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How to improve the efficacy of existing drugs?

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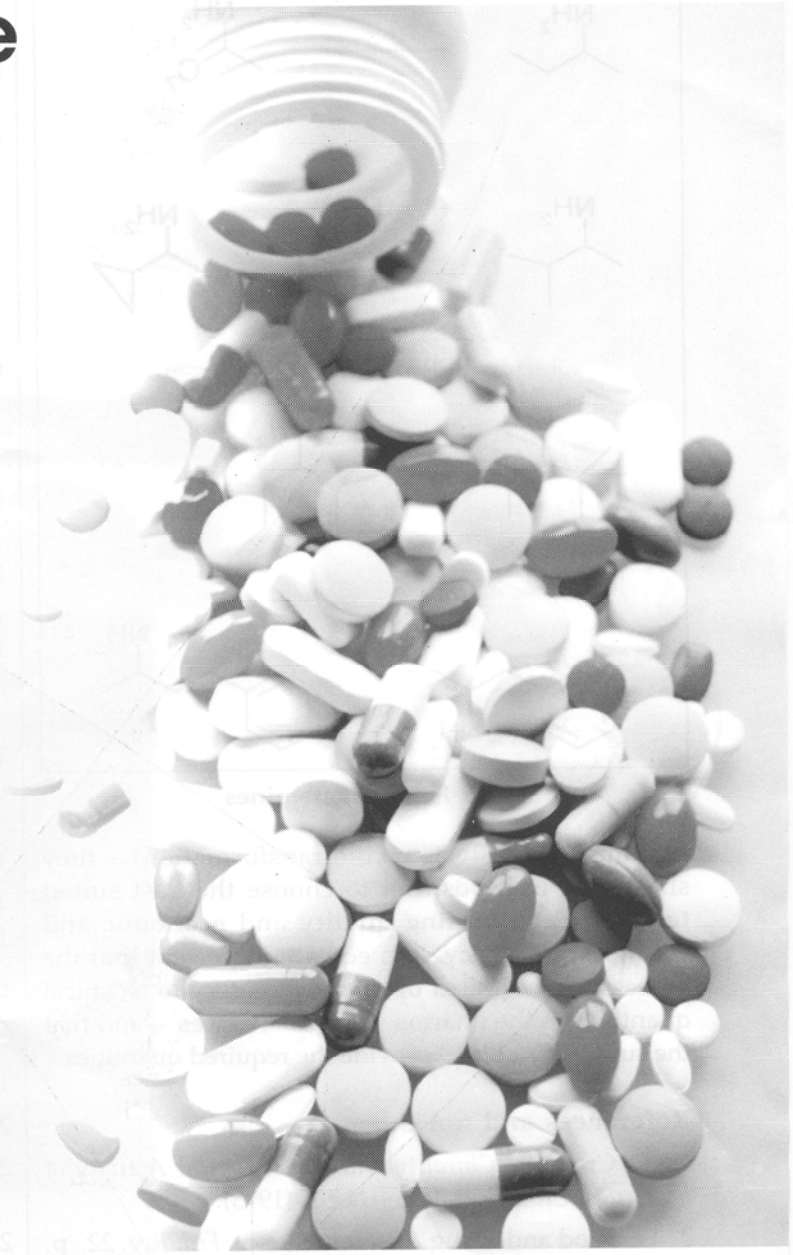

Pharmaceutical drugs have greatly contributed to public health across the globe. Yet there are evidences that drugs may perform differently in everyday clinical practice than in clinical trials which is the basis for licensing and prescribing decisions. This gap between efficacy and effectiveness of a drug is attributed to several factors. But with extremely low number of new compounds entering into the market, it is no surprise that industry is under pressure to improve efficacy and safety of the existing drugs, thereby making them more cost-effective. Therefore, in order to improve the efficacy of old drugs, besides developing several innovative delivery systems, other novel strategies have been experimented and adopted.

