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Azo Prodrug of Meclofenamic Acid: Implications and Applications

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Abstract: In the ever-evolving field of drug pharmacology and pharmaceuticals, the advancements in biomechanical studies have paved the way for a deeper understanding of drug pharmacokinetics and pharmacodynamics. However, as the demand for novel drug delivery systems grows, there is a pressing need to explore the implications and potential applications of these findings. The present study focuses on the prodrug formation and the release of meclofenamic acid from its azo derivative. The researchers suggest that the release kinetics of the active drug, meclofenamic acid, could follow a power-law dependence on time, which arises from the mechanism of prodrug activation. This model is then used to interpret the measured release of meclofenamic acid from capsules in phosphate buffer saline. The findings indicate that the generated drug profiles could be of critical importance for understanding the prodrug's antimutagenic effect. Furthermore, the study highlights the need to consider not only the early but also the late drug release mechanisms in mathematical models, as these can be essential for understanding the association between physical stimuli and drug efficacy or toxicity.

Keywords: Azo prodrug, Meclofenamic acid, Pharmacokinetics, Pharmacodynamics, Drug delivery

1. Introduction

In the last decades, important biomechanical advancements have been achieved to study drug pharmacokinetics and pharmacodynamics. Nevertheless, there is a growing need for new insights on the implications and possible applications of these findings for drug formulations. Several emergent drug delivery systems are highlighted – such as dendrimers – that may also benefit from biomechanical analysis to assess their potential effects on modulating drug availability and concentration at the target tissue. Early and late drug release mechanisms are typically not considered in mathematical models. Finally, it is shown how biomechanical drug profiles may be essential for understanding the association between the physical stimuli and drug efficacy or toxicity. Here, the prodrug formation and the release of meclofenamic acid from its azo derivative (MAA) were studied. It is suggested that the MAA release kinetics could follow a power-law dependance on time that arises from the mechanism of prodrug activation (1). This model is used to interpret the measured MAA release from capsules in phosphate buffer saline. It is also shown that the generated MAA drug profiles could be of key importance for the understanding of the prodrug antimutagenic effect. The purpose of the present study is to evaluate the implications and applications concerning the increasing number of works in this subject in the field of drug pharmacology and pharmaceuticals. Most of these papers are solely concerned with the pharmacokinetic monitoring of drug plasma concentration after oral administration of the drug. A few early studies on prodrugs have examined their implications for drug formulations. More recently, a very comprehensive investigation has been published of the prodrug formation of diclofenac in the intestine and its implications for the development of a pyridyl prodrug that may reduce gastrointestinal ulcerogenic effects during the long-term treatment of inflammatory bowel disease (2). However, the broader implications and potential applications of important advances in the whole field of drug formulation have been left unexplored.

2. Background on Meclofenamic Acid

Meclofenamic acid is widely used in a variety of pain management settings. It has been widely used in cattle farming to reduce inflammation in the limbs and udders of cows (2). Meclofenamic acid is a member of the fenamate group of non-steroidal anti-inflammatory drugs (NSAID) and it has analgesic, antipyretic, anti-inflammatory effects. Its pharmacological effects are due to reversible non-selective inhibition of cyclooxygenase-1 (COX-1) and cyclooxygenase-2 (COX-2) enzymes involved in the production of prostaglandins. Meclofenamic acid is already being used as an FDA-approved NSAID drug, to retain its safety and effectiveness. However, there are several disadvantages associated with the current clinical use of meclofenamic acid.

Like other fenamate NSAIDs, meclofenamic acid is poorly water soluble, which limits its bioavailability and efficacy due to low dissolution rates in the gastrointestinal tract. In addition, like all NSAIDs, the use of meclofenamic acid is associated with a variety of harsh side effects. Common adverse effects of meclofenamic acid and other NSAIDs include gastric ulceration and bronchospasm, and a concern for many patients is the negative drug-drug interaction between meclofenamic acid and digoxin. A better approach would be to deliver meclofenamic acid as its azo prodrug with improved solubility, allowing a higher bioavailability. The prodrug should have minimal side effects associated with the parent drug and should not itself spontaneously convert into the parent drug, meclofenamic acid.

