1

Modern Medicine and Pharmaceutics

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1. Introduction

There are evidences that people have been using medicine to cure illness from the early civilization in Africa, Asia and Europe. The wide varieties of treatments such as Shamanism, surgery and drug formulations have been practiced. The drug materials from the plants, animals, minerals were used for the medicinal purposes, are referred today as "Crude Drugs". As knowledge on disease and drugs is expanded further and more purified form of the materials were chosen to prepare further effective drugs and medicines. As the development of modern societies immersed in the world, two different philosophical approaches in the field of medicinal treatment came forward. In the Eastern societies such as in China and India, holistic approaches were adopted. In these societies, disease or illness is considered as an integral part of the body and can be corrected with the selected foods or formulation of crude drugs mainly derived from plants and a few from animals or minerals together with the body adoptation. But in contrast, in the Western society, disease is considered as the separate entity from the body and can be eliminated by surgery or using particular chemical substance. Especially in the western medicine, the practice of using purified form or pure chemical substances is developed. The knowledge on chemical sciences especially synthetic chemistry and purification techniques were rigorously developed to fulfil the need of chemical substance. This led to not only the foundation for the development of science and technology but also the concept of industrialization came forward.

In general, pure chemical substance is not administered directly to the disease condition to cure or treat the disease. Depending on the disease condition and chemical nature of the drug substance, several kinds of formulation and route of administration are in practice. Therapeutic effect of the drug substance will only be achieved, if the right chemical substance with sufficient amount be delivered in the targeted tissue sites for the sufficient length of time in the person having pathophysiological condition. Formulations play great roles in distributing drugs in the body. Moreover, according to the type and condition of the disease, same drug substance might provide separate therapeutic effects based on the types of formulation, route and interval of administrations. In general, the term 'drug' represents pharmacologically active chemical substance. Pharmaceutical sciences provide the

knowledge and technique to utilize the drug substance for the effective therapy. In recent years, because of the advancement in pharmaceutical sciences, several drug substances are better utilized for the health benefit. Pharmaceutical industries contributed enormously for the advancement of modern medicine together with the development of particular the formulation for desired route of administration in order to obtain optimum therapeutic value of the drugs substance.

2. Historical overview on the development of modern drugs

In fact, many of the drug substances which are used today commercially have certain historical links to the traditional uses. Among them, the history of morphine and acetyl salicylic acid (aspirin) are widely discussed and well documented.

There are evidences of using latex of opium plant (*Papaverum somniferum*) in Chinese traditional medicine, Ayurveda, and Ancient Greek medicine to relieve pain. The desire to obtain more effective and purer drug has always been remained as the deep thrust in human nature. The first report of morphine purification was made by Derosne in 1803 and further detail was published by Seguin in 1814. (Derosne, 1803; Seguin, 1814). A German pharmacist, Sertürner claimed the first purification of active compound from opium latex and published in 1805, later it was found that the isolated compound was not an alkaline narcotic component rather it was identified as meconic acid (Sertürner, 1805; 1806). On continuing, Sertürner extracted the opium poppy latex with hot water and precipitated with ammonia and obtained a pure crystalline compound having narcotic properties of opium (Sertürner, 1817). The compound was named as morphine (**1**) and structure was confirmed later. In 1874, Wright reported heroin (**2**), a diacetyl derivative of morphine (Wright, 1874), and it was commercialised by Bayer AG in 1898. Because of the strong narcotic properties, heroin was banned for the therapeutic use but morphine and codeine (**3**), another derivative of morphine, are still very important commercial drugs today after almost 200 years of their discovery (**Figure 1**).

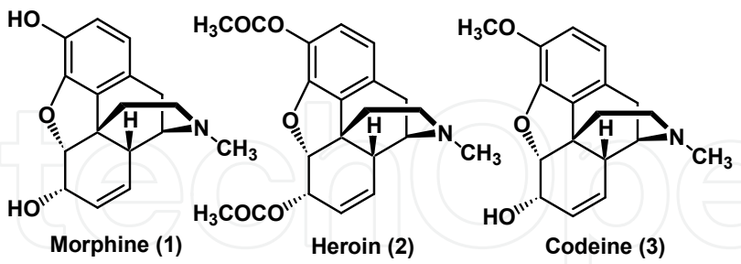

Fig. 1. Structure of morphine and its derivatives.

After extraction and purification of morphine, the technique was applied to isolate other important alkaloids and they were commercialized immediately. In 1817, Pelletier and co-worker reported emetine (**4**) from *Ipecacuanha* and strychnine (**5**) from *Strychnos* (Pelletier, 1817). In 1820, same group reported the isolation of quinine (**6**) from *Cincona* species (Pelletier, 1820) which was commercialized as the anti-malarial drug. Other important alkaloids such as brucine (**7**) and caffeine (**8**) in 1819, colchecin (**9**) in 1920, codeine (**3**) in 1833, atropine (**10**) in 1848 were isolated (Nicolaou & Montagnon, 2008). The complete structures of many of these compounds were confirmed later. Coniine (**11**) was isolated in