The article details some of the adopted strategies which can act as tools for enhancing the effectiveness of established drugs.

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Advances in scientific knowledge and technology have significantly changed the horizon for drug design, discovery and development to maintain public health and well being. Period before 20th century was considered to be the age of botanicals, where natural products and traditional medicines were utilized to cure diseases. But since early 20th century with the breakthroughs in chemistry, biochemistry, instrumentation and other technologies there have been significant developments in phar-

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maceuticals. Around the middle of the 20th century the drug discovery became more disease focused wherein interdisciplinary approaches were applied.

Prodrugs provide possibilities to overcome various barriers to drug formulation and delivery such as poor aqueous solubility, chemical instability, insufficient oral absorption, rapid pre-systemic metabolism, inadequate brain penetration, toxicity and local irritation thereby enhancing the pharmacokinetic and pharmacodynamic properties of a drug. Drug targeting can also be achieved via the use of a prodrug.

Despite significant advances in drug development that shifted the discovery paradigm over the last 100 years from serendipity to target specific drugs, and developments in clinical trials, the fact remains that for a variety of reasons, the efficacy of many drugs tend to be limited in the human body. The target specific drug post administration may interact with several receptors leading to polypharmacology. There could also be indequacies due to lack of bioavailability, drug-drug interaction, resistance, pharmacogenomics etc. Therefore, even after utmost precautions taken during the stages of clinical trials, many a times it has been found that there are drugs whose effectiveness in clinics falls short of expectation.

The gap between the efficacy and effectiveness coupled with steady decrease in the number of new drugs entering into the market has created pressures on the pharmaceutical industry to come up with new strategies to maintain profitability. One such strategy involves creating subtle improvement in the established drug for existing therapy. This strategy is always considered fruitful because the efficacy and safety of the active pharmaceutical ingredient has been already established. Some of the approaches which have been employed to enhance the effectiveness of the established drugs include:

- Increasing bioavailability
  a) Prodrug approach
  b) Pegylation
  c) Cocrystallization
- Combination therapy
  a) Drug-drug combination
  b) Antioxidant-drug combination
- Use of chiral drugs
- Pharmacogenomics
- Pharmacovigilence
- Molecular modelling

Increasing Bioavailability

To exert their therapeutic effect, active ingredient of the drug need to reach the systemic circulation for which they should be soluble and permeable to biological membranes. It is well known that all drugs and new molecular entities are classified in four groups according to their solubility and intestinal permeability. Class 1 contains drugs with a high solubility and permeability which are well absorbed with higher absorption rate than the excretion. Class 2 contains drugs with a low solubility and high permeability. Due to low dissolution rate the bioavailability of this class of drugs is limited. Class 3 drugs are highly soluble and dissolve very fast, although permeability is limited by the permeation rate. Class 4 drugs have poor bioavailability because of low solubility and permeability. It has been observed that they are not well absorbed and there is great degree of variability. Amongst these classes, drugs belonging to class 2 and class 4, due to enhanced solubility and permeability problems, have decreased effectiveness as only a part of them reach the systemic circulation. Aiming to increase the bioavailability of drugs, various measures are applied. Although most of these methods pertain to the drug delivery approaches, there are certain chemical approaches which help to increase the bioavailability. These are Prodrug approach, Pegylation and Cocrystallisation.

Prodrug Approach

Prodrugs are chemically modified versions of the pharmacologically active agent which undergo transformation *in vivo* to release the active drug. Prodrugs provide possibilities to overcome various barriers to drug formulation and delivery such as poor aqueous solubility, chemical instability, insufficient oral absorption, rapid pre-systemic metabolism, inadequate brain penetration, toxicity and local irritation thereby enhancing the pharmacokinetic and pharmacodynamic properties of a drug. Drug targeting can also be achieved via the use of a prodrug. Several blockbuster drugs being marketed today are indeed the prodrug form of the active API. These include Atorvastatin (anti-hyperlipidemic), Oseltamivir (anti-influenza), Famiciclovir (antiviral), Pivamplicillin (antibiotic) and so on (Figure 1). Prodrugs are known to increase the bioavailability by improving aqueous solubility or by improving passive intestinal absorption or by improv-

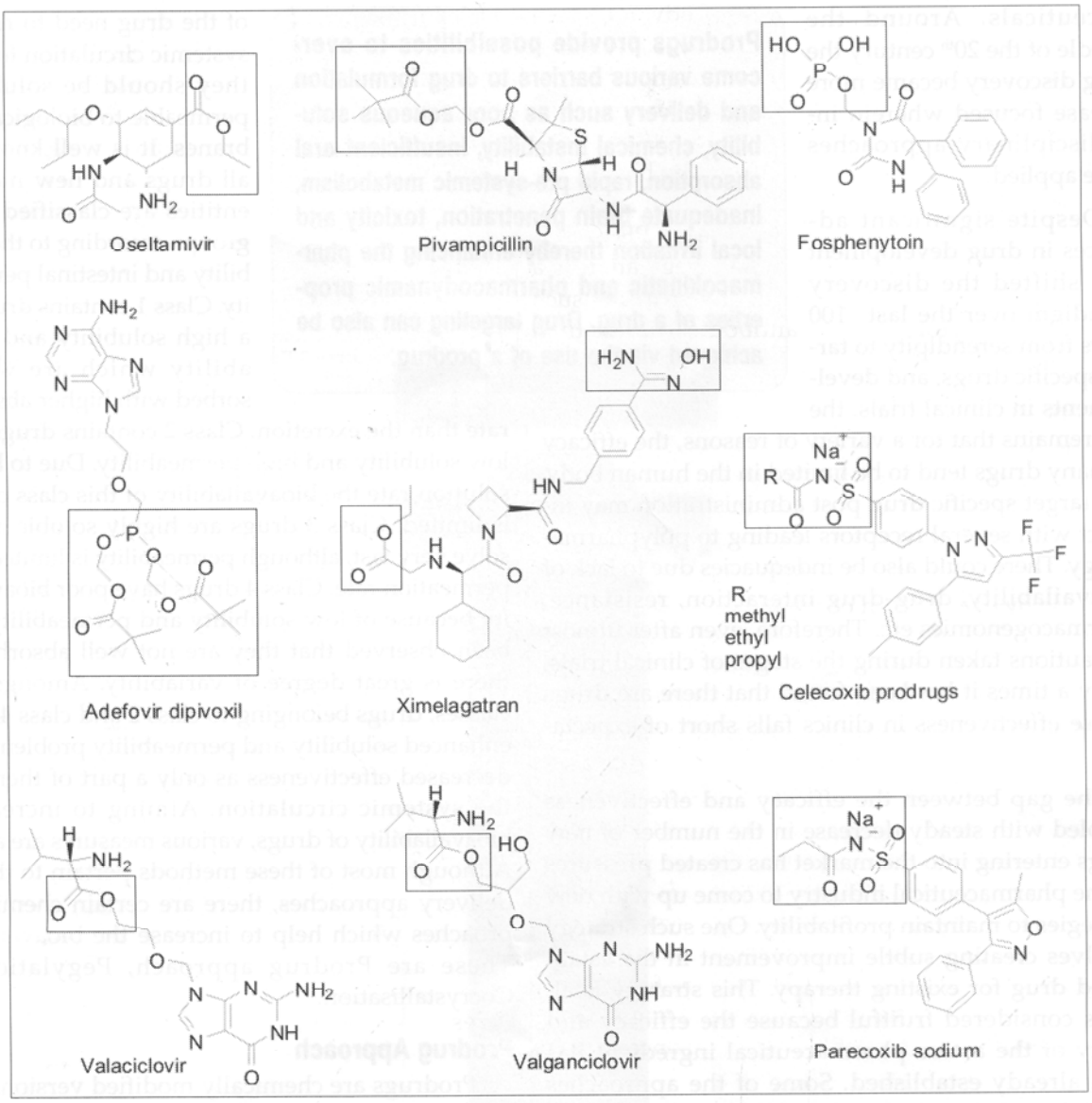

Fig 1. Drugs which are now marketed as prodrug to improve the bioavailability. The squares show the promoieties.

ing transporter-promoted intestinal absorption or by providing protection against rapid metabolism.