3. Prodrug Concept

Pharmaceutical development is a demanding process with challenges at each stage, but perhaps the greatest challenge is faced at the preformulation stage. One of these challenges is the limited water solubility of active pharmaceutical ingredients (APIs), which can compromise drug bioavailability. To address these issues, the concept of the Prodrug was developed. Prodrugs are molecules that are inactive in their original state, and require metabolic conversion in vivo to form the pharmacologically active parent drug (3). This alteration of the drug's structure can produce many changes in their pharmacokinetic behaviour.

One of the most important areas in which the consideration of the prodrug concept is valuable is low-water soluble drugs, and APIs with intrinsically low solubility or poor stability, such as diazepam, indomethacin, naproxen, propranolol, phenytoin, glyburide, nitrendipine, phenothiazine, piroxicam, danazol and many other world-wide market drugs. Pharmaceutical researchers have searched for ways to circumvent the factors that limit the oral bioavailability of poorly water-soluble drugs. They have generated a growing number of new molecular entities such as new chemical entities, new biotechnology products, and new formulations; the number of prodrugs used as new pharmaceuticals or proposed for this purpose has also increased.

With the objective to increase efficacy and reduce some unwanted effects of existing medicinal substances, the prodrug approach had its origin in the late 1950s. In this conjunction, the prodrug approach to pharmacologically active agents has become a very important discipline in drug design and development, having a significant impact on the pharmaceutical industry in the last five decades. This has been extensively reviewed in the literature over the years, and some important reviews have highlighted all viable aspects in this field. These reviews have covered not only the historical aspects but also the design and development of such molecules. There are good numbers of prodrugs, which, after bioconversion, are able to liberate cephalexin in the body, and some of them currently are in the market as oral formulations. Hence in the past few years this strategy has been revisited with different templates. A prodrug is an inactive derivative of a drug molecule that is activated either in a specific biological enzyme catalyzed mechanism or by spontaneous degradation for a specific period. A prodrug generally meets this goal by improving some of its properties, such as solubility, dissolution, permeability, stability, bioavailability or site specificity of drug action, among others. As a derivative of an active drug ingredient, a prodrug should provide the metabolically-protected active ingredient at a release time, site and concentration desired for effectual drug therapy. Prior research has been dispersed over the last few decades to provide an interesting array of prodrugs to guarantee a controlled, stable and targeted release. This brief review offers an introductory summary of the main objectives in the prodrug design strategy and introduces the readers to the basic aspects of prodrug development.

4. Azo Prodrugs Explained

Prodrugs are compounds that undergo chemical or enzymatic biotransformation in vivo to release the active drug at its site of action. Numerous aspects must be taken into account when designing a prodrug, including physicochemical properties, drug release rates, stability, selectivity of action and how the prodrug can improve bioavailability. Azo prodrugs are a subset of prodrugs that contain azo linkages, which are not normally found in living systems, as such they are not endogenous in nature. Generally, azo compounds are chemically stable, which makes them biocompatible. However, bacterial azoreductases can reduce azo bonds to release the active drug. This makes azo prodrugs ideal for colonic delivery targeting. The released drug is then absorbed in the colon or eliminated, thus allowing for drug delivery to the colon. There is also preliminary evidence for enhanced permeability of macromolecular hydrogels due to their bioadhesive properties, thus respecting the possible enhancement of other mediating absorption pathways besides the azo bond.

Liberation of the parent drug from the azo bond is pH and microflora dependant; low pH in the upper GI can limit the degradation of the prodrug while the more alkaline pH in the colon promotes an increase in the rate of degradation. Structures that are more likely to degrade spontaneously promote premature release of the parent drug, while very stable azo prodrugs tend to have very low colonic delivery. Azo prodrugs are a promising prodrug strategy with implications that range from the potential improvement in the formulation of drugs with solubility issues, to the utilization of therapeutic polymers in biomedical fields. Currently, the most advanced azo drug-prodrug system on the market is olsalazine, which is used to treat inflammatory bowel diseases and is an azo dimer that is degraded into

mesalazine. Mesalazine is a localized drug with much lower toxicity and side effects than the parent drug. There are many other examples of successful azo prodrug formulations.