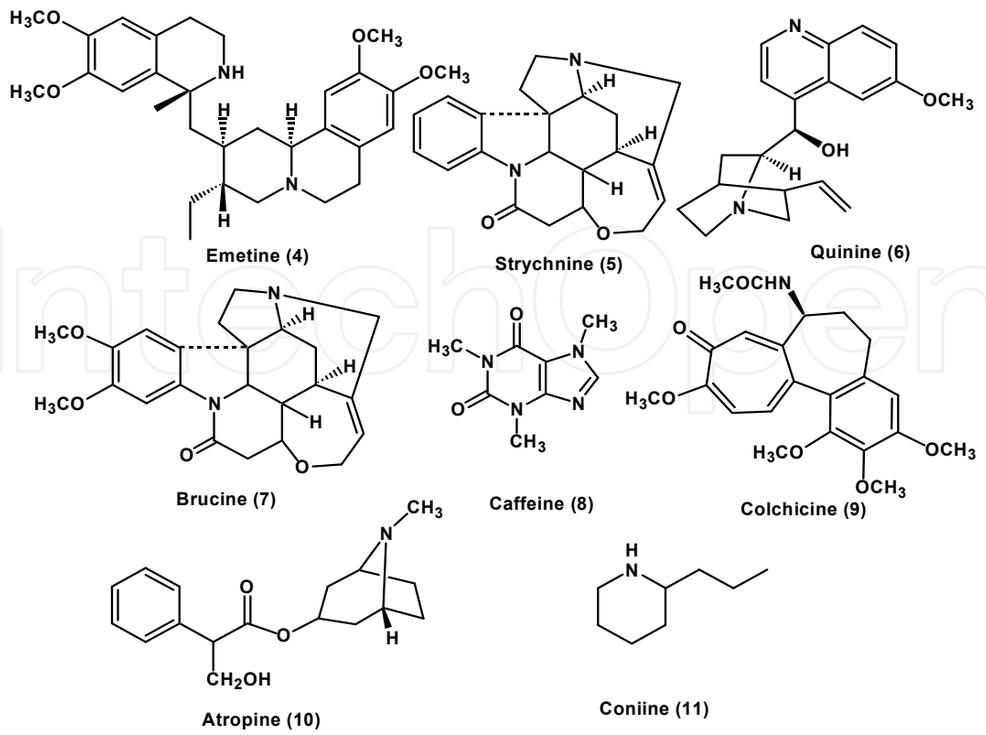

Fig. 2. Structure of alkaloids having therapeutic and commercial uses. Discovery of these alkaloids led to the foundation for the modern medicine and industrialisation.

1826, complete structure was elucidated in 1870 and later synthesized in 1881. All these drugs with almost of 200 years of history are still used in commercial scale (**Figure 2**) (Newman, 2010).

Another important modern drug with long history and widely discussed molecule is acetyl salicylic acid (aspirin) (**13**). In spite of development of several effective antipyretic drugs the importance of aspirin has never been diminished.

Acetylsalicylic acid (**13**), an acetyl-derivative of salicylic acid (**14**), is a mild, non-narcotic analgesic. It is useful in the relief of headache and muscle and joint aches. The drug works by inhibiting prostaglandins production which sensitizes nerve endings to pain. The discovery of aspirin (**13**) is linked to **14**, salicyl aldehyde (**15**) and salicin (**16**), a chemical component derived from the bark of Willow tree.

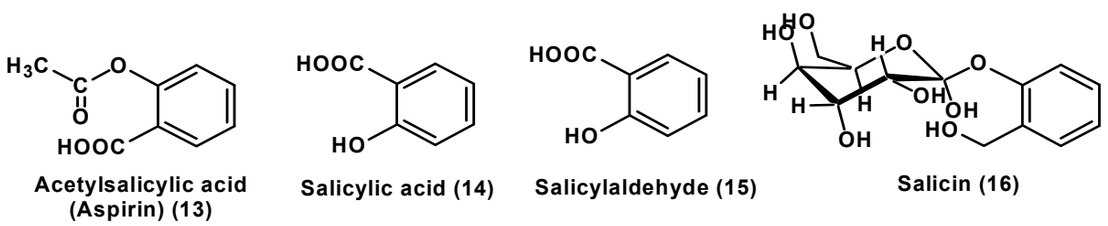

Fig. 3. Structure of aspirin and other related compounds. Salicin, a compound isolated from the bark of Willow tree led to the discovery of aspirin.

Hippocrates **(**460-377 B.C.), the father of modern medicine, described the prescription of using the powder made from the bark of the willow tree for the treatment of headaches, pains and fevers. By 1829, scientists discovered that the pain relieving compound as salicin (**16**) in willow plants. The active ingredient in willow bark was isolated by Johann Buchner, a tiny amount of bitter tasting yellow, needle-like crystals, which he called salicin. Two Italians, Brugnatelli and Fontana, had in fact already obtained salicin in 1826, but in a highly impure form. In 1829, Henri Leroux had extracted salicin, in crystalline form for the first time, and in 1839, Raffaele Piria succeeded in obtaining the salicylic acid by oxidation (Piria, 1839) (**Figure 3**). Although salicylic acid was found with analgesic and antipyretic properties, its strong side effect of stomach upsetting could not be utilized clinically. A French chemist, Charles Frederic Gerhardt in 1853, neutralized the side effect of salicylic acid by buffering it with sodium hydroxide (sodium salicylate) and acetyl chloride, creating acetylsalicylic acid. Gerhardt's discovery could not be commercialized (Gerhardt, 1853; Nicolaou & Montagnon, 2008).

In 1899, a German chemist, Felix Hoffmann, who worked for Bayer, rediscovered Gerhardt's formula. Felix Hoffmann made the formula for the treatment of his father who was suffering from the pain of arthritis. With good results, Bayer marketed the new wonder drug (Nicolaou & Montagnon, 2008). Aspirin was patented on February 27, 1900. The name Aspirin was given to- 'A' for acetyl, the "spir" for *Spiraea ulmaria* (source of salicylic acid) and 'in' for ending name for medicine.

Year	Drug substance	Therapeutic uses
1806	Morphine	Analgesic, sedative
1875	Salicylic acid	Analgesic, antipyretic
1884	Cocaine	CNS stimulant (serotonin-dopamin-norepinephrine reuptake inhibitor), local anesthetic
1888	Phenacetin	Analgesic, antipyretic
1889	Acetyl salicylic acid	Analgesic, antipyretic (cyclooxygenase inhibitor)
1903	Barbiturate	Sedative
1909	Arsphenamine	Treatment for syphilis and trypanosomiasis
1921	Procain	local anesthetics (sodium channel blocker)
1922	Insulin	Anti-diabetic
1928	Estron	Sex hormone
1928	Penicillin	Anti-biotic
1935	Sulphachrysoidin	Anti-bacterial
1944	Streptomycin	Anti-biotic
1945	Chloroquin	Anti-malarial
1952	Chloropromazin	Anti-psychotic (neuroleptic)
1956	Tolbutamide	Oral anti-diabetic
1960	Chlordiazepoxide	Tranquilizer
1962	Verapamil	Anti-hypertensive (calcium channel blocker)
1963	Propranolol	Beta-blocker (used for hypertension, anxiety and panic)
1964	Furosemide	Diuretics (congestive heart failure and edema)
1971	L-DOPA	Neurotransmitter (Parkinson's disease)
1975	Nifedipine	Calcium channel blocker (anti-hypertensive)
1976	Cimetidine	H_2-blocker (peptic ulcer)
1981	Captopril	Angiotensin-converting enzyme (ACE)-blocker (anti-hypertensive)
1981	Ranitidin	H_2-blocker (peptic ulcer)
1983	Cyclosporin A	Immunosupressive
1984	Enalapril	ACE-blocker (anti-hypertensive)
1985	Mefloquin	Anti-malarial
1986	Fluoxetin	Anti-dipressant (serotonin reuptake inhibitor)
1987	Artemisinin	Anti-malarial
1987	Lovastatin	Hypolipidemic (prevention of cardiovascular disease)
1988	Omeprazole	Proton pump inhibitor (Anti-ulcer)
1990	Ondansetron	5-HT3-Bolcker (anti-emetic)
1991	Sumatriptan	Anti-migraine headaches
1993	Risperidone	Anti-psychotic (Schizophrenia)

The list of drugs in the table was adopted from Böhm et al, 2002 with modification (Böhm et al, 2002).