The prodrug strategy has been very helpful in increasing the efficacy of some of the anticancer drug via accumulation of drug in the target tissues. Owing to the high proliferation rates of tumour cells, in addition to bioreductive activity, the levels of certain enzymes are often elevated in these cells. 5 Fluorouracil (5-FU), a highly cytotoxic drug, is extensively used for the treatment of cancer and tumour. However its high toxicity during administration affects the normal tissue too. To overcome this issue of toxicity, an orally administered carbamate prodrug of 5 FU known as Capecitabine (Xeloda) was developed and marketed by Roche. This prodrug requires a cascade of three enzymes for the bioconversion to the active drug. Intact capecitabine is absorbed from the intestine and undergoes bioconversion in tumours, thus, avoiding any systemic toxicity. The bioavailability of 5 FU after oral administration of cabecitabine is almost 100%.

PEGylation

PEGylation is a technique which involves the modification of a protein, peptide or non-peptide molecule via linking it to one or more polyethylene glycol (PEG) chains. It has been successfully employed to improve bioavailability of drugs for better efficacy. This polymer is non-toxic, non-immunogenic, non-antigenic, highly soluble in water and approved for human use.

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The PEG-drug conjugates have several advantages including a prolonged residence in body, a decreased degradation by metabolic enzymes and a reduction or elimination of protein immunogenicity. The common examples for the pegylated drugs in use are PEG-asparginase (Oncaspar) for acute lympho blastic leukaemia, PEG-adenosine-deaminase (Adagen) for severe combined immunodeficiency disease, PEG-Interferon α2a (Pegasys) for Hepatitis C. Pegylation is a technique more suited to classes of protein drugs, such as enzymes, cytokines and antibodies rather than small molecules.

Cocrystallisation

The formation of cocrystals can reduce the tendency of an API to hydrate or form solvates, largely a function of satisfied hydrogen bonding. Because of the low vapour pressure of the solids used as partners, co-crystals are more stable than solvates, which can degrade by evaporation of the solvent from the crystal lattice. Co-crystals can also exhibit polymorphism, although the experience to date indicates a generally low propensity. In addition, by altering the arrangement within a lattice, co-crystals can increase chemical stability in the solid state, particularly for those drugs which are prone to photochemical-mediated reactions. Co-crystal formation has also been shown to confer crystallinity to syrups and waxes, and to modulate drug dissolution, both enhancing and delaying, depending on the properties of the co-crystal former, which is probably one of the most prominent of the emerging utilities. Co-crystals can also be formulated with excipients and subjected to particle engineering as a means of further enhancing performance in vivo. The biggest advantage experienced with cocrystallization of established drugs is that the new form is patentable under modern laws.

Oral administration of Carbamazepine (CBZ), an important anti-epileptic drug, encounters multiple challenges, including low water solubility with high dosage required for therapeutic effect (i.e. >100 mg/day), dissolution and auto-induction for metabolism. CBZ is prone to photochemical reaction leading to short shelf life. CBZ: saccharin cocrystal shows significantly improved physical stability, possesses favourable dissolution properties, suspension stability, and pharmacokinetics as examined in dog models. The pharmacokinetic study reveals that the CBZ: saccharin cocrystal exhibits a higher Cmax (maximum concentration).

Itraconazole is a triazole antifungal agent that is prescribed to patients with fungal infections. Itraconazole is extremely water insoluble and administered both orally and intravenously. In order to achieve the required oral bioavailability, the oral formulation of itraconazole is the amorphous form coated on the surfaces of sucrose beads, and marketed as the Sporanox capsule. In addition, co-administration of acidified HP-β-cyclodextrin beverages with Sporanox capsules is required to achieve the maximal absorption of the API, even though such a co-administration can cause diarrhoea. In order to improve the absorption of the API and maintain the form crystallinity and stability, the pharmaceutical cocrystal approach has been

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evaluated in the formulation of itraconazole. Crystalline phases of itraconazole can be engineered by introduction of additional molecules to match hydrogen-bond donors and acceptors. A number of stable pharmaceutical cocrystals of itraconazole and 1,4-dicarboxylic acids were synthesized and characterized. Each cocrystal contains two API molecules and one acid cocrystal former, hydrogen-bonded through carboxylic acid–triazole supramolecular synthons, to form a trimeric assembly. The aqueous dissolution of itraconazole cocrystals was studied in order to assess their potential impact on bioavailability of the API. The dissolution of itraconazole cocrystals was observed to behave more akin to the Sporanox form than to the crystalline form of the pure API. It was noted that the itraconazole:L-malic acid cocrystal exhibits a similar dissolution profile to that of the marketed formulation. In a further pharmacokinetic study of itraconazole cocrystals, it was revealed that cocrystal formulation of the API gives similar oral bioavailability to the Sporanox form in the animal trial using a dog model.

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Combination therapy

Although, discovery of a new pharmaceutical agent, new indication for an established drug or new formulation often results in incremental innovation, small improvements in existing therapy are useful in present times. Combination therapy with two or more existing drugs having a complementary mechanism represents a good alternative to increase the window of therapeutic options for several diseases. A combination could be pharmacodynamically synergistic, additive or antagonistic if the effect is greater than, equal to, or less than the summed effects of the partner drugs. Drug combinations may also produce pharmacokinetically potentiative or reductive effects such that the therapeutic activity of one drug is enhanced or reduced by another drug via regulation of its ADME (absorption, distribution, metabolism and parameters). In addition, combining both agents in the same pill simplifies the drug regimen, which may improve adherence.

Besides their beneficial effects, a number of clinically useful drugs inflict collateral damages which are mediated by free radicals and related reactants when they are administered. Humans have antioxidant enzymes including superoxide dismutases (SOD), glutathione peroxidases (GSH-Px) and catalase (CAT) which can either function as direct free radical scavengers or by enzymatically metabolizing the reactants to innocuous species. However under several diseased states even the functions of natural bodyguards are impaired. There has been a great interest in the possibility of quelling this biological destruction with the use of agents that quench radical species and their toxic metabolites. Agents that are capable of carrying out these functions are referred to as free radical scavengers or antioxidants.

Combination therapy allows the patient compliance thereby leading to better efficacy of active ingredients. Common examples of such combination include flluoxetine with alprozam (anti-depressant and antianxiety), dispirin with atorvastatin (blood thinner and lipid lowering), dipirin with clopidegrel (blood thinner with anticoagulant) etc.

Food interactions

Interaction between foods and drugs can have profound influence on the success of drug treatment and on the side effect profiles of many drugs. The clinical significance of drug-food interactions can be variable. Drug-food interactions can lead to a loss of therapeutic efficacy or toxic effects of drug therapy. Vitamin and herbal supplements taken with prescribed medication can also result in adverse reactions. Therefore it is mandatory that the drugs should be carefully prescribed and the subject should follow the directions as indicated.

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Certain foods and specific nutrients in foods, if ingested concurrently with some drugs, may affect the overall bioavailability, pharmacokinetics, pharmacodynamics and therapeutic efficacy of the medications. Furthermore, the thera-

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peutic efficacy of many drugs depends on the nutritional status of the individual. In other words, the presence or absence of some nutrients in the gastrointestinal tract and/or in the body's physiological system, such as in the blood, can enhance or impair the rate of drug absorption and metabolism. Drug food interactions can happen with both prescription and over-the-counter medicines, including antacids, vitamins and iron pills. Food can alter the hepatic metabolism of some drugs. They can also alter the urinary pH, which can affect the activity of certain drugs. The half-lives of some medications can be significantly changed by altering the urinary pH. The half-life of acidic drugs will be extended in acidic urine because the drug is in its unionized form. Therefore, alteration made in the drug intake before, with or after meals can be helpful in improving the efficacy of the drug.

Use of Chiral Drugs

After the thalidomide tragedy which led to severe birth defects, chirality of bioactive compounds has been a major issue. The R-enantiomer of thalidomide was responsible for the birth defects whereas the S-enantiomer had sedative effective against morning sickness. For any new drug having chiral center, it is essential to demonstrate the efficacy and safety of both the enantiomers. Pharmaceutical drugs which were discovered earlier are marketed as racemates can be broadly classified into three categories. In the first category, the racemic pharmaceuticals have one major bio-active enantiomer (also called eutomer) while the other is inactive or less active (referred as distomer) or toxic or can exert other desired or undesired pharmacological properties. The second category is of drugs where the two enantiomers are equally active and have the same pharmacodynamics. The last one is racemic drugs having only one eutomer, but the distomer could be transformed in body into its bioactive antipode by chiral inversion. Therefore single enantiomers can present significant advantages in potency, efficacy, and safety over the corresponding racemate, but this varies by case and is not a general rule.

The third class of racemate drugs contain examples wherein one of the enantiomers of a drug has the potential to convert into other enantiomer. For this group, only S-enantiomer is active i.e. has an analgesic and anti-inflammatory effect. But in the body the inactive R-enantiomer undergoes chiral inversion by hepatic enzymes into the active S-enantiomer due to which it is not necessary to separate the two isomers.

Many calcium channel antagonists such as verapamil, nicardipine, nimodipine, nisoldipine, felodipine, mandipine etc are used under racemic form with two pairs of enantiomers. For example, the pharmacological potency of S (-)-verapamil is 10-20 times greater than its R(+)-antipode in terms of negative chromo-tropic effect on AV conduction and vasodilatator in man and animals. On the other hand, verapamil has another possible application in cancer chemotherapy as a modifier of multidrug resistance. Unfortunately for this purpose, verapamil must be used at high concentrations which results in high cardiotoxicity. However, it was found that as compared to the S(-)-verapamil, the R(+)-verapamil has far less cardiotoxicity. Therefore, the R-enantiomer would be preferable as a modifier of multidrug resistance in cancer chemotherapy, while the S-enantiomer or the racemate would be preferable as a calcium channel blocker for cardiovascular therapy.

It has been observed that most of the β-blockers are marketed as racemates though the levorotary-isomer of all β-blockers is more potent in blocking β-adrenoceptors than their dextrorotary-isomer. The antidepressant citalopram is sold as racemate though it has been observed that S(+)-citalopram is over 100-fold more potent as a selective serotonin reuptake inhibitor than R(-)-enantiomer.

Methadone, a central-acting analgesic with high affinity for μ-opiod receptors, has been used to treat opiate dependence and cancer pain. Methadone is a chiral synthetic compound used in therapy under racemic mixture. In humans, R(-)-methadone is about 25-50 fold more potent as an analgesic than its S(+) antipode. Therefore, use of R(-)-methadone would result in significant dose lowering for same effectiveness.

Tetramisole is a nematocide, first used under racemic form. Because of numerous side-effects (vertigo, headache, vomiting, abdominal pain) mainly due to d-isomer, therefore, only l-isomer called levamisole is now used in medicine thereby eliminating the side-effect caused by distomer.

Though the list of the racemic drugs containing an eutomer is too long, some of the racemates underwent chiral switch to single enantiomer. These drugs include nexium (from prilosec), escitazolam (from citalopram), esomeprazole (from omeprazole), dexketo-

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prophen (from ketoprophen), dexmethylphenidate (from methylphenidate), etc. This has not only saved the company's profit by obtaining new patents but also significantly increased the efficacy of the marketed drug.

For drugs like fluoxetine (antidepressants) and cyclophosphamide (anticancer) both the enantiomers have similar pharmacological effect. Under these circumstances the separation of the enantiomers does not affect the efficacy of the drug.

Lippow et al. from MIT designed an iterative computational design focused on electrostatic binding contribution and a single mutant. By combining multiple designed mutations, a ten-fold affinity improvement was engineered into the anti-epidermal growth factor receptor to which Cetuximab, a drug commonly used to treat colorectal cancer, binds.

The third class of racemate drugs contain examples wherein one of the enantiomers of a drug has the potential to convert into other enantiomer. For this group, only S-enantiomer is active i.e. has an analgesic and anti-inflammatory effect. For example, S-ibuprofen is over 100-fold more potent as an inhibitor of Cox-I than (R)-ibuprofen. But in the body the inactive R-enantiomer undergoes chiral inversion by hepatic enzymes into the active S-enantiomer due to which it is not necessary to separate the two isomers. It may be noted that the (S)-isomer of ibuprofen do not have capability to undergo chiral inversion.

There has been renewed interest in thalidomide which was withdrawn earlier because of its immunomodulatory, anti-angiogenic and anti-inflammatory effects. Moreover, it strongly inhibits the tumor necrosis factor α (TNF- α). Unlike ibuprofen, the two enantiomers of thalidomide have the property to go inter-conversion in the in vivo system because of which it is difficult to determine exactly the pharmacological effect of each enantiomer. Therefore, when the interconver-sion of the enantiomer takes place in the in vivo system, it is not economically viable to separate the two enantiomers to achieve better efficacy of a drug.

Pharmacogenomics

After sequencing the human genome it is now known that 99.9% of genetic chararcters are same in all human beings. However the remaining 0.1% of DNA accounts for all differences including variations in drug metabolism and increased disease risk. Single nucleotide polymorphisms, or SNPs, are variations in DNA caused by the substitution of one of its four chemical bases adenine, thymine, cytosine, or guanine for one of the other three. Some SNPs found within the gene's coding regions precipitate aberrations, which may redispose to disease or alter a person's ability to metabolize a specific drug. SNPs can affect all cells, including those in the liver that create and secrete the enzymes in the cytochrome P-450 (CYP) enzyme system, which metabolize and break down more than 30 classes of drugs, or roughly 60% of common prescription drugs. Variations in the genes that encode the CYP enzymes can increase or decrease a person's ability to metabolize drugs. Due to this fact medicines work better in some patients than others resulting in variation in effectiveness of the drug. Therefore in order to have better compliance and safety new diagnostic tests are being combined with old drugs.

Besides the use of diagnostic tests to evaluate the dose and efficacy of drugs, the effectiveness of the drug can be increased if one drug can influence the activity of a second drug by competitive inhibition of a CYP enzyme or by increasing gene expression or toxicity. One common example of such a drug interaction involves the HIV reverse transcriptase inhibitors ritonavir and indinavir. Ritonavir is an inhibitor of a CYP enzyme that has been used in combination with indinavir to boost the levels of each and therefore their combined antiviral activity is improved.

Pharmacovigilence

Effectiveness of a drug can also be improved by continuous monitoring via maintenance of drug registers once it is marketed. Drug registers may be based on a specific drug or a class of products. A recent example of a drug-specific register involves Natalizumab, a monoclonal antibody specific for integrin α4, used for the treatment of severe relapsing-remitting multiple sclerosis. Clinical trials and post-marketing data indicated that natalizumab was associated with an increased risk of progressive multifocal leukoencephalopathy (PML), a potentially fatal disease of the central nervous system. Natalizumab was voluntarily withdrawn from the market by the manufacturer in 2005 when the initial cases of PML associated with its use were identified. Following regulatory review of safety information and data on the benefits of the drug, natalizumab was reintroduced into the market in 2006 under a risk minimization programme in which patients receiving the drug are registered

and monitored.

Molecular modelling

Antibodies are extensively used in diagnostics and therapeutic agents. Achieving high binding is important for expanding detection limits, extending dissociation half-time, decreasing drug dosages and increasing drug efficacy. However, antibody affinity maturation *in vivo* often fails to produce drug with targeted potency. Lippow et al. from MIT designed an iterative computational design focused on electrostatic binding contribution and a single mutant. By combining multiple designed mutations, a ten-fold affinity improvement was engineered into the anti-epidermal growth factor receptor to which Cetuximab, a drug commonly used to treat colorectal cancer, binds. Similarly they can also enhance the effectiveness of the acute therapeutic antibody for bevacizumab (Avasitin).

Another aspect which may be helpful in improving the effectiveness of the established drugs relates to third party. It has been often observed that a drug is licensed into the market when benefits outweigh risk for a specific disease. By contrast, third-party payers (government agencies or insurance companies) base their reimbursement decisions predominantly on the health benefits of the drug relative to existing treatment options. In case the drug is too expensive it is not reimbursed under the plans leading to low rate of prescriptions. Therefore, the efficacy of the drug can also be improved by positioning it at an affordable cost which is acceptable for reimbursement purpose.

Conclusion

Even though new therapeutics will continue to arrive in the market, considerable efforts should be devoted to improve the effectiveness of known drugs. The prodrug approach and combination therapy which have already demonstrated their worthiness would continue to evolve. With significant development of asymmetric synthesis and evolution of separation techniques for enantiomers, it is expected that more and more chiral switches of the racemate drugs would be attempted to achieve better efficacy and safety. In addition, better understanding of genetic encoding of human being would assist in deciding the therapy and dosage in future thereby limiting the toxicity and increasing the usefulness.

References

1. Prodrugs: Design and chemical applications. J. Rautio; H. Kampulainen; R. Oliyai; D. Oh; T. Jarvinen; J. Sovolainen *Nature Rev. Drug Discov.* **2008**, *7*, 255.
2. Lessons learned from Marketed and Investigational Prodrugs P. Ettmayer; G. L. Amidon; B. Clement; B. Testa *J. Med. Chem.* **2004**, *47*, 2393.
3. The role of cocrystals in pharmaceutical science. N. Shan; M J Zawaratko *Drug Discov. Today* **2008**, *13*, 440.
4. Mechanism of Drug Combinations:interaction and network perspectives J. Jia; F. Zhu; X. Ma; Z. W. Coo; Y. X. Li; Y. Z. Chen *Nature Rev. Drug Discov.* **2009**, *8*, 111.
5. Combination Drugs: Innovation in Pharmacotherapy A. I. Wertheimer; A. Morrison. *P & T* **2002**, *27*, 44.
6. Method to improve therapeutic efficacy of radiolabelled drug. W. Krause US **20060127308**
7. Drug-food interactions and role of pharmacist. M. Y. M. Ismail *Asian J. Pharmaceut. Clinic. Res.* **2009**, *4(2)*
8. The patentability of chiral drugs post-ksr: the more things change, the more they stay the same. M. J. Sweet *Berkeley Technology Law Journal* **2009**, *24*,1.
9. Chiral Drugs. An Overview. L. A. Nguyen; H. He; C. Pham-Huay *Int. J. Biomed. Sci.* **2006**, *2*, 85.
10. Using Genetic Diagnosis to Determine Individual Therapeutic Utility. CT Kaskey *Annu. Rev. Med.* **2010**, *61*, 1.
11. Computational design of antibody-affinity improvement beyond in vivo maturation. S. M. Lippow; K. D. Wittrup; B. Tidor *Nature Biotechnol.* **2007**, *25*, 1171.