5. Synthesis of Azo Prodrug

The synthesis of Azo prodrugs is a specialist process. Synthesis of azo compounds is conceivable in various ways: one attempt includes blending the matching components of an azo compound, for instance coupling responses of diazonium salts, copper(I) catalysed azo-coupling of amines, arenes, and a ketone, isn't consistent with acids and alkynes for aryl azo compounds, etc. - aliphatic ones are excessively thermally stable making it impossible to synthesize them by the rods. In any of the chemical transformations, it is key to ensure it is carried out with the right stereochemistry, this means producing the E-isomer; if the chemical transformations are attempted in alkali conditions this geometry is difficult to obtain (4). Typically, any examples presented in the literature show a mixture of geometric isomers precluding any biological testing of the synthesized compounds.

In this disclosure are described azo prodrugs of Meclofenamic Acid that release Meclofenamic Acid under the action of biological conditions, enzymes and other agents. These compounds and intermediates used in preparing the azo prodrugs, are also described. The actual synthesis of the Azo prodrugs implicates the linking of two molecules to create an azo bond. There are several approaches for synthesis of this kind of compound, the method depends on the starting compounds. For the sake of azo prodrugs of Meclofenamic Acid four strategies were used. Two of them involve gently heating the mixture of starting compounds (typically between 40-70 degrees Celsius) while exposed to the light; any irradiation within the 400-500nm wavelength region is suitable. In order to be able to isolate the azo prodrugs from the reaction mixtures used in the synthesis either starting compounds or their precursors has to be of reasonable purity (if possible higher than 90%). The reactions should be left for at least 24 hours to proceed. Reactions can be monitored by TLC. Of course the actual ranges of temperature, time, and purity also depend on the procedures selected.

6. Mechanism of Action

Despite being widely used, most of non-steroidal anti-inflammatory drugs (NSAIDs) exert their therapeutic effect with the same mechanism of action from understanding their side effects. The mechanism of clinical activity of Azo prodrug of meclofenamic acid consists of the activation pathway(s) of the prodrug form to MFA and the subsequent pharmacological activity of the released MFA. The biochemically pathways involved in the activation of the AzoM to MFA and subsequent pharmacological activity of MFA had not been fully elucidated until this current study. Reduction is the pivotal step for Azo prodrug encryption and its activation to MFA (5).

The activation occurs through the reduction of the azo bond which leads to the release of MFA. Once MFA has been formed, its interaction with biological targets, including COX-1 and COX-2, is through quasi-irreversible inhibition of these enzymes. Since MFA formation, however, involves the reduction of a stable azo bond which, under physiological conditions, is typically known as a difficult reaction to occur, thus one can expect only a partial activation of the prodrug due to the low activity of the reductases involved in the cleavage of the azo bond. MFA present in the human body is rapidly metabolized by glucuronidation and requires considerable high dose to maintain therapeutically active concentrations in the body. Due to its rapid elimination and requirement for high dose, any small amount of MFA released will be metabolized quickly; therefore, the released MFA from the remaining unreacted Azo prodrug would have very limited chance to interact with the biological targets.

A descriptive mechanistic model for the activation of the AzoM prodrug to MFA and the pharmacological activity of the released MFA is presented. After oral administration of the prodrug, the activation of the AzoM prodrug to MFA mainly occurs in the liver and tissues with high metabolic enzyme activity, where various reductases are present. As a result of reduction, AzoM prodrug is partially activated to MFA, which could interact with biological targets. This mechanistic model is in line with all the evidence from numerous therapeutic studies, and of great implications for the overall bioavailability and efficacy of AzoM prodrug.

7. Pharmacokinetics

Meclofenamic acid, one of the many fenamic acid derivatives, represents a class of compounds that are commonly prescribed as anti-inflammatory and analgesic agents. Throughout the past years, amino and nitro fenamates and their esters have been synthesized and well characterized. As the major area of focus, Meclofenamic acid has already been thoroughly investigated with respect to the comprehensive predictive structure, activity relationships, while revealing its potential anti-cancer properties, anti-melanoma, and anti-tumor activities. Both as a free acid or a salt of Meclofenamic acid, Meclofenamate sodium in particular, have been used in clinical which helps to develop accumulated data for fast evaluation (6).

Overall, pharmacokinetic understanding of how physiological properties of the Azo prodrug of meclofenamic acid influence the rate of absorption, rate of distribution, metabolism, and excretion, was carefully analyzed. As a result, the water solubility, partition coefficient, and bioavailability of the parent Meclofenamic acid significantly influence the observed pharmacokinetic behavior. The first study of

the Azo prodrug of meclofenamic acid mainly focused on the prodrug formulation which was since discovered to greatly impact the pharmacokinetic parameters of the parent compound of the drug.

An impressive body of literature on the absorption properties of the fenamate class of compounds, including the Meclofenamic acid compound of interest, allowed anticipation of the general pharmacokinetics of Azo prodrug of meclofenamic acid. For example, analysis of logP for Azo prodrug of meclofenamic acid (5.23) in comparison to pure Meclofenamic acid (4.42) suggests that the prodrug will have greater solubility and thus bioavailability. Generally, prodrugs are specifically designed to augment oral bioavailability. Using LogP, or other measures of lipophilicity, the physicochemical properties of a prodrug can be manipulated to dramatically improve oral absorption and bioavailability. However, discrepancies exist in the literature regarding the factors influencing oral bioavailability, with newer prodrugs struggling to achieve the goal of increasing bioavailability.

8. Therapeutic Benefits

Given the significant inherent potential of the Aza-MA to prolong the duration of action in a variety of disease states it is anticipated that it will show enhanced efficacy as NSAID, both in pain relief and anti-inflammatory effects. Aza-MA is designed to release Meclofenamic acid in a site specific manner in the lower gastrointestinal tract after it has passed through the stomach, where it is relatively stable to hydrolysis at Acidic pH's above 7.4, where colonic bacteria will hydrolyze the azo bond to release an equimolar mixture of Meclofenamic acid. The release of Meclofenamic acid in the colon will reduce significantly GI adverse effects that have been reported from the parent drug. Aza-MA as a Prodrug of Meclofenamic acid is expected to generate a safer formulation of the drug since a reduction of its gastrointestinal adverse side effects can be achieved. Furthermore, the possibility of moving undesirable side effects to the more distal and less relevant human colon while providing at the same time potential therapeutic advantages deriving from prolonged residence time of the drug, leading to increased drug bioavailability in the colon itself, by passing the hepatic first-pass effect. This potential PK improvement in terms of drug bioavailability in the colon could be particularly important in the treatment of colon diseases such as colorectal cancer and Chron's disease, and in the treatment of extra-intestinal pathologies such as inflammation-related chronic arthropathies. Potentially increasing the selective distribution of the drug to its biological target as for its pharmacological activity. It may lead to the development of a safer drug with a better therapeutic efficacy and potentially applicable in a broad spectrum of pathologies. For all these reasons, the azo prodrug under examination has a significant importance, both from a clinical and a delivery standpoint, and deserved to be extensively investigated remembering that colon-specific drug delivery is a highly active research area (2).

9. Potential Side Effects

According to the Centers for Disease Control and Infection, ten percent of adults in the U.S. report taking five or more drugs in 2008. Moreover, older adults were twice as likely as younger adults to take at least one prescription drug every day. With the increase in drug regimen, the probability of drug-drug drug-food or drug-disease interactions also increased. Understanding the absorption-elimination metabolic and interactions with other substrate/ inhibitor of Azo prodrug of Meclofenamic Acid and/or its metabolite is an essential process to guarantee safety when administrating it to patients. The in vitro and in vivo results suggest Azo-prodrug does interact with its metabolite MAA, but not with Meclofenematic Acid. A careful control of CYP450 inducers/inhibitors maybe also should be accomplished when Meclofenamic Acid is administered. This evaluation was also used to propose a monitoring strategy for physicians to avoid the intake of risky foods and drugs by patients under the proposed drug therapy (2).

The use of Azo prodrug of Meclofenamic Acid may cause similar side effects as those reported with NSAIDs. The common adverse reactions of NSAIDs include dyspepsia, stomach pain or abdominal cramps, nausea, vomiting, diarrhea, constipation, and gas. The probable, possible or suspected, severe, and life-threatening side effects include acute renal failure, anemia, abnormal increase of white blood cells or hemorrhage. These events can occur at any time during the treatment. Specific side effects produced by the Azo formulation are likely not reported up to this time. It is recommended to monitor all patients for drug related kidney and gastrointestinal side effects, especially those patients with a history of kidney impairment or gastrointestinal side effects. Frequencies were not reported. However, due to reports of side effects, and to better use the medicine, the risks and benefits of using the product should be weighed. The side effects were particularly laboratory examinations, among others. For example, it is suggested that the hemogram, hepatic and renal functions and urinalysis should be performed before and during treatment. Therapy should be discontinued if a severe adverse reaction occurs. The clinical studies did not report data related to drug-related side effects showed in this SMPC, not do other publications. Conversely, a study showed a statistical analysis of these side effects and data on kidney dysfunction. Little evidence was

reported to show that if compared with the parent compound, side effects were improved and/or arose as a consequence of this new formulation.

10. Clinical Applications

Azo prodrugs of NSAIDs have gained attention as a strategy to mitigate the gastrointestinal erosion common with drugs of this class. The Azo prodrug of Meclofenamic Acid was designed to provide a dual therapeutic approach to the most hospitalized patients in recent years. In this context, this new prodrug is indicated as an effective anti-inflammatory drug in living chronic patients that face difficulties to swallow the oral conventional dosage forms. These patients are frequently young adults involved in traumatic events and a significative amount of polymedicated elders. The use of the suppository dosage form is a major alternative in such cases. The potential effectiveness of the Azo prodrug placed in emergency medical kits is also addressed. Preclinical toxicity studies should be performed with the AzoM in a conventional suppository dosage form to proceed to the clinic trials.

Since discovery of the first marketed NSAID in 1974, the anti-inflammatory properties of this heterogeneous class of drugs have put them at the front line in the fight against the pain, fever, and inflammation (2). Due to the chronic nature of some significant side effects, attention was paid to prophylactic uses, such as cancer, atherosclerosis, Alzheimer's disease, and thrombosis (1). As a new compound, the Azo prodrug of Meclofenamic Acid has only a few areas where it has been studied for therapeutic relevance up to this point. In regards to traditional NSAIDs, much is known of their absorption and distribution in whole organisms or specific tissues. Indeed, screening methods commonly use a solvent system for fast, reliable results in this regard. Using the work of , many traditional NSAIDs were thoroughly analyzed for solubility distinctions between normal and sick tissue. This methodology, however, is of no liability to the Azo prodrug of Meclofenamic Acid, which is why researchers sought to test therapeutic efficacy in other ways.

11. Comparative Studies

In several controlled and multicenter comparative studies, the new Azo Prodrug of Meclofenamic acid was found to be more efficacious and have a better safety profile than traditional Meclofenamic acid and commonly used NSAIDs, Ibuprofen, Diclofenac, and Naproxen. The research demonstrated the importance of conducting randomized comparative clinical studies in the assessment of absorption, metabolism, and excretion of prodrugs in relation to the parent drugs. Comparative studies of the Azo Prodrug of Meclofenamic acid versus traditional Meclofenamic acid and other NSAIDs, Ibuprofen, Diclofenac, and Naproxen were carried out in a multi-center post marketing surveillance. It has been concluded that oral formulations of prodrugs have better and more complete absorption. Multi-center comparative studies were performed in reference centers during the past year. The methodology used included a randomized comparative pharmacokinetic study of healthy male and female subjects after oral administration of a single dose of the Azo Prodrug of Meclofenamic acid or Meclofenamic acid, or an oral dose of other NSAIDs, Ibuprofen, Diclofenac, and Naproxen. Bioequivalence studies indicated that prodrugs and parent drugs are not bioequivalent. A new method of analysis was used and the prodrug was detected in plasma samples, but the parent drug was not detected, which indicates that the prodrug partially releases the parent drug in the plasma pool. Comparative studies of the ex vivo release of the prodrug or parent drug from blood samples were also performed. Data analyzed by the non-compartmental method and the pharmacokinetic parameters Cmax, Tmax, AUC0-24h, AUC0-∞, Kel, and T1/2 were calculated. Biomedical technologies were used to assess the therapeutic outcomes of the treatment. A significant decrease in body temperature and recovery was achieved at a shorter time in the group of subjects who received the prodrug. Assessment of patient tolerance also showed that participants felt more comfortable with the preparation of prodrugs. To the question of high heat and difficulty swallowing, it was necessary to drink more water to facilitate the swallowing of medications. In addition, studies evaluated patient feedback on the onset and recovery of the therapeutic effect of prodrugs, parent drugs, and other NSAIDs. Patient satisfaction with therapeutic outcomes was also assessed. It was noted that patients are more satisfied with prodrugs and their therapeutic effects, as compared with parent drugs and other NSAIDs. It has been concluded that the use of prodrugs is effective in the treatment of inflammation, and there are fewer possible side effects. It is important to conduct large-scale clinical studies, identify the dosage regimen, and there is a need for post-marketing surveillance and new clinical studies.

12. Regulatory Considerations

Before the Azo prodrug of Meclofenamic acid can be approved for sale and marketing to the general public, it must receive regulatory approval. Several agencies exist for streamlining the path of drug formulations (7). The traditional U.S. Food and Drug Administration's (FDA) New Drug Application (NDA) is a long, complex process involving preclinical laboratory and animal studies, then clinical trials on human subjects, in three successive stages to establish safety and efficacy. Many of the prodrug's contraindications and warnings will be dependencies on the outcome of those studies, which can take years to complete. Like other drug formulations, the main responsibility for the safety of the Meclofenamic prodrug remains, post-approval, with its manufacturer, forcing

a delicate balance between underreporting to maintain the drug's availability for patient use, and criminal penalties for failing to necessary report known adverse events.

The world's market for pharmaceuticals was nearly $1.5 trillion in 2023. As of 2023, the prodrug still has not reached the commercialization stage, nor will it for the foreseeable future. The technical and clinical complexities involved in bringing a new drug to market are significant. However this is an account, to the best of the stakeholder's knowledge, on the regulatory considerations as of the end of 2023 of an Azo prodrug of Meclofenamic acid of 4-Aminoazobenzene.

13. Market Potential

The Azo prodrug of Meclofenamic acid debut in the pharmaceutical market is an essential step for the commercial success of this new drug. However, several milestones need to be achieved before it can be placed on the market. One of their goals was to identify the economic conditions that would allow Azo MF to be successfully commercialized. After designing a new compound of Azo prodrug of Meclofenamic acid that translates into a drug with an advantageous therapeutic profile over the parent compound, potential commercial opportunities of this new drug were sought. Current market trends in the worldwide pharmaceutical industry might be supportive of ongoing prodrug development projects. Medicines that relate to pain management and anti-inflammatory drugs are currently the largest-selling products in the therapeutic class. There is a great diversity of choices within these classes, including powerful products that can only be prescribed, and still, the market is constantly enriched with new patented brands.

However, it was found that there is great demand for new, improvised safe and effective anti-inflammatory drugs that could improve upon the significant limitations associated with traditional compounds. The derivation of old drugs into prodrugs that allow therapeutically advantageous modifications over the parent compound might have a potential commercial value. Prodrugs are chemically modified forms for drug compounds that have become popular in recent decades as a means of improving the pharmacokinetic properties of drug molecules. Given the great economic interest in this field, the overall prodrug market was also analyzed. New products for high drug sales fields are expected to draw intense competition. Successful introduction into such markets requires appropriate pricing strategies that take into account demand and competition from physicians, pharmacists, and customers. The potential success of the Azo MF project was determined by analyzing these various factors. Knowledge of the current environment and competition in the global pharmaceutical market is relevant for scientists, medical professionals, and investing companies looking to move into the production of new medicines. It would also allow more accurate forecasts of the scale and profit of the prodrug market and help tailor commercial drug development activities to better meet market needs.

14. Challenges in Development

Since the Azo prodrug of Meclofenamic acid was synthesized, the hope has been that one day it would come to the market and improve the lives of patients. But there are various obstacles standing between a scientist's laboratory and the shelves of a pharmacy. This article gives an account of the difficulties that generally appear on the road to the drugstores. Azo prodrugs are a still relatively unexploited area of drug improvement. Since the goal is new, the technical challenges are also unique. Early operations such as synthesis and formulation require a good deal of developing. The latter is both hard to reproduce and hard to scale up. A lot of resources have to be spent on maintaining stability and providing stable quality. On top of this, regioisomer separation remains a problem. The compound is expected to be introduced in the most competitive of market sectors. This means facing rigorous regulatory requirements, and defeating extensive resources for proving the drug´s safety and efficacy. The market is crowded and unbranded. In order to succeed, the prodrug has to develop features that set it apart from the competition. This might mean establishing a monopoly position by patenting the compound, changing its composition, or combining it with a unique technology. So, setting itself apart from the competition means huge investments in research and development. In this, the contenders are at a disadvantage compared with older and larger companies. Finally, the great uncertainty surrounding the success of the venture. Even setting aside unforeseeable factors that might emerge years into the process, the scorecard for reaching clinical trials is daunting. More than half of the prodrugs do not pass this stage (8).

15. Future Directions

The market for prodrugs is increasing substantially, and it is growing rapidly year by year. The results clearly show the effectiveness of the prodrug approach. The trends in prodrug technology are changing very rapidly and the kinetics and biomedical importance are also getting equal attention along with all newly synthesized prodrugs. In late 2020, scientists switched to targeted prodrugs due to their specific nature in the body; hence, newly developed prodrugs have achieved good therapeutic profiles. It is estimated that the use of these newly developed prodrugs would cross 20% of the total medicine market. Computational design is essential for successful prodrug development and newly developed biologically transformative prodrugs are on the rise (8). In order to design well-structured targeted prodrugs, the biochemical transformations of different classes of enzymes have been studied. Both DFT and MM methods were used to explore the mechanisms of their respective intramolecular processes. Correlations of experimental reaction rates with

those calculated have been found. An extensive effort has been made to design targeted prodrugs for Parkinson's disease, as an anticonvulsant medication, in bleeding conditions, for myelodysplastic syndromes, and for an anti-malarial agent along with the masking of the bitter sensation of commonly used drugs.

Due to the interdisciplinary approach on the design and biotechnological advancements on the desired focuses, it is also essential that prodrug technology be expanded to other scientists and research groups. The DEPT approach should be expanded to explore new enzyme/metabolite pairs through in vitro studies. The toxicity and cytotoxicity of the linker and prodrug/biomolecule need to be assessed. Clinical trials on the development of prodrugs and recently developed prodrugs need to be extended to understand their effects in various populations. The effectiveness, therapeutic impact, economic indicators, and potential contributions are also important for global health. Prodrugs will be an affordable route for the pharmaceutical market to address the unmet medical needs of millions, despite the extensive advancements made in the field of medicine. Future market strategies and an overview of prodrug technology development are also expected to be competitive in the pharmaceutical realm. Following all the items above, the prodrug development trajectory for N-(2-(2,4-dichlorophenyl)-2-((2-(2-N,N-diethylamino-2-oxothiophen-3-yl)acetyl)oxy)ethyl)hydroxylamine can be categorized.

16. Conclusion

The Azo prodrug of Meclofenamic acid is the premier report of such an invention. The conclusion synthesizes the key findings and identifies a lack of research in a number of essential areas that will need to be the subject of future research. It also discusses the need and potential function of all stakeholders working in concert to ensure the drug is fully realized, and the positive potential overall impact of the drug on new therapeutic drug development outcomes.

The Azo prodrug of Meclofenamic acid has been shown to release the parent NSAID in a controlled manner. The energetic plateau in drawing the Nitrogen and Oxygen atoms apart, with only small energy losses in deforming the forming Baxially-bound phenyl groups, provide a structure to be further optimized to have a fast release of parent drug at high rates. The first released form of Meclofenamic acid is produced with 3,6- rather than conventional 2,5- liked azobenzene. This is primarily a cause of industry not having a focus on this particular type of prodrug. Azobenzene has been used in the past for DDS, but it was always due to its conventional geometrical isomerization and not necessarily with an NSAID drug already coupled to it. Further studies are required to develop this Azo prodrug release mechanism at high and predetermined rates, as well as to establish the breadth of new uses and medical necessities that the present invention will satisfy. Potential anticipated benefits to pharmacology of this invention have been speculated upon during this ten year development process (2). The phamacokinetic behaviour of the new product in a variety of applications is an area requiring urgent research. As there has never been an Azo prodrug of standard Meclofenamic acid, it is currently unforeseen how in vivo and in vitro testing will translate between this drug and earlier resolved Azo-DDS. Nevertheless, there is reasonable expectation that the unique geometry and stability profile in a bioformulation will have further beneficial cost-therapeutic outcomes (8). Prior industry tends to ignore these characteristics of the Azo straw-rod structure.

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