antimicrob Agents Chemother. 1995; 39(12): 2759–2764.

[40] Kim, I.; Chu, X. Y.; Kim, S.; Provoda, C. J.; Lee, K. D.; Amidon, G. L. Identification of a human valacyclovirase: Biphenyl hydrolase-like protein as valacyclovir hydrolase. *J. Biol. Chem.* 2003, 278, 25348–25356.

[41] Cundy, K. C.; Branch, R.; Chernov-Rogan, T.; Dias, T.; Estrada, T.; Hold, K.; Koller, K.; Liu, X.; Mann, A.; Panuwat, M. XP13512 [(+/-)-1-([(alpha-isobutanoyloxyethoxy)carbonyl] aminomethyl)-1-cyclohexane acetic acid], a novel gabapentin prodrug: I. Design, synthesis, enzymatic conversion to gabapentin, and transport by intestinal solute transporters. *J. Pharmacol. Exp. Ther.,* 2004, 311, 315–323.

[42] Markovic, M.; Ben-Shabat, S.; Dahan, A. Prodrugs for Improved Drug Delivery: Lessons Learned from Recently Developed and Marketed Products. *Pharmaceutics*., 2020, 12(11), 1031.

[43] Comparing NUC-1031 Plus Cisplatin to Gemcitabine Plus Cisplatin in Patients With Advanced Biliary Tract Cancer (NuTide:121); ClinicalTrials. gov Identifier: NCT04163900. [(accessed on 11 October 2023)].

[44] Arora, M.; Bogenberger, J. M.; Abdelrahman, A.; Leiting, J. L.; Chen, X.; Egan, J. B.; Kasimsetty, A.; Lenkiewicz, E.; Malasi, S.; Uson, P. L. S. Evaluation of NUC-1031: A first-in-class ProTide in biliary tract cancer. *Cancer. Chemother. Pharmacol.,* 2020.

[45] Alanazi, A. S.; James, E.; Mehellou, Y. The protide prodrug technology: Where next? *A. C. S. Med. Chem. Lett.,* 2019, 10, 2–5.

[46] Dahan, A.; Ben-Shabat, S.; Cohen, N.; Keinan, S.; Kurnikov, I.; Aponick, A.; Zimmermann, E. M. Phospholipid-Based prodrugs for drug targeting in inflammatory bowel disease: Computational optimization and in-vitro correlation. *Curr. Top. Med. Chem.* 2016, 16, 2543–2548.

[47] Markovic M, Ben-Shabat S, Dahan A. Prodrugs for Improved Drug Delivery: Lessons Learned from Recently Developed and Marketed Products. Pharmaceutics. 2020 Oct 29; 12(11): 1031.

[48] Gupta D., Bhatia D., Dave V., Sutariya V., Varghese Gupta S. Salts of Therapeutic Agents: Chemical, Physicochemical, and Biological Considerations. Molecules. 2018; 23: 1719.

[49] Jung, D.; Dorr, A. Single-dose pharmacokinetics of valganciclovir in HIV- and CMV-seropositive subjects. J Clin Pharmacol. 1999, 39(8), 800–804.

[50] Xie, A. Stimuli-responsive prodrug-based cancer nanomedicine. *EBioMedicine*. 2020, 56.

[51] Zhang, T. Y.; Synergistic effects of co-administration of suicide gene expressing mesenchymal stem cells and prodrug-encapsulated liposome on aggressive lung melanoma metastases in mice. *J. Control. Release*., 2015, 209, 260-271.

[52] Gennaro, R.; Alfanso, W. Remington: The science and practice of pharmacy, Lippincott Williams & Wilkins. 2003, 20(1), 913-914.

[53] Daniel, H.; Kottra, G. The proton oligopeptide cotransporter family SLC15 in physiology and pharmacology. Pflugers Arch. 2004, 447(5), 610–618.

[54] Wilska, J. B.; Wojcieszak, J.; Olejniczak, A. B. Prodrugs: a challenge for the drug development. *Pharmacol. Rep*., 2013, 65(1), 1–14.

[55] Patil, S. J.; Shirote, P. J. Prodrug approach: an effective solution to overcome side-effects. *Int. J. Med. Pharm. Sci.,* 2011, 1(7), 1-13.

[56] Ohlanet. Mutual prodrugs- a swot analysis. *IJPSR*., 2011, 2(4), 719-729.

[57] Longqin, H. U. Prodrug: Effective solutions for solubility, permeability and challenges Drugs. 2004; 7(8).

[58] Shargel, A. B.; Andrew, B. C. Applied in pharmaceutics & Pharmacokinetics, 4th Ed. McGraw-Hill Medical Publishing Division, US. 47-66, 129-154.