Table 1. A list of some important modern medicines in chronological order of discovery with therapeutic uses.

In the beginning, aspirin was sold in the powder form but in 1915, the first aspirin tablets were marketed. Aspirin and heroin were once trademarks of Bayer. After Germany lost World War I, Bayer was forced to give up both trademarks as part of the Treaty of Versailles in 1919 (Belis, 2012).

In addition to morphine and aspirin, there are several other chemical substances which initiated the industrialization and changed our social structure due to the development of corporate culture and globalization trends for the discovery of modern medicine. A list of some important drugs with their therapeutic uses and chronological order of discovery are given in **Table 1.**

3. Pharmaceutical Industry

3.1 Development of pharmaceutical industry

Merck in Germany was possibly the earliest company founded in Darmstadt in 1668. In 1827, Heinrich Emanuel Merck began the transition towards an industrial and scientific concern, by manufacturing and selling alkaloids (Merck Group History, 2012). GlaxoSmithKline's origins can be traced back to 1715, it was only in the middle of the 19th century that Beecham became involved in the industrial production of medicine, producing patented medicine from 1842, and the world's first factory for producing only medicines in 1859 (GSK History, 2012).

In the USA, Pfizer was founded in 1849, by two German immigrants, initially as a fine chemicals business. They expanded rapidly during the American civil war as demand for painkillers and antiseptics rocketed (Pfizer History, 2012). Whilst Pfizer was providing the medicines needed for the Union war effort, a young cavalry commander named Colonel Eli Lilly was serving in their army. A trained pharmaceutical chemist, Lilly was an archetype of the dynamic and multi-talented 19th century American industrialist, who set up a pharmaceutical business in 1876 and was a pioneer of new methods in the industry, being one of the first to focus on R&D as well as manufacturing.

Pharmaceutical industries grew rapidly in number and size after the advancement of basic knowledge on the isolation and purification of chemical component from the crude drugs. In the meantime, it encouraged to the development of synthetic chemistry. The pharmacological properties of pure compound obtained either from isolation from natural resources or synthesized in the laboratories were studied. The public and private investments were carried on pharmaceutical industry and drug market expanded rapidly. The pharmaceutical industries established in the early history are still continuing today and their economic impact in the development of country is extremely crucial. Some of the pharmaceutical industries which initiate some important drugs in the early development of modern medicine are listed as in the **Table 2.**

3.2 Economic impact of the pharmaceutical industry

Today, the revenue collection by big pharmaceutical industry is bigger than that of national budge of many small and poor nations. Based on the revenue collection, top ten pharmaceutical industries are listed in **Table 3** (Roth et al., 2010)**.** Because of the huge investment of pharmaceutical industries, it led to open the research and development of

Year	Drug substance	Commercial resource	Producer
1826	Morphine (natural compound)	Plant	Merck
1899	Acetyl salicylic acid		
	Aspirin (synthetic analogue)	Plant	Bayer
1941	Penicillin (natural compound)	Microbe	Merck
1964	Cephalothin (semi synthetic)	Microbe	Eli Lilly
1983	Cyclosporin A (natural compound)	Microbe	Sandoz
1987	Artemisinin (natural compound)	Plant	Baiyushan
1987	Lovastatin (natural compound)	Microbe	Merck
1988	Simvastatin (semi-synthetic)	Microbe	Merck
1989	Pravastatin (semi-synthetic)	Microbe	Snakyo/BMS
1990	Acarbose (natural compound)	Microbe	Bayer
1993	Paclitaxel (natural compound)	Plant	BMS
1993	FK506 (natural compound)	Microbe	Fujisawa
1994	Fluvastatin (synthetic analogue)	Microbe	Sandoz
1995	Docetaxel (semi-synthetic)	Plant	Rhone PR
1996	Topotecan (semi-synthetic)	Plant	SKB,Pharmacia-Upjohn
1996	Miglitol (synthetic analogue)	Plant, Microbes	Bayer

This table is taken from Grabley & Thiericke, 1999 with modification.

Table 2. Chronological order of commercialization of some important modern drugs.

further understanding in human biology and medicine. In the meantime, it is also partly responsible to widen the gap between rich and poor which made unstable and unhappy society. In term of wealth, these top pharmaceutical industries are able to challenge the whole nation and have power to change the social structure.

Top 10 pharmaceutical industries account for 59.40% of total revenue of the top 50 pharmaceutical companies. In the same top 20 pharmaceutical industries accounts for 81.53% of total revenue of the top 50 pharmaceutical companies. Therefore the global drug markets are dominated by a few large pharmaceutical industries. Several small pharmaceutical industries in developing countries are only able to produce generic drugs and their impact in the global market is negligibly small.

Pharmaceutical Industry		Revenue (Millions USD)
1.	Pfizer	58,523
2.	Novartis	44,420
3.	Merck & Co.	39,811
4.	Sanofi-Aventis	37,403
5.	Glaxo-SmithKline	36,156
6.	AstraZeneca	32,515
7	Johnson & Johnson	22,396
8.	Eli Lilly & Co	21,685
9.	Abbott Laboratories	19,894
10.	Bristrol-Myers Squibb	19,484
11.	Teva	16,121
12	Takeda Pharma	14,829
13.	Bayer Schering	14,485
14.	Boehringer_Ingelheim	12,883
15.	Astellas	11,161
16.	Daiichi-Sankyo	10,794
17.	Eisai	8,542
18.	Otsuka Pharmaceutical	8,440
19.	Gilead Sciences	7,390
20.	Mylan	5,404

Table 3. Top twenty pharmaceutical companies based on 2010 revenues (in million USD).

3.3 The most industrialized drugs

Each year new and more effective drugs come into the market and they replace previous drugs. There is hard completion among the pharmaceutical industries to make more profit for their industry. In addition, some drugs because of unreported side effects, they have to be withdrawn from the market. Therefore it is difficult to stand top selling drug of all the time. According to revenue collection, a list of top ten selling drugs is listed in **Table 4** (Top ten selling drug, 2011). The revenue obtained by selling single drug is much higher than that of a national budget of a small and poor country.

Drug name	Treatment for	Produced by	Sale (billions)
1. Lipitor (Atorvastatin)	Statin i.e., a cholesterol-lowering drug. Lowers LDL cholesterol and triglyceride levels	Pfizer	13.5
2. Plavix (Clopidogrel)	Inhibits blood clots in arteries such as coronary, carotid and peripheral arteries of the limbs and prevents ischemia and thrombosis	Bristol-Myers Squibb & Sanofi-Aventis	7.3
3. Nexium (Esomeprazole)	A proton pump inhibitor (H^+/K^+-ATPase enzyme) which is used in the treatment of dyspepsia, peptic ulcer disease, gastro esophageal reflux disease.	AstraZeneca	7.27
4. Seretide/ Advair (Fluticasone+ salmeterol) -	It is a bronchodilator which relaxes the muscles in the walls of the small air passages in the lungs.	GlaxoSmith Kline	7.1
5. Enbrel (Etanercept)	A tumor necrosis factor (TNF)-blocker, is widely used in immune diseases (rheumatoid arthritis, juvenile idiopathic arthritis, ankylosing spondylitis, psoriatic arthritis, plaque psoriasis) and reduce inflammation.	Amgen and Wyeth	5.3
6. Zyprexa (Olanzapine)	An atypical antipsychotic used in the treatment of schizophrenia, depressive episodes associated with bipolar disorder, acute manic episodes and maintenance treatment in bipolar disorder.	Eli Lilly	5.3
7. Risperdal (Risperidone)	Risperidone is an antipsychotic used to treat schizophrenia including adolescent schizophrenia, the mixed and manic states associated with bipolar disorder, and irritability in children with autism.	Janssen-Cilag	4.9
8. Seroquel (Quetiapine)	An antipsychotic used in the management of schizophrenia and bipolar I disorder, including insomnia and anxiety disorders.	Astra Zeneca	4.6
9. Singulair (Montelukast sodium)	A leukotriene receptor antagonist used in the treatment of asthma and to relieve symptoms of seasonal allergies.	Merck & Co., Inc	4.5
10. Aranesp (Darbepoetin alfa)	A synthetic form of erythropoietin which stimulates erythropoiesis to treat anemia, commonly associated with chronic renal failure and cancer chemotherapy.	Amgen	4.4

Revenue collection is expressed as in 1 year (billion).

Table 4. Top ten pharmaceutical products world wide based on yearly revenue collection.

3.4 Global pharmaceutical market

The global pharmaceutical market grew to $808 billion in 2009, at a compound annual growth rate of 9.3% between 1999 and 2009. Year-on-year growth in the global pharmaceutical market decreased to 4.6% in 2009, largely as a result of cost containment in the US and major European markets and the impact of several blockbuster patent expiried in 2008 and 2009. Almost 125 pharmaceutical drugs generated more than 1 billion USD in global sales. The leading therapy areas by global pharmaceutical sales in 2009 were CNS with a 15.8% market share and cardiovascular with 14.5%. The CNS pharmaceutical market will decrease from $127.8 billion in 2009 to $118.5 billion in 2014. The major five Germany, France, Italy, Spain and the UK, together accounted for over 60% of all European pharmaceutical sales. The global pharmaceutical market is expected to earn over a trillion dollar in revenues by 2012 according to "Global Pharmaceutical Market Forecast to 2012". These include the shift of growth from the developed markets to the emerging ones, increasing focus on biotech-based drugs, fewer new drug approvals, and a strong growth in the prevalence of generics (Global market, 2012).

4. Role of pharmaceutical technology

4.1 Dosage form of modern medicine

In general, drugs are not administered as pure chemical substance alone rather given formulated preparation as medicines. With appropriate additives or excipients in the formulation, drug is administered to human body. The main objective of the using additives to prepare various dosage forms is to obtain the optimum therapeutic action. Dosage forms also contributed for the development of modern pharmaceutical industry. Currently available important dosage forms are shown in **Table 5** (York, 2007).

Route of administration	Dosage forms
Oral	Tablets, capsules, powder, granules, emulsion, suspension, syrup, solution
Topical	Cream, pastes, lotions, ointments, gels, solution, transdermal patches, topical aerosol
Rectal	Ointment, Suppositories, creams, powder, solutions
Parenteral	Injections (solution, suspension emulsion), implant
Inhalation	Aerosols, spray, gases
Nasal	Solution, inhalation, spray
Eye	Solution, ointment, cream
Ear	Solution, suspension, ointment, creams

Table 5. Currently available some important doses form of the modern medicines.

During early development of drugs, most of the drugs given to patient were in the powder form and route of administration was oral. It was difficult to administered right amount. The first aspirin powder was formulated in the tablet form. This gave new direction to the pharmaceutical industries. Today, more and more patient compliance adopted and choice of formulation is based on the patient interest. The flavour was introduced on the drug to make more palatable. Drug compound in the tablet or in the capsules is coated in order to make palatable and slow dissolution to carry the drug substance into the targeted sites.

Same drug can be administered by different route to obtain different therapeutic effects. For example drug substance administered *i.v.* route comes in blood circulation within a few seconds, while it might take minutes to hours if it is taken by oral route depending on the type of formulation. Some coated tablets or capsules deliver the drugs into the blood circulation after several hours. Therefore the design of formulation and selection of route can provide the controlled bioavailability of the drugs. The knowledge of pharmaceutical technology optimized the therapeutic value of the drugs and reduced the side effect. The major routes used for the administration of drugs are shown diagrammatically in **Figure 4**.

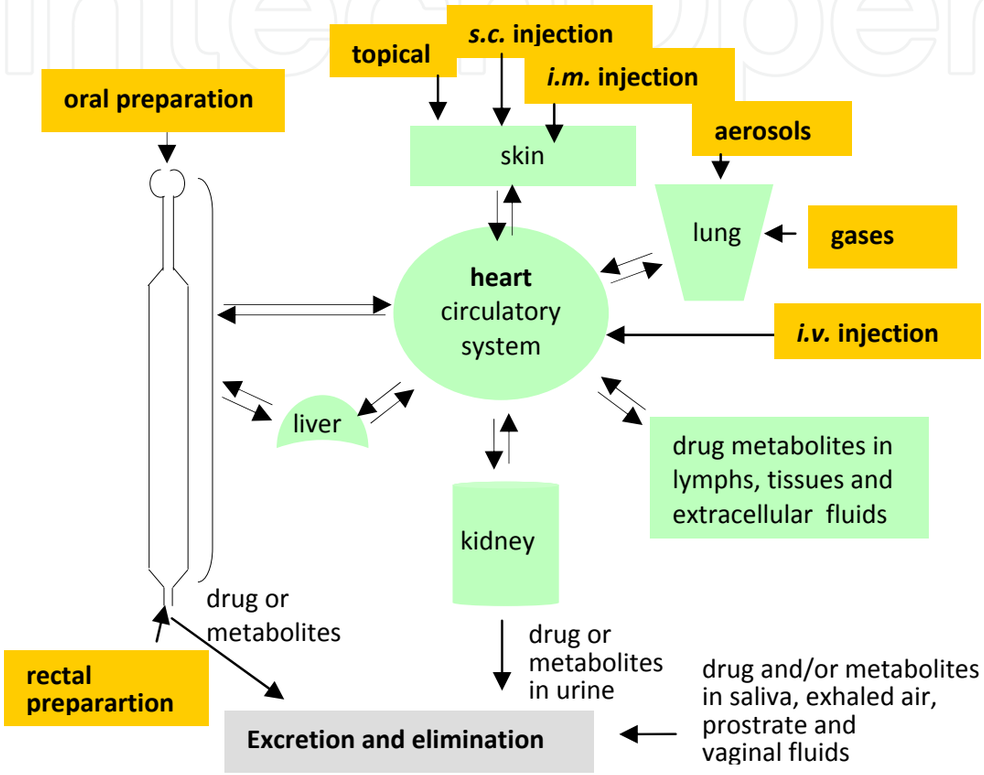

Fig. 4. Schematic diagram showing major routes of administration in the human body and drug metabolism.

4.2 Drug target

In general, drug formulation is administered through one of the routes into the human body. To obtained the therapeutic effect of the drug, all pharmacological properties of the drugs have to be explained. The drug action mechanisms of most of the modern drugs are well explained otherwise it would not be approved by the authority. The stability and activity of the drugs are thoroughly monitored from the point of administeration to the point of elimination. In order to understand the drug action, the action of drugs on particular receptor or enzymes is studied. In spite of growing knowledge on gene analysis and understanding, almost half of the drugs efficacies are targeted to the receptor on the cells. The drugs bind directly or activate certain protein to bind on the receptor molecule which results the cascade of the molecular activity inside the cells to cure disease. Some of

the pathophysiological conditions appear because of the excessive or decreased production and activity of certain enzyme. Thus drugs are targeted to particular enzyme activity. Almost close to one third of the drugs available today are targeted to enzymes. Some major targets of the modern drugs for their action are shown in **Figure 5** (Drews, 2000). Understanding on drug target to DNA, nuclear receptor and ion channel are relatively low at present, however, it is expected to increase in the future.

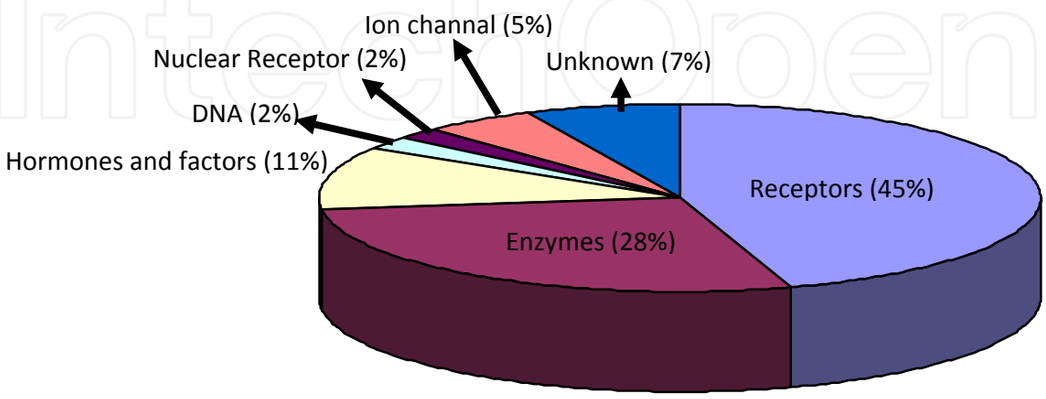

Fig. 5. Biochemical classes of drug targets of current therapies.

4.3 Drug discovery

Drug discovery project is a great challenge of knowledge, human resources and money. In order to make one successful medicine, generally it needs up to 14 years to complete all steps if all the steps remain successful according to our present knowledge. In mean time it might cost up to a total of 800 million US dollar investment. A general outline of drug discovery strategy is presented in **Figure 6**. According to the current trend, a new drug is hardly marketed even after detail analysis of almost 100000 small molecules in initial study.

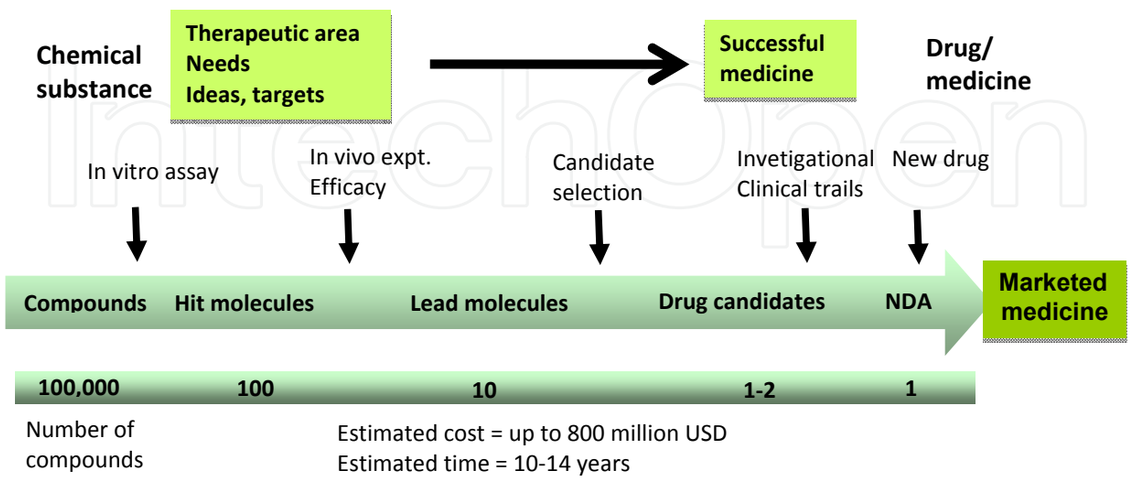

Fig. 6. Schematic diagram of drug discovery strategy.

In spite of huge effort there is still high percentage drug candidates fails to reach as new drug agent (NDA). There are several factors which contribute to the failure of drugs. In general most of the drug candidate showing potent pharmacological property in *in vitro* and animal experiment fails during the translation to human. It is mainly due to difficulty to study the pharmacokinetic properties in human. A general trend of failure rate during the drug discovery is presented in **Table 6.**

Failure rate	Percentage
Poor pharmacokinetic properties in human	39
Clinical efficacy	29
Toxicity and adverse effects	21
Commercial limitations	6

Table 6. Failure rate (%) of drug development process at different stages.

4.4 Preclinical strategy of drug discovery

Almost 70 to 80% of the total budget and two third of the total time period in the drug discovery project are consumed by the clinical trial. Therefore in order to enhance the success rate, preclinical strategy should be strong, effective and logical. A diagrammatic outline for preclinical strategy is given in **figure 7.**

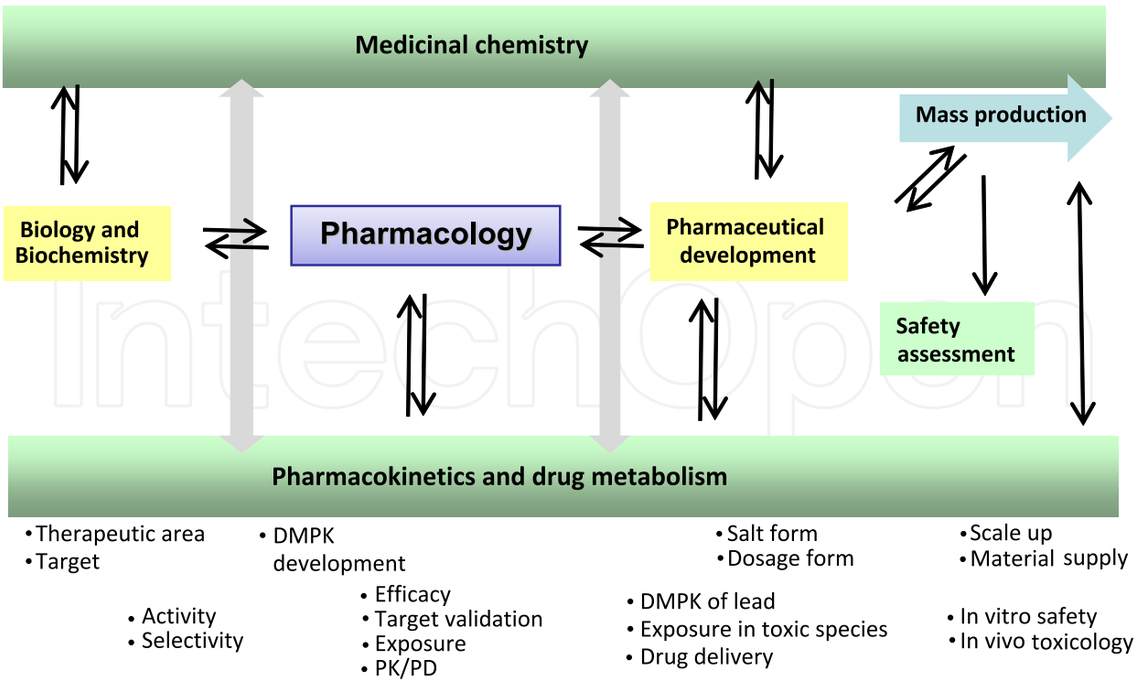

Fig. 7. Diagrammatic representation of preclinical strategy in drug development.

4.5 Evaluation for bioavailability

In addition to technological advancement, most of the drugs are taken from oral route and dosage form is tablet. Even a good drug cannot exert its therapeutic beneficial effects if it is not **reaching its target site** in the body at an **appropriate concentration** for a **sufficient length of time**. Swallowing a pharmacologically active chemical compound in the tablet or any other form by the patient might not be enough to obtain medicinal value.

Several other factors have to be considered:

- In the stomach, the tablet might not be disintegrated, the drug might not be released from the dosage form
- Drug might not be soluble into the gastrointestinal fluids
- If drug is not soluble, in general, it will not be absorbed and will not be able to reach the targeted site passing through the epithelial membranes of gastrointestinal tract
- Some drugs chemically or enzymatically degrade in the stomach or might have gastric irritation
- In some case the drug dissolves very fast and is absorbed very quickly from the gastrointestinal tract, in spite of high plasma concentration peak and fast elimination, such drug type might have short duration of action so drug has to taken very frequently and leading to strong fluctuations in plasma concentration.
- Some drugs can not be delivered by the oral route as they are metabolized in the intestine and/or liver, before reaching to systemic circulation
- Some drugs may have strong side effect profile, which may prohibit efficient treatment.

Drugs administered through the oral route must pass through the intestinal barrier to reach into the circulatory system. Therefore the drugs which are easily absorbed in gastrointestinal track with high permeation and remains stable during circulation in different tissue especially in the liver and kidneys provide optimum bio-availability. In general, the chemical nature of the drugs determines its bioavailability. Bioavailability of the drugs can be predicted mainly by the molecular size and hydrogen bonding capacity (Lipinsky Rule of 5).

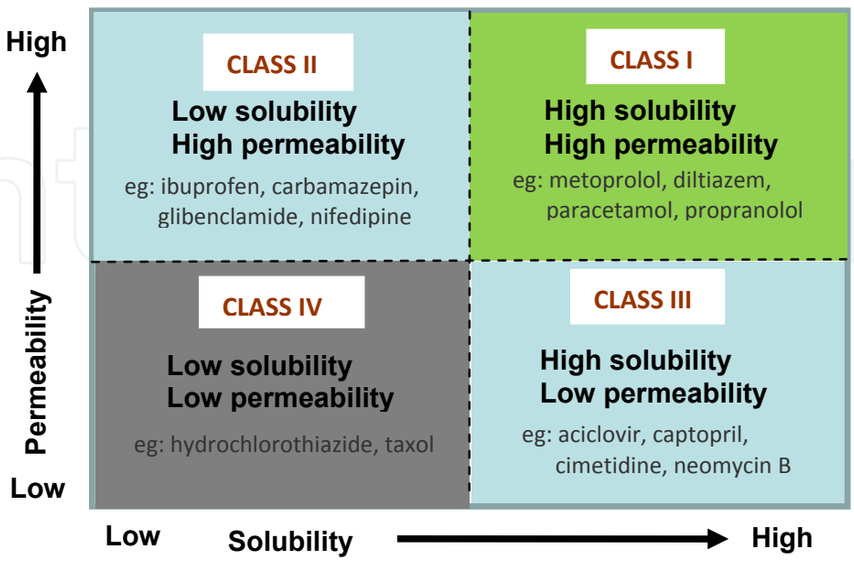

Fig. 8. Classification of drugs based on the solubility and permeability.

Based on the permeability and solubility, the drug substance can be classified into four groups **(Figure 8)**. In case of Class I drugs (high solubility and high permeability) the desired bioavailability can easily be reached and the role of formulation will be minimum. In case of Class IV drugs (low solubility and low permeability), it is very difficult to attain sufficient bioavailability. But in case of Class II or Class III drugs because of the improvement of formulation, bioavailability can be enhanced by increasing solubility or permeability.

For those drug candidates having low solubility or low permeability, by the simple structure modification or use of additives the bioavailability can be increased. A flow chart scheme to enhance the bioavailability is give in **Figure 9.**

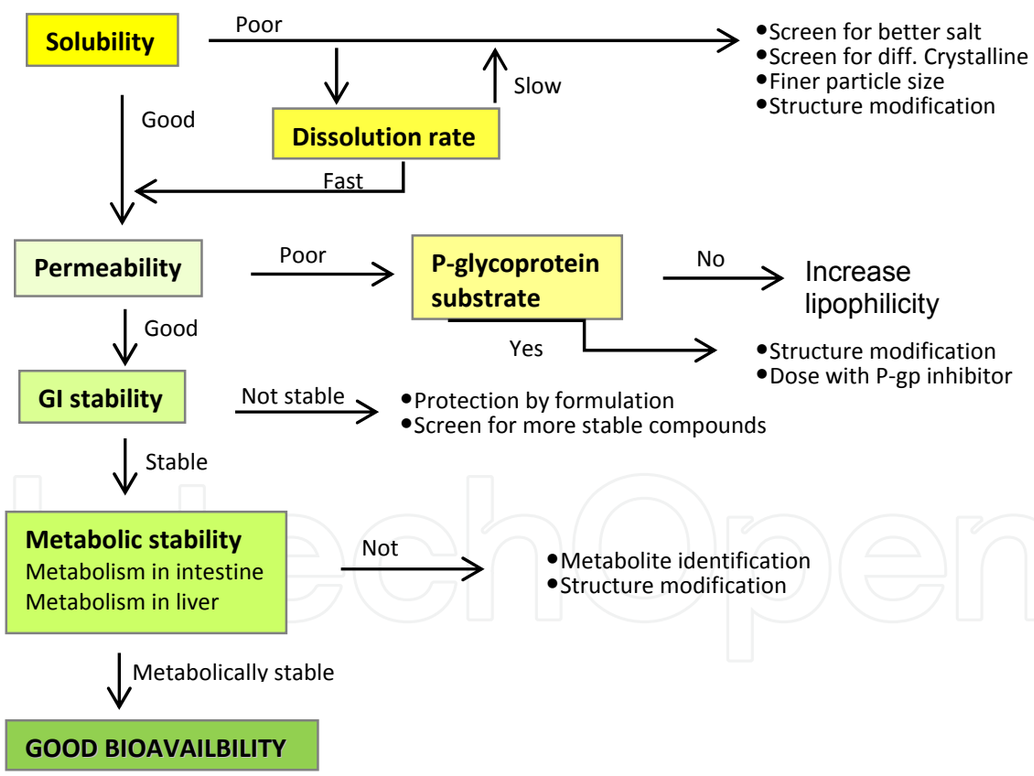

Fig. 9. Flowchart showing to increase the bioavailability.

4.6 Multifunctional pharmaceutical nano-carriers drug delivery

Drug discovery is very expensive and time consuming process. In addition to this, it is not sure that the successful candidate will appear at the end. Therefore the research on development of drug, especially the delivery system to enhance the bioavailability will make more fruitful therapeutic outcome. The development of new drug-delivery technologies also made the existing drug more useful. In the present book, the nano-carrier as delivery system is discussed in brief.

Nano-carrier drug delivery is mainly focused to those drugs which are potent pharmacologically but it could not be utilized fully because of toxicity (side effect) or less efficacy due to low bioavailability. In general, less soluble or less permeable drugs can not reach to optimum concentration in the systemic circulation. Therefore these classes of drugs are easily packed into the lipid nano-particles in the form of liposome or micelle. Because of the drug encapsulation inside the lipid molecule cluster, the physical properties of the drug molecules dominated by the lipid cluster particle and therefore lipid molecule cluster serves as nano-carrier and drug molecule can be delivered to the targeted site. Nano-particle of lipid encapsulated with drug molecules can easily be solubilised and penetrated into the cell.

There are already several drugs based on nano-carrier delivery formulations. A good example of nano-carrier delivery is liposomal formulation of amphoteracin B. Amphoteracin B has a broad spectrum of activity and is a drug of choice for life threatening invasive fungal infections, including disseminated candidiasis, aspergillosis and protozoal infection affecting the internal organ (*Viscerel leishmaniasis*). However, its use is compromised by associated adverse side effects.

But because of nano-carrier delivery liposomal formulation three products such as **AmBisome** *(*a small unilameller liposomes formulation with the size of 80 nm, composed of hydrogenated soy phosphatidyl choline, cholesterol, disteroyl phosphatidyl glycerol and amphotericin B in a 2:1:0.8:0.4 molar ratio with α-tocopherol), **Abelecet** (composed of amphotericin B, dimyristoyl phosphatidyl choline and dimyristoyl phosphatidyl glycerol in a 1:1 drug-to-lipid molar ratio with sizes is up to 1.6-11 μm) and **Amphotec** (containing amphotericin B in a complex with cholesteryl sulphate at a molar ration (1:1) with the particle size of 100-140 nm) are commercialized. Lipid-based nano-carrier formulations are found to be superior in clinical efficacy.

Based on the lipid type and physical condition, the size of particles, nature of the particles can be designed. In addition one or more desired ligands can me inserted to drug encapsulated nano-particle which allows the drug molecule to be delivered into the targeted sites in controlled manner. The additional ligands might be monoclonal antibody (binds to specific site), polyethylene glycan (remains longer time in circulation), binding with heavy metal (allows to trace the particle), cell penetrating peptide (allows the particle to penetrate into the cells), DNA binding (allows the DNA to be delivered) and magnetic nano-carrier (to trace the particles) (**Figure 10**).

These one or more ligands can be incorporated in the same particles therefore multi-functions of nano-carriers can be achieved together with the delivery of the drugs. Already

the first generation of multifunctional nano-carriers is developed. For example, the nano-carrier type (B+C) having immunospecific and PEG ligands, should have ability to carry the drug molecule to the immunospecific cells where ligand binds and deliver the drugs and PEG allows the nano-carrier to remain longer hours in the systemic circulation (**Figure 11**).

The future medicine will be the nano-particles packed with several ligands which will be able to carry the drug molecules to particular targeted cell with monoclonal antibody and penetrated the cell membrane and required drug can easily be delivered without interfering with the circulatory system and other tissues or biomolecules (**Figure 12**). Such smart drug delivery will reduce the side effect and enhance the drug efficacy. This will be the foundation of 'Intelligent Therapeutics' of future drug formulation.

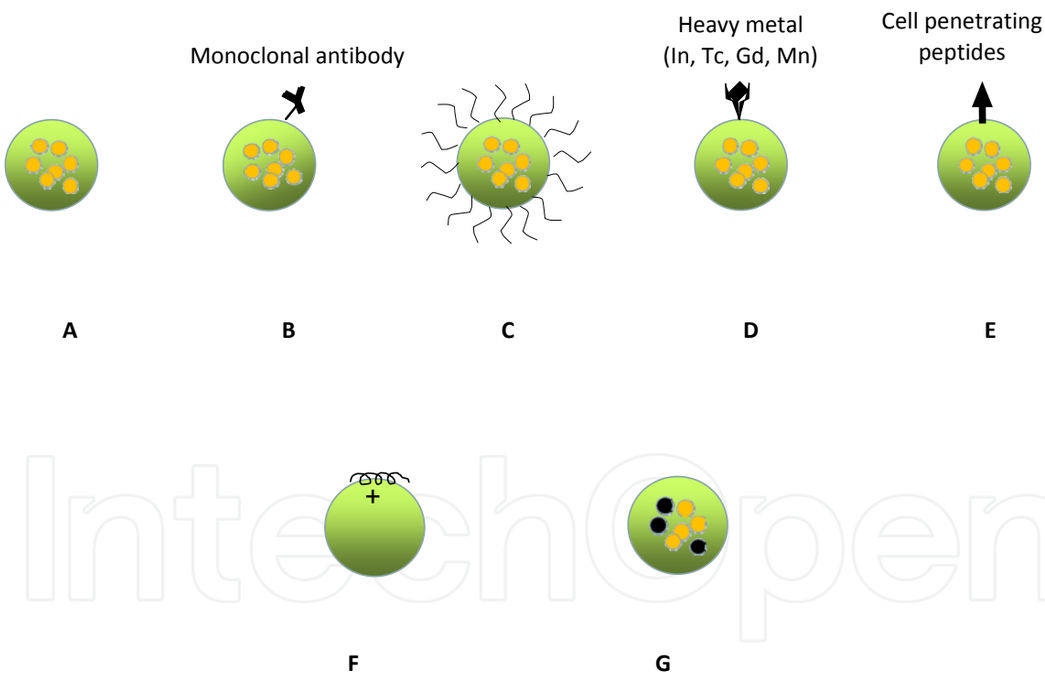

Fig. 10. Diagrammatic representation of nano-carrier designed for the pharmaceutical purpose. **A**: Traditional nano-carrier; **B**: Targeted nano-carrier (Immunospecific); **C**: Long circulating nano-carrier (PEG protected); **D**: Contrast nano-carrier (for imaging); **E**: Cell-penetrating nano-carrier; **F**: DNA-carrying nano-carrier; **G**: Magnetic nano-carrier.

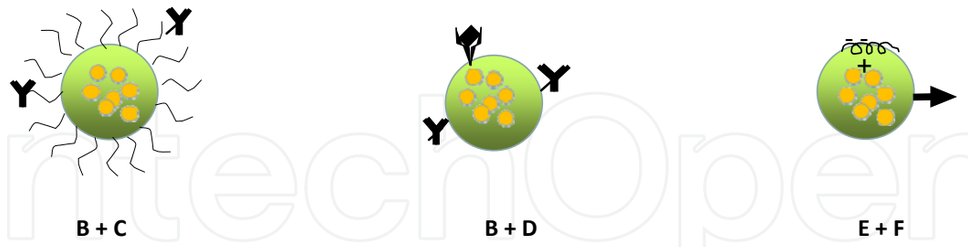

Fig. 11. Diagrammatic representation of first generation multifunctional nano-carriers.

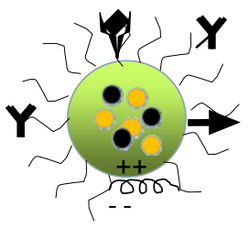

Fig. 12. Dream multifunctional nano-carrier.

5. Conclusion

Happy life, healthier life and long life have been remained as the goal of human life philosophy. Modern medicine, at least in a part, contributed to humanity to become more prosperous and more civilized. In fact, in searching of more effective medicine in the quest of healthier and longer lives, it led to the development of basic chemistry and human biology. The traditional agricultural based human demographical society transformed to industrialisation and pharmaceutical industries have great role for the globalization of the world. Moreover, modern medicine discovery and development not only supported to healthier and longer life but also encouraged to prosper the development of the modern science and technology.

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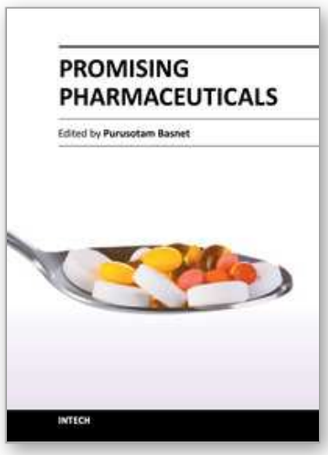

Promising Pharmaceuticals

Edited by Dr. Purusotam Basnet

ISBN 978-953-51-0631-9
Hard cover, 148 pages
Publisher InTech
Published online 23, May, 2012
Published in print edition May, 2012

From the dawn of civilization, humans have been dreaming of happy, healthy and long-life. Our life expectancy is twice longer than 100 years ago. We know more about the diseases. Therefore we have developed new drugs to fight against them. The demand for drugs was so high that we developed Pharma industries. Although Pharma industries took responsibility of producing the needed drugs and gave us a quality of life, misuse of drugs brought further complication. Therefore, discovery, production, distribution, and the phase of administration of patients' quality assurance has to be controlled with a technological procedure and tight regulations to make the system as effective as possible for the benefit of human health. Our book provides selected but vital information on the sources, tools, technologies and regulations regarding the current status of medicine development.

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