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Τριμηνιαία έκδοση με θέματα Φαρμακευτικών Επιστημών

Τόμος 24, Τεύχος ΙΙΙ, Ιούλιος - Σεπτέμβριος 2012

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ΖΙΤΑ ΣΥΝΕΔΡΙΑΚΕΣ
ΚΑΙ ΤΟΥΡΙΣΤΙΚΕΣ ΕΠΙΧΕΙΡΗΣΕΙΣ ΑΕ
1ο χλμ Παιανίας - Μαρκοπούλου
19002, Παιανία, Ελλάδα
Τηλ: +30 211 100 1770-71
E-mail: info@zita-congress.gr

Hellenic Society of Medicinal Chemistry Management Office
ZITA CONGRESS SA
1st klm Peanias-Markopoulou
19002, Peania, Greece
Tel: +30 211 100 1770-71
Email: info@zita-congress.gr

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Το τεύχος αυτό είναι το δεύτερο της νέας περιόδου της "Φαρμακευτικής" και ελπίζουμε να έχει την ανάλογη θετική απήχηση που συνόδεψε το πρώτο τεύχος.

Με χαρά θα θέλαμε να σας ενημερώσουμε ότι ενεργοποιήθηκε εκ νέου η συνεργασία του περιοδικού με τις βάσεις δεδομένων EMBASE και Scopus του εκδοτικού οίκου Elsevier. Ηδη τα άρθρα που δημοσιεύτηκαν στο πρώτο τεύχος έχουν συμπεριληφθεί στους καταλόγους και εμφανίζονται στη σχετική ιστοσελίδα (www.scopus.gr). Η αυξημένη αναγνωρισιμότητα της "Φαρμακευτικής" επιφορτίζει και εμάς αλλά και τους συγγραφείς των άρθρων με μεγαλύτερες ευθύνες για την ποιότητα του περιοδικού. Με τη στήριξή σας θα συνεχίσουμε τις προσπάθειες μας .

Αγαπητοί αναγνώστες

Πριν λίγες ημέρες ο φαρμακευτικός χώρος έχασε ένα άξιο μέλος του, έναν ακούραστο εργάτη της Φαρμακευτικής Επιστήμης, δάσκαλο και συνάδελφο πολλών από εμάς που αποτελούμε τη Συντακτική Επιτροπή της "Φαρμακευτικής". Έφυγε από κοντά μας πλήρης ημερών ο ομότιμος καθηγητής Σκεύος Φιλιάνος. Ως ελάχιστο φόρο τιμής στο δάσκαλό μας, που σημάδεψε με την ήρεμη και σεμνή παρουσία του την νεώτερη ιστορία του Τμήματος Φαρμακευτικής του Πανεπιστημίου Αθηνών, το παρόν τεύχος αφιερώνεται στη μνήμη του.

Η Συντακτική Επιτροπή

ΑΡΘΡΟ ΕΠΙΣΚΟΠΗΣΗΣ REVIEW ARTICLE
ΦΑΡΜΑΚΕΥΤΙΚΗ 24, ΙΙΙ, 44-56, 2012 PHARMAKEFTIKI 24, III, 44-56, 2012

Pharmaceutical Industry and Green Chemistry: New Developments in the Application of Green Principles and Sustainability

Athanasios Valavanidis* and Thomais Vlachogianni
Department of Chemistry, Faculty of Natural Sciences, University of Athens, University Campus Zografou, 15784 Athens, Greece

Summary

"Green or Sustainable Chemistry" and "Green Engineering" are now universally accepted as terms to describe the movement towards more environmentally acceptable chemical processes and industrial products. In the last decade the most important chemical industries have been influenced by Green Chemistry and Green Engineering principles. The changes introduced in the chemical industry towards "greener" raw materials, alternative organic synthetic methods, biocatalysis, less use of toxic organic solvents, higher yields and less waste, focused primarily on the economy of industrial processes, but also on the protection of workers and consumers and minimization of environmental pollution. The pharmaceutical industry is very responsive to these "greener" industrial alternatives. Drug manufacturing industries look towards lowered regulatory risk, smaller environmental footprint and manufacturing technologies with green credentials. They would like to promote an environmentally friendly "image" and responsibility towards modern society. The pharmaceutical industry is embracing more and more "green" processes and innovative technology operations. The research departments of many big drug manufacturers in the developed countries are advancing new "green" methodologies, biocatalysis reactions, less solvents and cuts in waste production, and at the same time introduced safety and health regulations to protect their workers. Safety, Efficiency, Reliability and Economy are the four pillars of change and their promotion is considered as a competitive advantage. In this paper we present a comprehensive review of the latest trends in the pharmaceutical industry in promoting and applying the fundamental principles of Green Chemistry and Green Engineering for sustainable development

Key words: Pharmaceutical industry, green chemistry, green engineering, toxic solvents, biocatalysis, waste reduction, new synthetic routes

Introduction. Can the Pharmaceutical Industry Embrace Green Chemistry?

Although the seeds of "Green and Sustainable Chemistry" and "Green Engineering" have been around for some time, the collaborative efforts (between industry, academia, government and environmental groups) were lacking. This collaboration was initiated 20 years ago and encouraged new manufacturing principles and marketing of commercially successful green and sustainable products. Industry, academic institutions (universities and research institutes) and governments teamed up to find new solutions to old problems, not only in manufacture but also for safer consumer products. The goals were obvious, initiating and promoting the collective know-how and deliver technological advances with better financial cost. But at the same time showing that "green' products are better investment for a sustainable future. The most important aim in the present period towards sustainability is to minimise the use of valuable natural resources (energy, water etc) of the planet and facilitated the cooperation of all stakeholders with green innovations and environmentally benign products.[1-3] .

The Pharmaceutical industry is the most dynamic part of the chemical industry. It is in the forefront for big changes towards "greener" feedstocks, safer solvents, alternative processes and innovative ideas. All these changes will increase the environmental credentials of the pharmaceutical industry, but at the same time will cut down cost and materials for the manufacturing operations making a step in the right direction of sustainability.[4,5]

* *Corresponding author: Athanasios Valavanidis. e-mail: valavanidis@chem.uoa.gr*

The pharmaceutical industry for years was embracing more and more "green" processes and technology operations. The research departments of many big drug manufacturers in the developed countries made many advances for new methodologies, better biocatalysis reactions, less solvents and cuts in waste production. Researchers noticed that it took several years for pharmaceutical companies to translate green principles into measurable goals for environmental sound research, development and production.

Among industrial enterprises drug manufacturers introduced rigorous safety and health regulations to protect their workers and environmental criteria for their products. Safety, Efficiency, Reliability and Economy are the four pillars of change and their promotion is considered as a competitive advantage, better environmental credentials and economical benefits.[6,7]

Global Trends for the Pharmaceutical Industry in the Last Decade

The global spending on prescription drugs has increased substantially the last decade. In 2006, global spending on prescription drugs topped $643 billion, even as growth slowed down in Europe and North America. Statistical data showed that the United States of America (USA) accounts for almost half of the global pharmaceutical market, with $289 billion in annual sales followed by the EU and Japan. Emerging markets such as China, Russia, South Korea and Mexico outpaced that market, growing at a huge 81%. All pharmaceutical industries showed a positive profit growth (4-6%). In 2010 the global pharmaceutical market was worth $825 billions. In the annual Fortune 500 survey, the pharmaceutical industry topped the list of the most profitable industries, with a return of 17% on revenue. It is well known that the pharmaceutical industry invests heavily on research for new drugs. In 2009, it contributed for research, development and investment $66.3 billions. [8,9]

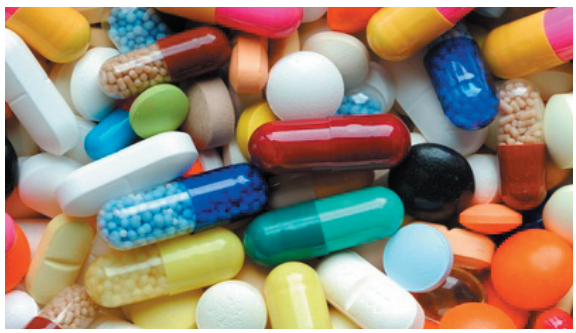

Figure 1. *Drug manufacturing is the most profitable chemical industry*

TABLE 1. MAJOR PHARMACEUTICAL COMPANIES (ANNUAL FOR 2004).

Company	HQ location	Revenue of pharmaceutical segment, mln USD ($)	Total sales, mln USD ($)	Share of pharmaceutical segment, %
Pfizer	NY, U.S.	46,133	52,516	87.85%
GlaxoSmithKline	UK	31,434	37,324	84.22%
Johnson & Johnson	NJ, U.S.	22,190	47,348	46.87%
Merck	NJ, U.S.	21,494	22,939	93.70%
AstraZeneca	UK	21,426	21,426	100.00%
Novartis	Switzerland	18,497	28,247	65.48%
Sanofi-Aventis	France	17,861	18,711	95.46%
Roche	Switzerland	17,460	25,168	69.37%
Bristol-Myers Squibb	NY, U.S.	15,482	19,380	79.89%
Wyeth	NJ, U.S.	13,964	17,358	80.45%
Abbott	IL, U.S.	13,600	19,680	69.11%
Eli Lilly	IN, U.S.	13,059	13,858	94.23%
Takeda	Japan	8,648	10,046	86.09%
Schering-Plough	NJ, U.S.	6,417	8,272	77.57%
Bayer	Germany	5,458	37,013	14.75%

The cholesterol drug Lipitor (Pfizer) remains a best-selling drug worldwide with annual sales at $12.9 billion. Second drug with around $6 billion sales was Plavix (blood thinner from Bristol-Myers Squibb and Sanofi-Aventis). Third is Nexium (AstraZeneca), the heartburn pill and fourth the drug Advair, the asthma inhaler, from GlaxoSmithKline. IMS Health publishes annual analysis of trends expected in the pharmaceutical industry, including increasing profits in most sectors despite loss of some patents, and new 'blockbuster' drugs on the horizon.[10,11]

The countries that have the largest number of big pharmaceutical industries are USA, Germany, UK, Japan and France (*The Global Magazine of the Pharmaceutical and Biopharmaceutical Industry*, www.pharma-mag.com). In all these countries the promotion of Green Chemistry and Green Engineering applications has been advanced in recent years and supported strongly by governmental, scientific and industrial initiatives. The pharmaceutical industry strives to keep in the forefront of the manufacturers which apply most of the "green" innovations and make its products safer for workers and consumers.[12]

The pharmaceutical industry for many decades was characterised for its intensive use of many petrochemical starting materials, conventional synthetic routes, high energy requirements, high use of organic solvents for separation and purification, and production of high volume waste. Also, it was known that drug manufacturers produced more waste per Kg of product than other chemical industries (petrochemical, bulk & fine chemicals, polymer, etc). The pharmaceutical industry produces, for 6-8 steps organic synthetic routes, 25-100 kg of waste for every one Kg of product. This was considered for a long time as very high and wasteful.[13]

The pharmaceutical industry depended on organic synthetic processes and used a variety of organic solvents. A big pharmaceutical company, such as GlaxoSmithKline (GSK, UK), for example, uses large amounts of solvents and its non-water liquid waste contain 85-90% organic solvents.[14,15]

Green Chemistry and Engineering Applications in Drug Manufacturing

Green Chemistry and Green Engineering applications in the synthetic steps of manufacturing

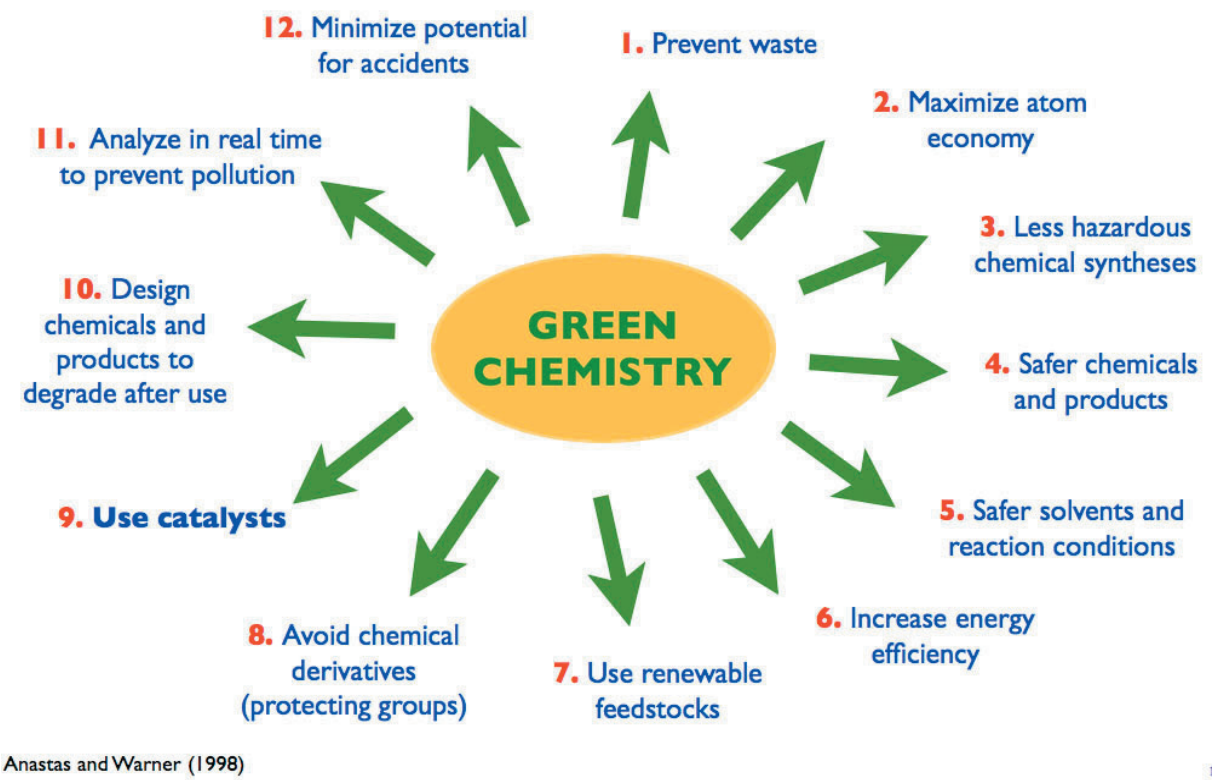

Figure 2. *The 12 principles of Green Chemistry. The pharmaceutical industry feels that their commitment is both an obligation and a significant opportunity to its environmental credibility (Anastas and Warner, 1998).*[16]

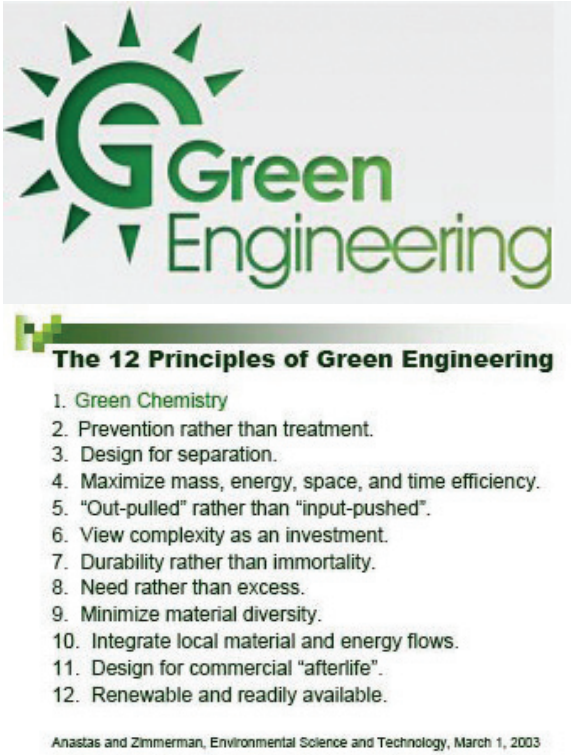

Figure 3. *The 12 Principles of Green Engineering can apply to the pharmaceutical industries (Anastas and Zimmerman, 2003).*[18]

can be proved very important for the pharmaceutical industry and can increase its environmental credentials. The 12 principles of Green Chemistry, followed by the 12 principles of Green Engineering are fundamental steps that every manufacturing enterprise can apply.[16]

The "image" of pharmaceutical manufacturers in the last decades was suffering from the environmental concerns of the consumers. The impact of pollution on the quality of life was a universal concern in industrialized countries. Sustainability problems of natural resources, higher costs for energy and feedstocks were a thorn on the side of the manufacturing enterprises. In the other hand, new technological advances gave drug manufacturers the opportunity to embrace green chemistry ideas.

The investment for research and development for new drugs was already very high, and despite the numerous failures and drawbacks, drug enterprises had very good return to their revenues. The pharmaceutical enterprises recognized the need to promote their environmental credentials and to increase the efficiency of their manufacturing processes. The Research and Development (R&D) departments (with around worldwide total of 50-60 billions per year) of most pharmaceutical companies used a larger percentage of their capital for investment in research for "greener" synthetic routes,

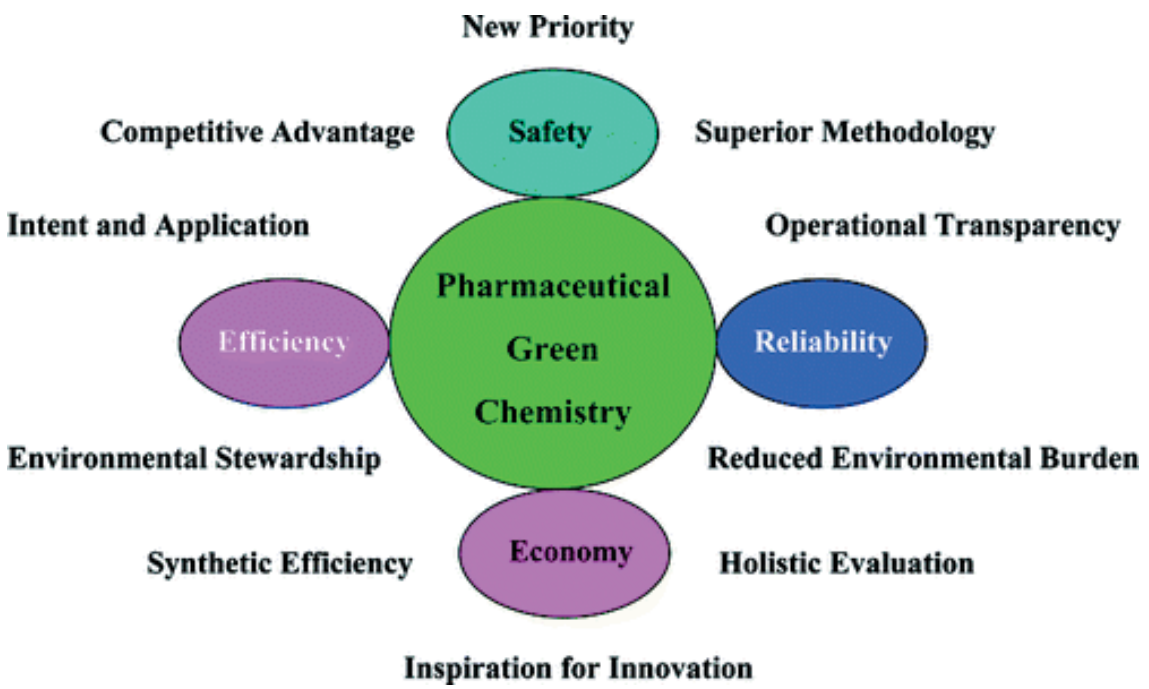

Figure 4. *Schematic representation of the activities of pharmaceutical industries towards green chemistry principles and better applications of green engineering methodologies (from Tucker J.L 2006)* [7]

Figure 5*. The Pharmaceutical manufacturers have some of the most advanced manufacturing technologies and very high caliber scientific staff. Inevitable they are the most suitable for innovation, research and experimentation with new and "greener" innovations*

less solvents and less waste. It is estimated that the discovery, research, clinical trials and distribution of a new drug is valued at $70 million. It is inevitable that pharmaceutical companies would like to invest also in better synthetic efficiency, less toxic reagents and solvents, and environmental protection.[17]

Green Engineering is an additional advance in Green Chemistry principles. The 12 principles of Green Engineering provide guidance for designers and engineers to optimize products, processes and systems. GE is the design, commercialization and use of processes and products that are feasible and economical, while reducing pollution at the source and minimizing the risk to human health and the environment.

Green Chemistry and Green Engineering advanced new opportunities for the drug manufacturers for innovative industrial operations. A schematic presentation of new priorities for the four main pillars (safety, efficiency, reliability and economy) are presented below.

An additional problem with the pharmaceutical companies is the new regulations for environmental pollution of water sources, not only from industrial waste, but also from traces of the drugs and medicinal products released in the aqueous environment as municipal liq1uid waste. It has been found that low concentrations of drugs and their metabolites pollute rivers, lakes and coastal regions. Drugs are toxic and higher concentrations affect aquatic organisms (fish, benthic organisms). Nowadays, there is great awareness that drugs pollute surface and drinking

waters. Pharmaceutical manufacturers are aware of the facts and take very seriously the environmental problems. It is hoped that future changes into "greener" methods, less toxic reagents and solvents and minimizing effluents and solid waste might alter the extent of the problem.[19,20] Also, drug recycling and reduction of waste from households is considered very important. [21]

The potential of Pharmaceutical Green Chemistry will only be realized if scientists are empowered and rewarded based upon higher expectations of efficiency. It is a competitive advantage to reduce the cost of manufacture beyond mere acceptability, and greener chemistry reduces cost.

Pharmaceutical Industry and the Use of Solvents. Can they do Better?

Pharmaceutical industries are known for the use large of amounts of solvents. Solvent use consistently accounts for between 80 and 90% of mass utilization in a typical pharmaceutical/fine chemicals (non-polymer). Moreover, within these operations, solvents play a dominant role in the overall toxicity profile of any given process; i.e. on a mass basis, solvents account for the largest proportion of chemicals of concern used in the process. However, for the typical synthetic organic chemist, solvents are just a medium in which a reaction takes place; the interest is in the reactivity and building of a molecule, not in the means by which this is carried out. So, in a typical retrosynthetic analysis, solvent and solvent-reactant interactions, separability, and particle engineering are generally not included. Green Chemistry puts enough emphasis on solvent use and a case for greater awareness of solvent issues in batch chemical operations typically found in the pharmaceutical industry.[22]

The biggest pharmaceutical companies in the USA manufacture more than 50% of drugs and medicinal product worldwide. Studies showed that U.S. pharmaceutical processes use large amounts of organic solvents and their liquid waste is 85% non aqueous. The reduction in the use of organic solvents is an important issue in the pharmaceutical industry. New organic synthetic routes with minimum of "zero" solvents are in the research stage.[23]

The solvents which are lately more acceptable for organic synthetic processes have low toxicity: acetone (CH_3COCH_3), ethanol (CH_3CH_2OH), methanol (CH_3OH), 2-propanol ($CH_3CH(OH)CH_3$), ethyl acetate (EtOAc), isopropyl acetate, methyl ethyl ketone ($CH_3COCH_2CH_3$), 1-butanol and tert-butanol.

Solvents that are used for their ability to dissolve other chemicals, despite their toxicity, are: cyclohexane, n-heptane, toluene, methylhexane, methyl t-butyl ether, isooctane, acetonitrile, tetrahydrofuran (THF), 2-methylTHF, dimethylsulfoxide (DMSO), acetic acid and ethylene glycol.

Solvents that are been replaced in organic syntheses because of their high toxicity are: pentane, bis-isopropyl ether, diethyl ether, dichloromethane, chloroform, dimethyl formamide (DMF), N-methyl-2-pyrrolidone Pyridine, dimethyl acetate, 1,4-dioxane, benzene, carbon tetrachloride, trichloroethylene (TCE). [24]

The pharmaceutical industry has initiated many studies on the replacement of toxic solvents with solvents that are benign to human health (especially to their neurotoxicity and skin effects) and the environment. [25,26]

The E factor is a simple metric of Green Chemistry which can measure the efficiency of an industry concerning solvents and waste (defined and introduced by Roger A. Sheldon). The E-factor calculation is defined by the ratio of the mass of waste per unit of product:

E-factor = total waste (kg) / product (kg)

The Green Chemistry metric is very simple to understand and to use. It highlights quantitatively the waste produced in the process as opposed to the reaction. It is one the 12 Principles of GC that measures the waste production. The E-factors ignore recyclable factors such as recycled solvents and re-used catalysts, which obviously increases the accuracy but ignores the energy involved in the recovery. It is well known from industrial data that the Pharmaceutical industry produces 25-100 kg of waste per kg of products, compared to 0.1 kg for the industry of oil refining, 1-5 kg in bulk chemicals industry and 5-50 kg in fine chemicals industry. [27]

Pharmaceutical industries are in the forefront of industrial enterprises which try to modernise their manufacturing operations and reduce their waste production.[28] New and innovative techniques are developed for chemical synthesis at room temperature, with ionic liquids, with the use of microwave and sonochemical techniques, supercritical CO_2 and biocatalysis.[29,30] Also, the pharmaceutical industries promote research in "green solvents" for more than a decade. [31]

Solvents are very important for separation and purification of drugs but their properties can change under different conditions (temperature, pressure) A slight change in the manufacturing process can also influence the use of a certain solvent. Comparison

TABLE 2. SOLVENT USE (RANK) IN GSK IN 2005 AND IN THE PERIOD 1990-2000

Solvent	2005 (rank)	1990-2000 (rank)
2-propanol (+)	1	5
Ethyl acetate (+)	2	4
Methanol (+)	3	6
tetrahydrofuran (THF) (--)	6	2
toluene (--)	7	1
Dichloromethane (--)	8	3
acetic acid (+)	9	11
acetonitrile (+)	10	14

**Constable et al. Org Process Res Dev 2007.*[22]

of solvent use in GlaxoSmithKline pharmaceutical company (GSK) in pilot plant processes.[22]

Toluene, THF and trichloromethane ranked 1-3 (in the 1990-200 period) of the most used solvents. But in 2005 were replaced by other less toxic solvents such as 2-propanol, ethyl acetate and methanol.
The pharmaceutical manufacturers have altered many industrial processes, separation and purification techniques for their drugs. Tailored solvents and replacements have advanced "greener" manufacturing techniques.[32-35]

The pharmaceutical industry and biocatalytic applications

Enzymes were used for ages in food industries and in the last decades enzymatic methodology was applied to various organic synthetic routes. New catalytic synthetic methods in organic chemistry that satisfy increasingly stringent environmental constraints are in great demand by the pharmaceutical and chemical industries. In addition, novel catalytic procedures are necessary to produce the emerging classes of organic compounds that are becoming the targets of molecular and biomedical research. Enzyme-catalysed chemical transformations are now widely recognized as practical alternatives to traditional (non-biological) organic synthesis, and as convenient solutions to certain intractable synthetic problems. After many years of research the application of enzymes and biological materials in the pharmaceutical manufacturing has come to fruition and has become widespread in many organic synthetic methods. [36-39]

Biocatalysis has become a central issue of Green Chemistry and the application in chemical manufacturing can become very promising. Enzymes (proteins) can accelerate a reaction, lower the use of energy, use alternative starting materials, reduce the use of solvents and the production of waste. Enzymes are biomaterials that can biodegrade under environmental conditions. They are considered alternative and renewable chemicals and their cost is very low for application in the pharmaceutical industries. The enzymes have the advantage to cut down the number of steps in an organic reaction and can produce clean products with no need for purification.[40, 41]

The well known pharmaceutical industry Pfizer has been experimenting for years with biocatalytic reactions in their manufacturing processes of drugs. Pfizer changed the process of an active substance, called pregabalin, in their drug manufacturing. Is the active ingredient of the medicine Lyrica (trade name). Pregabalin (2003) is an anticonvulsant drug used for neuropathic pain and as an adjunct therapy for partial seizures. The drug has annual sales of approximately, 1.8 billion $ (2007). The synthetic route was conventional and used organic solvents. After many years of research, in 2007 Pfizer used enzymes for biocatalysis of the basic steps in the synthesis, reducing by 90% the use of solvents and by 50% the starting material. The E factor of the synthesis was reduced from 86 to 9. It is estimated that the company will reduce its industrial waste by 200.000 metric tones, compared to the old method, in the period 2007-2020.[42]

There are many successful examples of biocatalysis in the pharmaceutical industry. Pfizer synthesized the antiparasitic drug Doramectin (under commercial, trade name Dectomax). Changing into biocatalysis in the synthesis increased efficiency of the reaction by 40% and reduced the by-products and the waste caused by the purification of the product.[43]

Another successful introduction of biocatalysis by the same company was for the synthesis of the drug atorvasratin, and the synthesis of artemisinic acid for the antimalaria drud artemisinin. Pfizer did some thorough research for the improvements of the yeast *Saccharomyces cerevisiae* in biocatalytic mechanisms.[44]

Biocatalysis improved the efficiency of synthetic routes for the industrial production operation of the drugs Oselravimit and Pelitrexol.[45,46]

Another well known pharmaceutical industry that applied Green Chemistry principles and biocatalytic methods in the drug manufacturing is Merck. These changes brought substantial reductions in the use of solvents and increased efficiency. A success story is the synthetic biocatalysis of the antibiotic drug Gemifloxacin.[47,48] Similar success was achieved in the asymmetric hydrogenation reaction for the synthesis of the drug Taranabant.[49]

A second generation synthetic route of the drug pregabalin in water has been published recently by Pfizer researchers.[50, 51]

The other well known chemical and pharmaceutical companies BASF and DSM Pharmaceuticals (New Jersey) have advanced their research into biocatalysis and applied the method for the synthesis of their drugs. At BASF they used biocatalysis primarily for the production of chiral chemical intermediates required for the production of medicines. Enzymes in living organisms quite selectively prefer one form over the other of chiral compounds in the biological conversion process. BASF takes advantage of this principle in the biocatalytic manufacture of substances in technical plants. The chemical industry Johnson Matthey recently bought the German research company X-Zyme (Dusseldorf) for its biocatalytic innovative methods. The company after years of research establish biocatalytic transformation of ketones and keto-esters in chiral amines. These are starting materials for the production of chemicals and drugs.[52]

An interesting success story of the pharmaceutical industry is the enzymatic catalysis of one of the active substance in the famous medicine Lipitor (reduction of cholesterol). The synthetic route is considered a representative "green" synthesis of an intermediary (key component) for the active compound atorvastatin.[53]

The Codexis (Redwood City, CA, USA) is an international company that markets enzymes and intermediates to global pharmaceutical manufacturers. Codexis biosolutions improve product purity and yields, reducing production process steps, eliminating toxic substances from the manufacturing process. Tailored enzymes enable targeted chemical processes to manufacture the specific pharmaceutical product with efficient manufacturing, lower costs and greater profitability. Merck and Codexis have jointly developed a new manufacturing process for sitagliptin, the active ingredient in Januvia (Type 2 diabetes). Merck and Codexis reported a 10-13% increase in overall yield, a 53% increase in productivity. Codexis is supplying pharmaceutical intermediates for the cholesterol-reducing drug Lipitor from Pfizer. Codexis won the US EPA Presidential Green Chemistry Challenge Award in 2006 (www.codexis.com/pharmaceuticals).

These examples are some of the applications of biocatalytic methods in the pharmaceutical industry which support at the same time Green Chemistry principles and work for the sustainable future of the chemical industry. Enzymes frequently display exquisite selectivity, particularly chemo-, enantio- and regioselectivity, making them attractive catalysts for a wide range of chemical transformations. Also, enzymes operate under mild conditions of pH and temperature leading to the formation of products of high purity. Modern tools of protein discovery and engineering aid the development of novel biocatalysts and their tailor-designed implementation into industrial processes. Consequently, they find wide application in the production of pharmaceutical intermediates, fine chemicals, agrochemicals, novel materials, diagnostics, biofuels and performance chemicals.[54, 55]

Has Green Chemistry a significant impact in the pharmaceutical industry?

All these new developments in the pharmaceutical industries and other changes which are not been described for lack of space in this book, showed that Green Chemistry and Green Engineering principles are spreading to the most efficient chemical industry.

The new methods of Green Chemistry have positive results in the pharmaceutical industry because their R & D investment is very robust and can cover research expenses and support innovative ideas. By applying Green Chemistry methods the pharmaceutical industries have better efficiency and lower cost for their operations, lower solvent use, less waste and improvement in the "green" credentials of the industry.[56-58]

In the last decade the pharmaceutical industry encounters some intractable problems with the disposition of large amounts of their products in landfills. There are no solution "cradle-to-cradle" and some products after their expiring date have to be destroyed (by incineration). Also, the environmental pollution of water sources from rejected medicines, metabolites and medical products is a serious problem.[58, 59]

An article in Chemistry World (monthly

magazine of Royal Society of Chemistry, July, 2008) describes the attractive combination of Green Chemistry principles and the economic benefits in the pharmaceutical industry at a period that patent expiries of bestselling drugs are in the near future and companies must meet the cut of costs.[59]

"...The pharmaceutical industry's current drive to curb spending is helping to speed the adoption of green chemistry, say experts in the industry. Faced with looming patent expiries of their big-selling blockbuster drugs, and a lack of candidates set to replace them, many companies in the industry are looking to dramatically cut their costs. But far from being driven off the agenda by core activities, the importance of green chemistry is growing in many companies. "There's clearly a lot more cost pressure in the pharmaceutical industry these days, especially as the cost of discovering and developing drugs continues to increase", Peter Dunn, green chemistry lead at Pfizer, told *Chemistry World*. "But green chemistry offers significant cost advantages and hence is part of the solution to the problem."

Figure 6. *The Pharmaceutical industries have successfully applied the lessons of Green Chemistry and Engineering for the production of drugs.*

"...The savings come about because efficient syntheses that avoid exotic reagents, minimise energy use and replace organic solvents with water are invariably cheaper to perform. "Even at lab scale, cost savings can be realised, and manufacturing scale process changes can save millions of dollars," says James Long, who's also on Pfizer's green chemistry team.

In 2005, several firms, along with the American Chemical Society's Green Chemistry Institute (GCI), established the GCI Pharmaceutical Roundtable, to promote the integration of green chemistry and green engineering in the industry. Nine companies - including Pfizer, Johnson & Johnson, AstraZeneca and GlaxoSmithKline (GSK) - are now roundtable members. At GSK as at Pfizer, belt-tightening has led to an increased focus on Green chemistry. "Specifically for GSK, the appointment of Andrew Witty as CEO has shone a spotlight on manufacturing efficiencies, and green chemistry has received a great boost as a result," says David Constable, responsible for promoting sustainable practices in R&D and manufacturing through green chemistry and engineering at GSK. "Going green is cost beneficial; it just has the perception that it is more expensive to do. In every case I know, the green option is the low cost option".

The industry is also starting to analyse the green credentials of chemical feedstocks bought in from external suppliers - an important shift, given that increased outsourcing is another outcome of pharmaceuticals' cost-cutting drive. At the 2007 pharmaceutical roundtable meeting, members agreed to include outsourced feedstocks when calculating their total mass productivity - the number of kilograms of material used per kilogram of final product - as a metric to compare performance from company to company. This agreement forces us to engage with our suppliers, to come up with the best solution,' says Henderson. The roundtable was set up to share best practice, but we're also very competitive...." [60]

Conclusions

The potential of Pharmaceutical Green Chemistry will only be realized if scientists are empowered and rewarded based upon higher expectations of efficiency and less toxic products.

It is a competitive advantage to reduce the cost of manufacture beyond mere acceptability, and greener chemistry reduces cost. It is encouraging that metrics have been developed which may help business leadership to better understand and reward greener chemistry. It should be clear though that while Pharmaceutical Green Chemistry can be measured by metrics of environmental health and safety, the real driver of Pharmaceutical Green Chemistry is synthetic efficiency.[61-63]

Scientists believe that Green Chemistry is going to transform the pharmaceutical industry and drug manufacturing in the future. Green Chemistry can deliver both environmental and economic benefit and the pharmaceutical industry is keen to adopt most of its principles. Although Green Chemistry philosophy has been generally accepted by the scientific community, technical Green Chemistry evolution through education and investment has yet to achieve the appropriate attention and effort.[64, 65]

Extensive coverage of scientific aspects of Green Chemistry and Green Engineering, in Greek and in English, is presented in the recent publications of the Chemistry Dpt, University of Athens.[66,67]

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Φαρμακευτική Βιομηχανία και Πράσινη Χημεία Νέες Εξελίξεις στην Εφαρμογή των Πράσινων Αρχών και της Αειφόρου Ανάπτυξης

Αθανάσιος Βαλαβανίδης,
Θωμαΐς Βλαχογιάννη
Τμήμα Χημείας, Σχολή Θετικών Επιστημών, Πανεπιστήμιο Αθηνών, Πανεπιστημιούπολη Ζωγράφου, 15784 Αθήνα

Περίληψη

Η «Πράσινη ή Αειφόρος Χημεία» και η «Πράσινη Τεχνολογία ή Μηχανική» είναι δύο νέοι επιστημονικοί όροι που περιγράφουν ένα παγκόσμιο ριζοσπαστικό κίνημα στην παραγωγή προϊόντων και βιομηχανικών διεργασιών με περιβαλλοντική αποδοχή. Την τελευταία δεκαετία οι σημαντικότεροι χημικοί βιομηχανικοί κλάδοι έχουν επηρεασθεί από τις αρχές και τις φιλοδοξίες της Πράσινης Χημείας και της Πράσινης Μηχανικής. Οι αλλαγές που εφαρμόσθηκαν στη χημική βιομηχανία για πιο «πράσινες» πρώτες ύλες, εναλλακτικές οργανικές συνθετικές μέθοδοι, βιοκατάλυση, λιγότερο τοξικούς οργανικούς διαλύτες, υψηλότερες αποδόσεις και λιγότερα απόβλητα, επικεντρώθηκαν αρχικά στην εξοικονόμηση πόρων, αλλά και στην προστασία των εργαζομένων και των καταναλωτών και κατ' επέκταση του περιβάλλοντος. Η φαρμακευτική βιομηχανία ήταν φυσικό να ανταποκριθεί σε όλες αυτές τις «πράσινες» εναλλακτικές τεχνικές. Οι βιομηχανίες φαρμάκων αποβλέπουν στη μείωση των κινδύνων από νομοθετικές ρυθμίσεις, μικρότερο περιβαλλοντικό αποτύπωμα και βιομηχανικές τεχνολογίες με «πράσινες» περγαμηνές. Στην ουσία, οι φαρμακευτικές βιομηχανίες θεωρούν ότι είναι προς το συμφέρον τους να προωθήσουν το περιβαλλοντικό τους ενδιαφέρον και την υπευθυνότητα για την περιβαλλοντική δράση σε όλες τις πλευρές των βιομηχανικών τους διεργασιών. Θέλουν να προστατεύσουν τους εργαζόμενους από προβλήματα υγιεινής, υγείας και ασφάλειας στους εργασιακούς χώρους. Αλλά ενδιαφέρονται και για την ασφάλεια των καταναλωτών από τα προϊόντα τους. Ασφάλεια, Αποδοτικότητα, Υπευθυνότητα και Οικονομία είναι οι τέσσερεις πυλώνες των αλλαγών και της προώθησης των εναλλακτικών προσπαθειών στη βιομηχανική παραγωγή. Στην εργασία αυτή ανασκόπησης παρουσιάζουμε μία σύντομη και συνεκτική ανασκόπηση των τελευταίες δραστηριοτήτων εφαρμογής των Αρχών της Πράσινης Χημείας και της Πράσινης Τεχνολογίας (Μηχανικής) από τις σημαντικότερες φαρμακευτικές εταιρίες.

Λέξεις κλειδιά : φαρμακευτική βιομηχανία, πράσινη Χημεία, πράσινη τεχνολογία, τοξικοί διαλύτες, βιοκατάλυση, περιορισμός αποβλήτων, νέες συνθετικές μέθοδοι

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ΑΡΘΡΟ ΕΠΙΣΚΟΠΗΣΗΣ REVIEW ARTICLE
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Fractal Analysis of Liposomal Aggregation.

Natassa Pippa, Costas Demetzos*
Faculty of Pharmacy, Department of Pharmaceutical Technology, University of Athens, University Campus Zografou, 15784 Athens, Greece

Summary

The physical stability, the aggregation process of colloidal systems, as well as the surface phenomena are described using the **D**erjaguin-**L**andau-**V**erwey-**O**verbeek (**DLVO**) theory. Liposomes represent one of the most studied categories of colloidal nanoparticles with potential application as advanced Drug Delivery nano Systems (**aDDnSs**). Colloidal aggregation using liposomes has already been studied, including the fractal approach. The research orientations on the aggregation process in colloidal science and in biological phenomena are of great importance because by using the fractal analysis we have the opportunity to quantify the morphology of colloidal and biological surfaces. The fractal analysis can be used as a tool to elucidate the dimensionality and the morphology of liposomal aggregates because the aggregation phenomena are irreversible. In pharmaceutical applications, Fractal Geometry contributes to elucidate the physical and structural properties of innovative drug delivery systems in order to shed more light to a new formalism of pharmaceutical delivery of bioactive compounds based on the development of science and technology. The tool of fractal analysis would be a state of art for the developing process of a new drugs and open attractive horizons for the Pharmaceutical Nanotechnology, too. This review presents the most important advances in scientific research and experiments for aggregation phenomena, using fractal analysis for the delineation of structural hologram of liposomes.

Keywords: Fractal dimension, liposome, aggregation kinetics

Introduction

The **D**erjaguin-**L**andau-**V**erwey-**O**verbeek (**DLVO**) is the central theory for colloidal stability and has been extensively reviewed and it stands today as the only quantitative physical formalism of the colloidal and biocolloidal scientific fields.[1-3] Colloidal aggregation phenomena are related to the physical stability while the role of temperature and concentration of biomaterials is considered as essential. The DLVO theory is the only quantitative theory up to now which describes the colloidal stability. According to this theory, the interactions between similar colloidal particles in polar solutions are attractive Van der Waals and repulsive electrostatics forces. ***Figure 1*** presents aggregation of spheres and clusters after

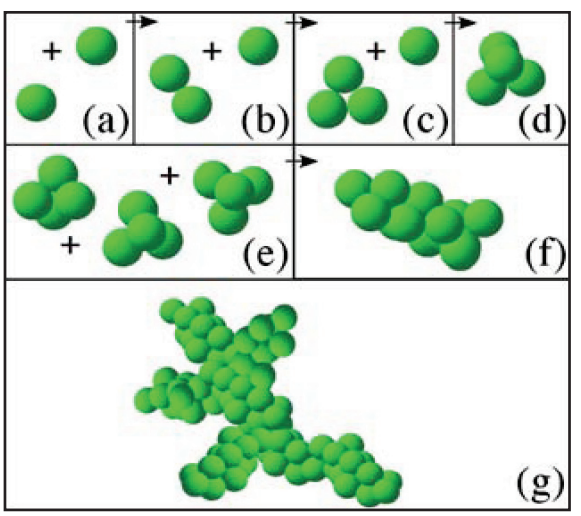

Figure 1. *Aggregation of nanoparticles: (a) monomers diffuse and aggregate to form a dimer (b). A dimer and a monomer aggregate to form a trimer (c). A trimer and a monomer (or two dimers) aggregate to form a tetramer (d). Tetramers (e) are the minimal clusters of larger scale aggregates that are stable against thermal fluctuations (i.e., shear-rigid) and form extended, non-spherical structures (f), even fractal aggregates. At sufficiently large concentrations, the aggregates can form extended networks (g). (Adapted from [3]).*

* *Corresponding author: Costas Demetzos, e-mail: demetzos@pharm.uoa.gr*

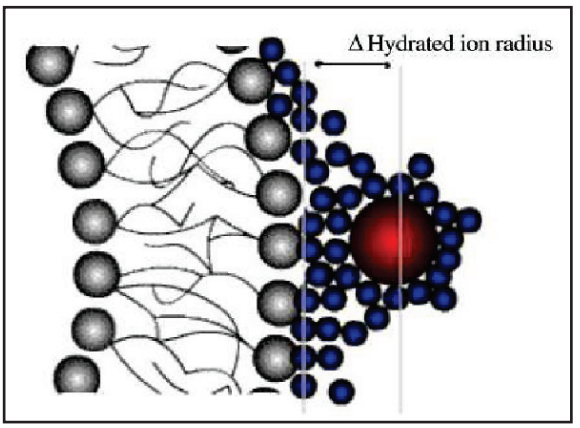

Figure 2. *A schematic configuration of the hydration forces effect. (Adapted from [7]).*

the sudden onset of a short-range, central-force, non-shear-rigid attraction, generally.[3] According to the literature, the hydration interaction energy can play an important ***(Figure 2)*** role in the colloidal aggregation and cluster morphology.[4-7]

Liposomes are thermodynamically unstable nano-colloidal dispersions (the term *nano*-is used for dimensions less than 100 nm), in which the free energy (G) of their surface area depends on their interfacial or intra-facial phenomena.[8,9] Liposomes can be applied as containers of drug, genetic material, vaccines and bioactive molecules and their aggregation process is a challenge for studding not only their stability but the process of aggregates of protein which are involved in several illnesses. An ideal liposomal delivery system should be stable, long – circulating, accumulate at a target site and release its drug in a controlled manner. Conventional liposomes are in general unstable thermodynamically and kinetically. The size, the size distribution and the ζ-potential of liposomes are important biophysical characteristics that indicate their physical properties, which are crucial issues for acceptance in pharmaceutical applications.[8,9]

By using the Euclidean approach we can determine the mean size and the Polydispersity Index (PD.I.) of a particular liposomal dispersion by using the Eistein-Stokes expression for the diffusion coefficient of liposomal particle (*i*) with an hydrodynamic radius of R_h. Apparent hydrodynamic radii, R_h, at finite concentrations was calculated by aid of Stokes - Einstein equation:

$$R_h = \frac{k_B T}{6\pi\eta_0 D} \qquad (1)$$

where k_B is the Boltzmann constant, η_0 is the viscosity of water at temperature T, and D is the diffusion coefficient at a fixed concentration. Experimentally D can be determined by fluorescent by diffraction, scattering and spectroscopic techniques.

Smoluchowski, in his pioneering work on colloidal stability, formulated the kinetic equations for irreversible aggregation of monomers into clusters. Smoluchowski considered a system of diffusing particles, which stick together irreversibly upon collision. The kinetics of the aggregation process can be consistently described in terms of the Smoluchowski kinetic equations:

$$\frac{d\eta_k}{dt} = \sum_{i+j=k}^{\infty} \eta_i k_{ij} \eta_j - 2 \sum_{j}^{\infty} \eta_k K_{kj} \eta_j \qquad (2)$$

which *i*-mers are at concentration N_i and *j*-mers at a concentration N_j form *(i+j)*-mers, $n_i = N_i/N_0$, with $N_0 = N_1$ (t=0) and K_{ij} is the collision matrix.[10]

A desire to obtain a better understanding of the development of morphology in biological systems has provided one of the main motivations for the study of non-equilibrium growth models. Probabilistic growth models can also lead to complex structures which mimic certain types of biological morphologies, like liposomes. The morphology of aggregates is an important issue and can affect the properties of the colloidal dispersion.

Nano-colloidal dispersions and fractal aggregation phenomena

The fractal geometry can be used to describe the morphology of aggregates by measuring their fractal dimension. The dimensionality **d**, for Euclidean objects, is the exponent which describes how the mass **M** of the object, scales with some characteristic length **l** which describes the overall size:

$$M \sim l^d \qquad (3)$$

In this case **d** is an integer (3 for sphere, 2 for a plane and 1 for a line). Many objects are found in nature for which the form of the mass-length scaling relationship given in equation (**3**) is preserved, but the exponent is no longer equal to the Euclidean dimensionality of the embedding space in which the object exists:

$$M \sim l^{df} \qquad (4)$$

In general $\mathbf{d_f}$ is not an integer and satisfies the condition

$$\mathbf{d_f < d} \qquad (5)$$

that means fractal dimensionality $\mathbf{d_f}$ is distinctly smaller than Euclidean.[11] The mass-length scaling relationship given in equation (**5**) is the basis for all methods to measure the fractal dimensionality of real objects or objects generated in computer simulations. The mass fractal dimension (M) scales

with the radius of the aggregate as

$$M \sim R^{dm} \quad (d_m < 3) \qquad (6)$$

There are several branched clusters which have been referred in an irreversible aggregation process ($1.75 < d_m < 2.1$).[12-15]

One of the simplest non-equilibrium growth processes that generates branched structures in colloidal systems characterized by a fractal dimension (d_f), which is synonymous to mass fractals, different from the Euclidean dimensionality (d), is the Diffusion-

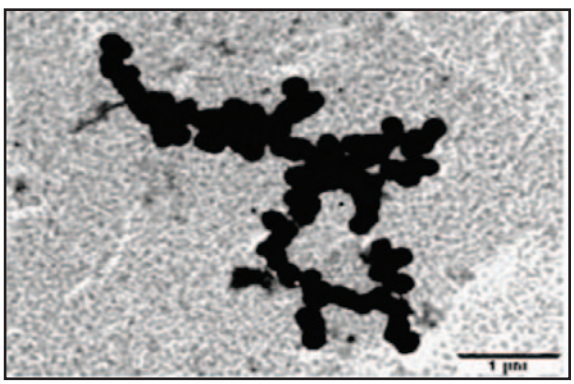

Figure 3. *A branched and open liposomal aggregate typical of the DLCA aggregation regime (d_f= 1.8). (Adapted from [33]).*

Controlled or Limited Aggregation process introduced by Witten and Sander and the Diffusion – Controlled Deposition introduced by Rácz and Vicsek.[16,17] The Diffusion-Limited Cluster Aggregation was improved by Meakin and is an extension of DLA.[13] In this model, the cluster's growth is controlled by diffusion, the sticking probability is equal to one, all collisions between particles are effective and the aggregates are open and branched in their structure ***(Figure 3)***. The fractal dimension was estimated to be 1.8 in three

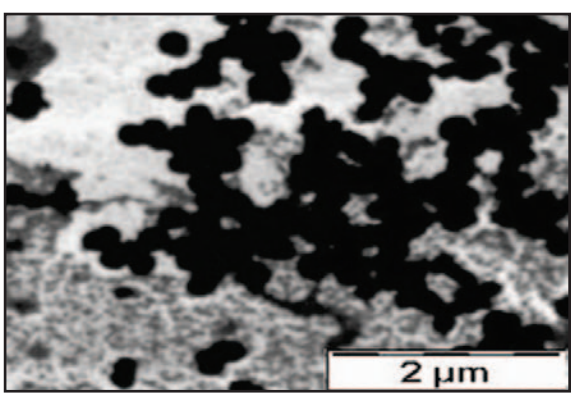

Figure 4. *A compact and dense liposomal aggregate typical of the RLCA aggregation regime (d_f= 2.1). (Adapted from [33]).*

dimensions from computer simulations. DLCA is a fast aggregation process, following a power law for the average radius of gyration, R_g:

$$R_g \sim t^{1/df} \qquad (7)$$

where *t* is the time and d_f the fractal dimension.[18] On the other hand, Reaction Limited Cluster Aggregation (RLCA) or Eden model is the slow aggregation process. The Eden model is a simple lattice model for the growth of the clusters, in which the particles are added one at a time at random to sites adjacent to occupied sites. The growth is limited by reaction kinetics due to the presence of an energy barrier to aggregation. The sticking probabilily is smaller than one because a large number of collisions are needed before the particles bind. The fractal dimension was estimated to be 2.1 in three dimensions from computer simulations and the aggregates are more compact and dense than DLCA clusters ***(Figure 4)***. The kinetics of RLCA are characterized by a power law for the average radius of gyration, R_g:

$$R_g \sim e^{at} \qquad (8)$$

where *a* is a constant. The value of *a* depends on the sticking probability. The surface fractal dimension is d_s and the expresssion which decribes the surface fractals is:

$$d_f = 6 - d_s \qquad (9)$$

From an experimental point of view it is difficult to find aggregation phenomena described by the concept of surface fractals. Roldán-Vargas et al., reported the first experimental observation of a transition from surface fractals to mass fractal structures in a suspention of aggregating lipid vesicles and presented a detailed description of structural and kinetic aspects of liposomal surface to mass fractal transition controlled by magnesium concentration.[4,5] It must be noted that these two limiting regimes of irreversible growth of aqueous colloidal aggregates are universal. The "universality" of these aggregation phenomena was supported by Lin and co-workers.[19]

There are a large number of techniques available for the characterization of the structure of aggregates formed from suspensions and dispersions of particles in micro and nano scale and for the determination of their fractal dimension.[20] Light scattering provides the greatest potential for use as a tool for elucidation and characterization of the structure of nanoparticles and aggregates, alike. The physical theories, which were developed for aggregation phenomena, include fractal formalism for elucidating the shape and quantifying the morphology of the resulting aggregates. Recently, this formalism has been introduced to study the geometry of liposomal aggregates.

TABLE 1: THE AGGREGATION KINETICS AND THE FRACTAL DIMENSION OF LIPOSOMAL AGGREGATES (ADAPTED FROM [28,31]).

Liposomal Composition	Dispersion medium	Aggregation kinetics	Fractal Dimension
DPPC	HPLC water	$R_h(t)=101.7t+55.196$ ($r^2=0.7415$)	2.50
DPPC	FBS	$R_h(t)=1.9193t+71.434$ ($r^2=0.8061$)	1.80
DPPC: cholesterol (9:1 molar ratio)	FBS	$R_h(t)=4.362t+135.96$ ($r^2=0.6617$)	2.40
DPPC:DODAP (9:1 molar ration)	PBS	$R_h(t)=1.9942t+39.653$ ($r^2=0.7381$)	1.80
DPPC:DPPG (9:1 molar ratio)	FBS	$R_h(t)=3.37t + 43.69$ ($r^2=0.967$)	1.4

Such fractal aggregation phenomena underlie a wide variety of biological, chemical and physical processes of great practical importance. Taking these developments into consideration, there is a strong relationship between fractal approach and the physical properties of the drug delivery systems, like solubility which may plays an important role for the effectiveness, the efficacy and the safety of the encapsulated bioactive compound.[21] According to the literature, the fractal dimension of cell cytoplasmic membrane correlates with the cell membrane biophysical behavior and with their specific membrane dielectric capacitance.[22] However, an important aspect which can correlate the fractal dimensionality with diseases, is the fractal dimension of cell membrane morphology which is used to reveal brain structure irregularities in patients with schizophrenia, breast cancer cell migration and biological and physical properties of cells in lymphoma and leukemia.[23-25]

The fractal hologram of liposomal dispersions.

At the mesoscopic level of Pharmaceutical Nanotechnology, the principles and the laws of physics are quite different from the Classical Newtonian Physics and Euclidean approach especially at nanoscale dimension.[25,27] The investigation of the aggregation process of liposomes is of paramount importance due to their applications in pharmaceutical nanotechnology as drug delivery systems and as membrane models, in biosciences. The elucidation of the dimensionality of liposome aggregates obeys the fractal approach because the aggregation phenomena are irreversible.

Aggregation of uncharged Dipalmitoylphosphatid ylcholine (DPPC) liposomes in aqueous medium was observed, while d_f was 2.5 and remained unchanged during an ageing study ***(Table 1)***.[28] The existence of Lateral Cluster-Cluster Aggregation could be a possible explanation to the observed behavior.[29] Physicochemical stability was observed for liposomes with cholesterol [DPPC: cholesterol (9:1 molar ratio)] liposomes in aqueous and biological (Fetal Bovine Serum) medium. The structural properties of DPPC liposomes in aqueous medium are quite different from those in FBS, as demonstrated from fractal analysis, especially for liposomes without cholesterol ***(Table 1)***. Cholesterol plays a major role on the fluidity of membranes by regulating their functions, as shown by the slight variation of mass and surface fractal dimension in the two media.[30] Anionic [DPPC:DPPG* (9:1 molar ratio)] and cationic [DPPC:DODAP** (9:1 molar ratio)] liposomes in aqueous medium were found to retain their original physicochemical characteristics at least for the time period that they were studied.[31] The liposomal stability indicates that electrostatic repulsion should be responsible for keeping the liposomes far enough to avoid aggregation or fusion. On the other hand, aggregation of reconstituted anionic liposomes was observed in FBS. The first order kinetics describes the protein induced aggregation of cationic liposomes

* Dipalmitoylphosphatid ylglycerol

** 1,2- Dioleoly-3-Dimethylammonium propane

with serum components ***(Table 1)***.[30]

Finally, we wanted to generalize these findings to control the stability and the responsiveness of conventional liposomes to changes in temperature and concentration in two dispersion media.[28,31] Of paramount importance is to identify any gaps in the scientific understanding of liposomes and to facilitate a better understanding of pharmaceutical characteristics of liposomal vectors for designing colloidal nanocarriers, especially for gene delivery. It is well established in the literature, that the regulatory considerations are of great importance aiming proofs concerning not only the design and preparation of liposomal delivery systems but also the final formulation's physicochemical and morphological characteristics.[31,32] In conclusion, the fractal dimension illustrate the self-assembly and the morphological complexity of charged liposomal carries, which could be a useful tool for the development of innovative nanocarriers for drug or gene delivery with complete knowledge of their structural characteristics.

Conclusions

The physical theories, which developed for aggregation phenomena, include fractal formalism for the elucidating the shape of the resulting aggregates. Recently, this formalism has been introduced to study the geometry of liposomal aggregates. The physical theory which is used to describe the behavior of fractal liposome aggregates is the extended DLVO theory. Due to the complexity of the problem, a complete characterization of the structure of the resulting liposome aggregates is still lacking and some controversial questions remain to be clarified. One the other hand, the fractal approach of the dimensionality of liposome aggregates and the extended DLVO theory would be the tools to explain the phenomenology and the functionality of lipidic Drug Delivery Systems like liposomes. Moreover, these tools would be a state of art for the developing process of a new drugs and open attractive horizons for the pharmaceutical industry.

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Η Μορφοκλασματική Ανάλυση της Λιποσωμιακής Συσσωμάτωσης.

Νατάσσα Πίππα, Κώστας Δεμέτζος
Τομέας Φαρμακευτικής Τεχνολογίας, Τμήμα Φαρμακευτικής, Πανεπιστήμιο Αθηνών, Πανεπιστημιούπολη Ζωγράφου, 15784, Αθήνα

Περίληψη

Η φυσική σταθερότητα, η διαδικασία της συσσωμάτωσης των κολλοειδών συστημάτων, καθώς και τα φαινόμενα επιφανείας περιγράφονται χρησιμοποιώντας της θεωρία των **D**erjaguin-**L**andau-**V**erwey-**O**verbeek (θεωρία **DLVO**). Τα λιποσώματα αποτελούν την πιο διαδεδομένη και μελετημένη κατηγορία κολλοειδών νανοσωματιδίων, με δυνατότητες εφαρμογής τους ως προχωρημένα συστήματα μεταφοράς φαρμακομορίων της νανοκλίμακας (**a**DVANCED **D**rug **D**elivery **n**ano **S**ystems **-aDDnSs**). Η κολλοειδής συσσωμάτωση έχει ήδη μελετηθεί με τη χρήση λιποσωμάτων με βάση την προσέγγιση της Μορφοκλασματικής (Fractal) Γεωμετρίας. Οι ερευνητικοί προσανατολισμοί στην κατεύθυνση της διαδικασίας της συσσωμάτωσης στην Επιστήμη των κολλοειδών, όπως και σε βιολογικά φαινόμενα, χρησιμοποιώντας τη μορφοκλασματική ανάλυση, παρέχουν την δυνατότητα για ποσοτικοποίηση της μορφολογίας των κολλοειδών και βιολογικών επιφανειών. Επίσης, η μορφοκλασματική ανάλυση μπορεί να χρησιμοποιηθεί ως εργαλείο για τη διασαφήνιση της διαστατικότητας και της μορφολογίας των λιποσωμιακών συσσωματωμάτων, διότι τα φαινόμενα της συσσωμάτωσης χαρακτηρίζονται από μη αναστρεψιμότητα. Όσον αφορά την εφαρμογή της στη Φαρμακευτική Επιστήμη, η Γεωμετρία των Μορφοκλασματικών Συνόλων συμβάλει στη διασαφήνιση των φυσικών και δομικών ιδιοτήτων των καινοτόμων συστημάτων μεταφοράς φαρμακομορίων, καθώς και στις διαστάσεις τους στη νανοκλίμακα, με στόχο να αποκαλύψουν ένα νέο φορμαλισμό για την περιγραφή των συστημάτων μεταφοράς βιοδραστικών μορίων. Το εργαλείο της fractal ανάλυσης θα μπορούσε να αποτελέσει καινοτομία και όσον αφορά τη διαδικασία ανάπτυξης νέων φαρμακομορίων και να ανοίξει νέους ορίζοντες για τη Φαρμακευτική Νανοτεχνολογία. Η παρούσα ανασκόπηση παρουσιάζει τις σύγχρονες ερευνητικές κατευθύνσεις για την περιγραφή της μορφολογίας των λιποσωμιακών συσσωματωμάτων με βάση το μορφοκλασματικό ολόγραμμα της δομής τους.

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ΣΥΝΤΟΜΗ ΕΠΙΣΚΟΠΗΣΗ SHORT REVIEW
ΦΑΡΜΑΚΕΥΤΙΚΗ 24, ΙΙΙ, 63-67, 2012 PHARMAKEFTIKI 24, III, 63-67, 2012

Personalized Medicine and Patient-Centred Care

Stavroula Piperaki*
S.I. Piperaki Pharmacy,
4, avenue Andrea Papandreou,
Melissia, GR-15127, Athens, Greece.

Summary

Human genetic variation is what makes "personalization" of disease treatment and prevention both necessary and possible. Over the last decade, the revolution in genomic technologies has vastly increased the ability to analyse and evaluate this variation putting it in the service of patients and resulting in an ever-increasing number of powerful new tools for elucidating the genetics of complex diseases and traits. Recently, scientists carried out an extensive meta-analysis of a series of studies seeking to integrate genomic medicine to the clinical management of several diseases. On the other hand, FDA has been supported on his ongoing efforts to create a more favorable regulatory framework for diagnostic products and to work with Evaluation of Genomic Applications in Practice and Prevention (EGAPP) to consider alternative pathways to demonstrate clinical utility. For example FDA regulators and leaders have relabelled warfarin and abacavir to recommend genetic testing before beginning therapy. As a result of these evolutions on the field of Personalized Medicine a lot of questions have been arisen: What are the outcomes of genomic medicine? What is the current level of consumer understanding about genomic medicine? What information do consumers need before they seek services? How genomic medicine is best delivered? What are the challenges and barriers to integrating genomic medicine into clinical practice? Genetic information technologies are forecasted to completely revolutionize medicine by the year 2050. Patients will be diagnosed and treated, to a large extent, according to their genetic profiles and blood proteomics information, are we prepared for the novel challenges? Are we fully aware of the societal and ethical dilemmas that will come along with the revolution in medicine? On the other hand, consumers are worried about the possible adverse consequences of genetic testing, particularly the privacy issues and discrimination against receiving employment and health insurance. These concerns are coupled to angst regarding the lack of regulatory oversight of genetic testing. Cost uncertainty, both in terms of delivery and reimbursement for genomic testing, is also an important issue. As with any new innovation, genomic testing must be demonstrated to be clinically useful, cost effective, and of value. But because genomic technologies inherently involve diagnostic or prognostic testing, and the complexities of incomplete gene penetrance and multiple gene and environmental interactions, their assessment can be more challenging. In addition clarity is needed on the drivers of cost-effectiveness of genomic technologies and consideration must be given to approaches that include value-based reimbursement for genomic testing technologies. Based on the overview of all issues related to the development of Personalized Medicine specific examples of drugs applications currently on the market will be presented as well as future perspectives are commented.

Introduction

Human genetic variation is what makes "personalization" of disease treatment and prevention both necessary and possible. Over the last decade, the revolution in genomic technologies has vastly increased the ability to analyse, to evaluate this variation and to put it in the service of patients; resulting as well in an ever-increasing number of powerful new tools for elucidating the

* *S.Piperaki, e-mail: inapiperaki@otenet.gr*

genetics of complex diseases and traits.

Despite clear advances in technology that bring genomic information closer to physicians, patients, and the public, looming even closer are issues that are outside the sphere of the genome sciences and more in the area of genome policy. Recently, scientists carried out an extensive meta-analysis of a series of studies seeking to integrate genomic medicine to the clinical management of several diseases[1].

As a result of these evolutions on the field of Personalized Medicine a lot of questions have been arisen: What are the outcomes of genomic medicine? What is the current level of consumer understanding about genomic medicine? What information do consumers need before they seek services[27] How genomic medicine is best delivered? What are the challenges and barriers to integrating genomic medicine into clinical practice? Genetic information technologies are forecasted to completely revolutionize medicine by the year 2050. Patients will be diagnosed and treated, to a large extent, according to their genetic profiles and blood proteomics information, are we prepared for the novel challenges? Are we fully aware of the societal and ethical dilemmas that will come along with the revolution in medicine[3]?

Personalized medicine

Personalized medicine in the sense of the "right treatment for the right patient at the right time" has been practiced for millennia. After the completion of the Human Genome Project in 2000, it was believed that this fact will revolutionize the diagnosis, prevention and treatment of most human disease as well as our power to heal.

"Personalized Medicine" refers to the tailoring of medical treatment to the individual characteristics of each patient. It does not literally mean the creation of drug or medical devices that are unique to a patient, but rather the ability to classify individuals into subpopulations that differ in their susceptibility to a particular disease or their response to a specific treatment. Preventive or therapeutic interventions can then be concentrated on those who will benefit, sparing expense and side effects for those who will not.

Physicians and pharmacists have long observed substantial variation in patient response to treatments for different cancers as well as for such common conditions as hypertension, heart failure, depression, high cholesterol and asthma. Finding the best medication for a given patient often involves trial and error; sometimes we may exhaust all possibilities without finding an option that is effective. The ability to distinguish in advance those patients who will benefit from those who will incur cost and suffer side effects could **both reduce costs and improve quality of care**.

It may be considered that the new language of genomics, as applied to medicine, is less a revolution than an evolution: the ability to more precisely describe phenotypes has allowed us to change the specifics but not the fundamental practice of medicine. Thanks to our increase knowledge of genetic end genomic variation, we have gone from the diagnosis of "blood disease" in 1900 to over 38 leukemia and 51 lymphoma subtypes in 2008. If you are suffering from a chronic myelogenous leukemia as a result of the rare Philadelphia chromosome translocation, we have a drug that addresses that phenotype, at least temporarily. If your form of breast cancer is overexpressing a specific gene, we have a drug that may work better for you than for others without that genetic variation. And so forth[4,5].

What is the meaning of the term "Pharmacogenomics" [6] ?

More than 1.4 million single-nucleotide polymorphisms were identified in the initial sequencing of human genome, with over 60,000 of them in the coding region of genes. Some of these single-nucleotide polymorphisms have already been associated with substantial changes in the metabolism or effects of medications.

The way a person responds to a drug (this includes both positive and negative reactions) is a complex trait that is influenced by many different genes.

Pharmacogenomics is a science that examines the inherited variations in genes that dictate drug response and explores the ways these variations can be used to predict whether a patient will have a good response to a drug, a bad response to a drug, or no response at all.

More specifically **Pharmacogenomics** can be defined as the genome-wide analysis (e.g. whole-genome single nucleotide polymorphism, maps, haplotype marker and alterations in gene expression) of genetic determinants of drug efficacy and toxicity, including the identification of drug targets. The field of pharmacogenomics began with a focus on drug metabolism, but it has

been extended to encompass the full spectrum of drug disposition, including a growing list of transporters that influence drug absorption, distribution and excretion[7].

PharmacoGenetics can be defined as the study of inter-individual differences in drug response due to genetic variations.

The distinction between the two terms is considered arbitrary, however, and now the two terms are used interchangeably.

The privacy and discrimination issues

Consumers are worried about the possible adverse consequences of genetic testing, particularly **the privacy issues and discrimination against receiving employment and health insurance.** These concerns are coupled to angst regarding the lack of regulatory oversight of genetic testing. The uniqueness of genomic information is clearly debatable over whether it warrants special protections beyond those in place for standard medical information.

Despite the Universal Declaration of Human Genome and Human Rights of 1997 (UNESCO)[8] there are some new regulations and projects that , new Genetic Information Non-discrimination Act (May 2008)[9], a new federal law in Switzerland, in France, in Italy, etc … most recently one Project of UNESCO Report on the Human Cloning and the necessity of International Governance (March 2009).

It is worth while to focus on the GINA which is a USA federal law that prohibits **discrimination in health coverage and employment based on genetic information**. GINA, together with already existing non-discrimination provisions of Health Insurance Portability and Accountability Act, generally prohibits health insures or health plan administrators from requesting or requiring genetic information of an individual or an individual's family members, or using such information for decisions regarding coverage, rates, or pre-existing conditions. GINA also prohibits employers from using genetic information for hiring, firing, or promotion decisions, and for any decisions regarding terms of employment. GINA requires regulations pertaining to both titles (I & II) to be completed by May 2009 [9,10].

Regulatory Bodies

FDA has been supported on his ongoing efforts to create a more favourable regulatory framework for diagnostic products and to work with *Evaluation of Genomic Applications in Practice and Prevention (EGAPP), in 2004,* to consider alternative pathways to demonstrate clinical utility.

Furthermore FDA issued, among others, two guidances for Industry and FDA staff regarding

- Pharmacogenomic Data Submissions, March 2005 [11].
- Pharmacogenetic Tests and Genetic Tests for Heritable Markers, June 2007 [12].

On the other hand EMEA evaluate all Pharmacogenomic Data Submissions through the procedures (Pharmacogenetics Briefing Meetings) of the European Organism but a joined guidance has been released on May 2006, e.g.,

- Guiding principles: Processing Joint FDA EMEA Voluntary Genomic Data Submissions within the framework of the Confidentiality Arrangement ,

Reimbursement for genomic testing

Cost uncertainty, both in terms of delivery and reimbursement for genomic testing, is also an important issue. As with any new innovation, genomic testing must be demonstrated to be clinically useful, cost-effective, and of value. But because genomic technologies inherently involve diagnostic or prognostic testing (as we will see during the presentation of specific examples), and the complexities of incomplete gene penetrance and multiple gene and environmental interactions, their assessment can be more challenging. In addition, perhaps more than in any other area of medicine, questions have arisen concerning the economic incentives to develop these technologies. Clarity is needed on the drivers of cost-effectiveness of genomic technologies and consideration must be given to approaches that include value-based reimbursement for genomic testing technologies.

It is important to mention that genomics-based molecular diagnostic tests, concerning drug already on the market, are currently reimbursed at the same rate as other laboratory tests.

Specific examples of drugs applications currently on the market

Based on the overview of all issues related to the development of *Personalized Medicine* specific examples of drugs applications currently on the market will be presented as well as future perspectives will be commented.

Personalizing clopidogrel dosing

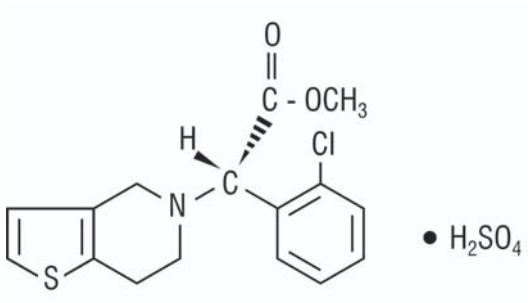

Figure 1. *Chemical structure of clopidogrel*

The drug Plavix® commonly known as *clopidogrel* (Figure 1), [13], is an antiplatelet agent used in treating coronary heart disease, peripheral vascular disease and cerebrovascular disease. Plavix® requires biotransformation to an active metabolite by cytochrome P450 enzyme to realize its antiplatelet effect. Therefore, any variation in the *CYP2C19* gene may cause a reduced function of drugs that are metabolised by it. Thus, patients treated with *clopidogrel* with a reduced function *CYP2C19* genetic variant had lower levels of active metabolite, resulting in a reduced antiplatelet response to the drug and a threefold risk of stent thrombosis.

Gleevec® – Sprycel® [14]

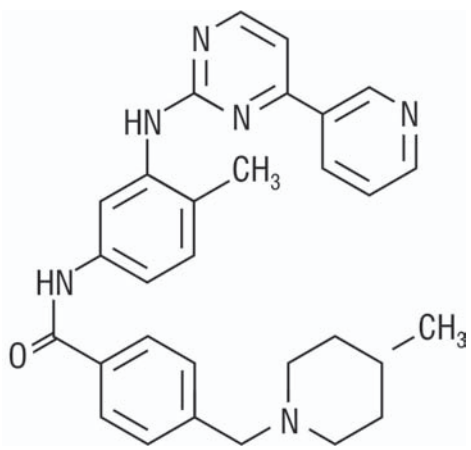

Figure 2. *Chemical structure of imatinib*

Gleevec® (imatinib mesylate, Figure 2) approval for the treatment of a specific form of leukemia was considered a milestone in the development of targeted therapeutics. Gleevec® is indicated for patients with Philadelphia chromosome-positive (Ph+) chronic myeloid leukemia (CML) in chronic phase. It is also indicated for the treatment of patients witk kit (CD117) positive unresectable and/or metastatic malignant gastrointestinal stromal tumors.

Captosar®/ Capto® (irinotecan)[15]

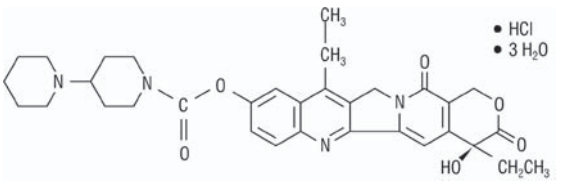

Figure 3. *Chemical structure of irinotecan*

Captosar® is indicated for colon cancer. Variations in the UGT1A1 gene can influence a patient's ability to break down irinotecan, which can lead to increased blood levels of the drug and a higher risk of side effects.

Herceptin® [16]

Herceptin® (trastuzumab) is a monoclonal antibody which utilises the natural immune system to kill tumour cells.

Herceptin® is a monoclonal antibody for the treatment of patient with metastatic breast cancer whose tumours over express the HER2 protein and who have received one or more chemotherapy regimens for their metastatic disease.

Each HER2 gene results in the expression of a receptor on the surface of the cell. If the gene makes too much receptor, it is referred to as being "over expressed". