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Prodrugs as therapeutics

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Prodrugs are bioreversible derivatives of drug molecules used to overcome some barriers to the utility of the parent drug molecule. These barriers include, but are not limited to, solubility, permeability, stability, presystemic metabolism and targeting limitations. The patent literature shows a dramatic increase in numbers of prodrug patents (> 2000% increase in 2002 compared to 1993), with claims for cancer treatment comprising 37% of these. This increase is largely due to the rise from North American-based multinationals and some smaller drug delivery companies mirroring the overall trend. In 2001 and 2002, 14% of all new approved chemical drugs were prodrugs. It appears that prodrugs to overcome barriers to the delivery of problematic drug candidates are becoming an integral part of the drug discovery paradigm.

Keywords: bioreversible derivative, prodrug

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1. Introduction

What are prodrugs? The prodrug concept can be best explained by Scheme 1. When a new chemical entity has some barrier or limitation to utility, it may not be developable as a therapeutic agent. For example, the drug may be water-insoluble, making it difficult, if not impossible, for a safe injectable form of the drug to be developed for human use. Another limitation might be that the drug, although effective if given by injection, cannot be absorbed from the gastrointestinal tract (GIT). This may be because it is too polar to cross the cells lining the GIT or because the chemical is metabolised (destroyed) by enzymes present in these cells or in the liver, thus preventing the drug from reaching systemic circulation. A goal of many researchers is to achieve Ehrlich's 'magic bullet'. That is, the design of a drug that hits only the drug target while minimising drug exposure to other sites in the body, thus minimising toxicity. This 'targeting' idea has been the goal of numerous researchers via the use of prodrugs. Thus, the identified barrier is the lack of 'drug targeting'. Another barrier might be an 'economic' barrier. What if this new entity were a natural product or a chemical previously reported and therefore in the public domain? Commercialisation would be discouraged by the lack of protection. Thus, bioreversible prodrug derivatives with sufficient utility/novelty/non-obviousness to warrant patentability can be used to overcome these barriers and justify commercialisation, market issues willing.

2. Evaluation of patents and research to date

Approximately 5 – 7% of all commercialised drugs worldwide are prodrugs. Bernardelli *et al.*, reported that there were 25 new therapeutic chemical (18), and biological (7), entities approved worldwide in 2001 [1]. Of the new chemical entities, three were clearly prodrugs, and two other compounds, although not labelled as such, may behave as prodrugs. Doherty reported that during 2002, 33 new entities were approved worldwide, 31 labelled as chemical and 2 as biological [2]. Of the 31 new chemical entities (NCEs), 4 were clearly prodrugs, 1 was probably acting as a prodrug and one compound was a soft drug. Therefore, over the last 2 years, of the 49 NCEs, 7 were clearly prodrugs

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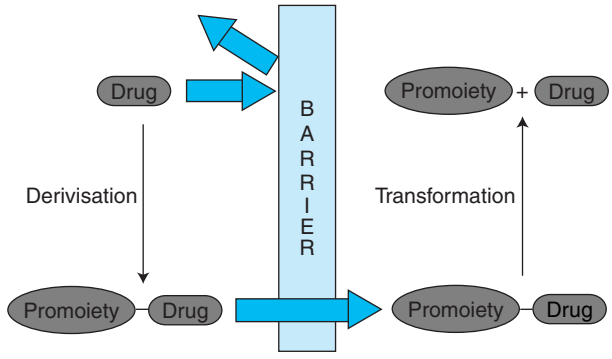

Scheme 1. A scheme illustrating the prodrug concept.

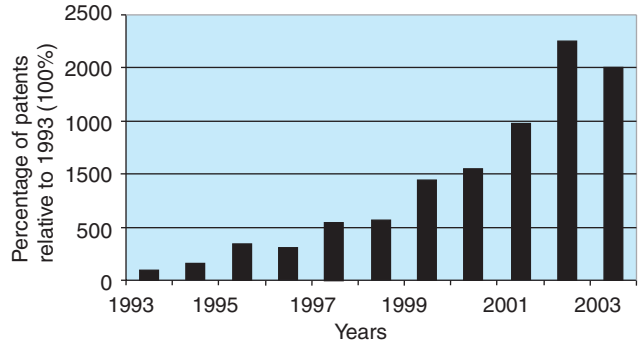

Figure 1. Plot showing the increasing numbers, expressed as a percent, of patents claiming prodrugs relative to the number 10 years ago (1993) set at 100%. The number for 2003 was estimated based on approvals to mid-year and may not reflect the final numbers.

(14%), with that number rising to possibly 11 (22%) if the 'possible' and the soft drug candidates are included.

When asked to write this editorial, a patent search was initiated with the following keywords: prodrug(s), latentiation, bioreversible derivatives and antibody-directed enzyme prodrug therapy (ADEPT) using a database compiled from Thomson Current Drugs' Patent Fast Alert®. The search for patents issued since 1993 resulted in 1,396 hits. A separate search initiated using just the word 'prodrugs' at the US patent office website, led to ~ 6,500 hits (1976 to present). Since many bioreversible derivatives are not necessarily labelled as prodrugs *per se* but may in fact be acting as prodrugs, this number probably underestimates the total number of prodrug-related patents. Nevertheless, both searches presumably identified a cross-section of prodrug patents. For convenience, the smaller number identified in the Patent Fast Alert search were further analysed. A plot of the percentage of patents per year relative to the number in 1993 (19, set at 100%) from the smaller of the two searches is shown in Figure 1. A significant increase in the numbers over time can be seen, indicating an increased interest in this area. When an analysis of each patent was undertaken, however, 605 of the 1396 patents (43%) claiming prodrugs could not be assigned a reason, or the barrier that was overcome. That is, as of 1994, many patents reporting NCEs began including terms such as 'and prodrugs thereof' or similar language. Some drugs found to have flaws encouraged researchers in other companies or academia to file patents on prodrug improvements of such drugs while still under patent. Although such prodrug patents might be allowed, their use was not because the active form of the prodrug, the parent drug, was covered by the composition patent on the parent drug. Nevertheless, companies then found themselves having to negotiate the rights to the prodrug or engineer around it if the prodrug was, in fact, superior. By including and justifying 'and prodrugs thereof' in the original patent and/or its extensions, this concern was addressed somewhat. That is, the claim of the drug substance and 'and prodrugs' appeared to be a defensive posture on the part of the patentee. This was particularly the case for patents from large pharmaceutical drug companies from Europe, North America and Asia.

Further analysis of the individual patents showed some interesting trends. One variable considered was region of origin broken down into the following: North America (small companies and multinationals), Asia (including Australia and India), Europe/Africa (including Eastern Europe, the Middle East and South Africa), worldwide research institutes (including foundations and universities), individuals and others. Over the past 10 years, the number of patents issued to North American and mainly US-based small and multinational companies represented 31 – 54% of all patents per year, with numbers following the general trend of increasing numbers of patents with time. The most aggressive company was Pfizer. If Pharmacia/Upjohn, Warner-Lambert and Agouron patents are included with the Pfizer numbers, as these companies are now a part of Pfizer, clearly Pfizer holds the dominant number of patents that can be identified as including the term prodrug. However, as mentioned above, many of these patents were part of a larger claim of the active drug substance. A few smaller companies seem to have a focus on prodrugs. Three examples are Metabasis, Xenoport and Nobex.

The percentage of all prodrug patents issued to institutes varied from 9 – 32% (peaking in 1996, but since decreasing as a percentage), from 0 – 4% to individuals and 0 – 4% to patentees of unknown country. The only interesting aspect in these numbers is that since 1997, the number of patents issued to research institutes, foundations and universities has remained in the range 22 – 30 per year.

An interesting trend is seen with Asian-based company patents. Prior to 1999, Asian-based companies were not that active, 0 – 10% (except for 1995, 26%). Starting in 2000, however, the numbers of approved patents jumped from 11 (1999) to 56 (33%), 55 (24%) and 83 (24%) for 2000 through 2002 and 45 or 28% for patents issued through to mid-year 2003. The most active companies during this time were Shionogi and Takeda. Unlike the North American data, interest in prodrug solutions to drug design and delivery

problems by our Asian colleagues is a fairly recent phenomenon. Note, however, that much of the jump in patents from the two Japanese companies would fit under the category of defensive patents discussed above. In many cases a look at the structure of the active drug with the additional claim of prodrugs suggested that prodrugs would serve very little advantage.

The numbers for European companies (broadly defined) show some similarities to the North American company data. As a percentage of issued patents, the numbers varied from 13 – 26%, with the high mark for numbers being 69 (2002) and percentage at 26% in 1998. The major players were Boehringer-Ingelheim, Aventis, Novartis, GlaxoSmith-Kline, AstraZeneca and Hoffmann-La Roche but no one company stood out from the others either in numbers or percentage. Clearly, the number of patents per year in this sampling are increasing with time. This was also seen from PubMed searches for the number of published papers per year identified by the word prodrug(s).

Why the renewed interest in prodrugs? Many potential modern drug candidates are initially identified using purified or semipurified receptors or enzymes thought to represent the 'active' site for the chemical. High throughput screens (HTS) are used to sift through the large numbers of molecules in a company's 'library' to identify what has been termed as structural leads. Further refinement then leads to chemicals being classified as drug product candidates. Unfortunately, this approach to drug discovery often results in what has been called the high affinity trap, meaning that chemicals identified in this manner result in poor clinical candidates because it is difficult to build in drug-like characteristics after the receptor interaction is optimised. That is, these molecules have physical/chemical and or pharmacokinetic properties that make them unsuitable as drugs. The more recent paradigm, whereby HTS for pharmaceutical properties also identifies drugable properties, has led to greater success in identifying drug leads and ultimately better drug candidates. However, as Lipinski and colleagues [3-5] have shown, modern drug molecules are becoming larger and more complex, resulting in a larger number of these possible clinical candidates not being deliverable. This is where the renewed interest in prodrugs appears to originate. That is, when drug-like properties cannot be built in without destroying the intrinsic activity, temporary modification of those properties through prodrug manipulation can solve the barrier limiting the use of the drug; prodrugs can be used to help build in the drug-like properties. Currently, the pharmaceutical industry and academics have rediscovered the prodrug strategy and appear to be making it an integral part of the drug design paradigm.

Is there any one therapeutic area that seems to 'require' the use of prodrugs to solve design/delivery issues? In the 1,396 patents, the following observations were made. The application of prodrugs to anticancer agents makes up 36.8% of all prodrug patents. More effective targeting of drugs makes up 14.9% of patents (out of 1,396). A high percentage of these relate to tumour or metastatic site targeting. The use in cardiovascular drugs is the next most addressed therapeutic area at 25.6%, while antimicrobials are similar at 22.6%. This number can be further broken down in antivirals (12.6%) and other antimicrobials (10.0%). Two other prominent areas are CNS drugs at 18.7% and anti-inflammatory drugs at 17.6%. Smaller numbers were seen for hormones (11.1%) and drugs used to treat immunological diseases (10.3%); there were also 4.6% of cases that could not be categorised. These numbers mirror the prevailing research emphases in many companies. Because of the toxic nature of many anticancer drugs and the goal of discovering more selective agents in an effort to minimise toxicity, it was not surprising to see the large number of prodrug patents in this area.

As with many non-prodrug patents, many patents do not show a high degree of creativity but build upon the initial creativity of others. This was clearly seen with the introduction of the novel ADEPT and gene-directed enzyme prodrug therapy (GDEPT) prodrug concepts prior to 1993, with a large percentage of the 1993 – 2003 anticancer prodrug patents claiming variations on this approach. In analysing the 1,396 patents, what percentage could be considered truly novel and unique? This is a very subjective judgement. Although not all the 1,396 patents were read in detail and the abstracts often provide inadequate detail to judge, it is my opinion that the vast majority of prodrug patents contain little true novelty either in the chemical or biological sense. Researchers are still making and claiming esters of carboxylic acids and alcohols. In my opinion, < 5 – 10% of the 1,396 patents represent true creativity.

The barrier to drug delivery proposed to be overcome was not easy to identify in many patents (605 or 43% of the 1,396) and, in many cases, more than one barrier to drug utility might have been mentioned. Of the remaining 791 patents, 208 claimed to target drugs to their site of action after parenteral (injectable) administration. Many of these were ADEPT-, GDEPT-based prodrug combinations or variants thereof. These numbers were seen to slow in 2002/2003, perhaps reflecting the lack of commercial success in this area. The predominant drugs used in many of these patents were the anthracycline glycoside family of anticancer drugs. For drugs intended for parenteral use, 93 examples of prodrugs with increased aqueous solubility were reported. Twenty-three of these patents included the anticancer drug paclitaxel and eight included camptothecins. Thirty patents attempted to claim sustained release of drugs after injectable dosing. Prodrugs for the delivery of nitrous oxide (NO) and various prodrugs useful in the treatment of ischaemic diseases were quite novel. There were at least 32 prodrug-related patents claiming improved transdermal, ophthalmic or intranasal advantages, while a number of patents just claimed better activity (9) or greater safety (37).

Oral drug delivery is the most popular form of drug delivery worldwide and the poor oral availability of many experimental drugs due to limited aqueous solubility or poor

transcellular permeability is reflected in the patent literature. These include 150 patents where produgs solved permeability limitations (many of these were for the newer antiviral drugs), 46 solubility limitations (an increasing trend is the use of phosphate ester-based prodrugs) and 49 patents that claimed improved oral bioavailability. There were 21 patents that reported improved oral sustained release whilst 26 patents included formulation advantages. A number in this latter category included the delivery of gases NO and CS_2 and the liquid butyric acid. Targeting transporters in the GIT for improved oral drug delivery were claimed in 21 patents. Surprisingly, only two patents claimed prodrugs specifically for the prevention of presystemic metabolism. There were a number of patents claiming improved delivery of CNS drugs, with many of these reflecting a more recent trend. There were also a number of methods patents.

Examples of recent, commercially introduced prodrugs include Hepsera® (adefovir dipivoxil) and Viread® (tenofovir disoproxil fumarate), antivirals from Gilead Sciences used in the treatment of hepatitis and AIDs, respectively; Valcyte™ (valganciclovir), another antiviral (Roche Holding AG); Benicar® (olmesartan, Sankyo Co. Ltd), an antihypertensive drug; and Dynastat® (paracoxib), an analgesic (Pharmacia, now Pfizer). Prodrugs in development include Aquavan™ (GPI-15715), a water-soluble prodrug of the anaesthetic agent propofol [6,7] from Guilford/ProQuest and ximelagatran (Exanta™) and BIBR-1048 (dabigatran etexilate), oral anticoagulant drugs being developed by AstraZeneca [8].

3. Future prospects

In conclusion, it appears that the prodrug or chemical approach to solving drug delivery problems is becoming an integral part of the drug design and discovery paradigm. To effect a prodrug programme clearly takes a team approach involving synthetic medicinal chemists, biologists and toxicologists, drug metabolism specialists, pharmacokineticists and formulators. The frustrations that drug discovery teams encounter with the new bigger, more complex drug molecule candidates have renewed the interest in this novel problem-solving technique and have led to some significant recent commercial successes. As in any area of research, there are many needs, such as bypassing drug efflux mechanisms, achieving true drug targeting and preventing presystemic metabolism that could use some creative prodrug solutions. In one of my current capacities as a consultant to the pharmaceutical industry, I have probably been asked to talk about and consult on the application of prodrugs as a problem-solving tool more in the last 2 years than in my previous 30 years in that capacity. I see a bright future for this old drug delivery tool.

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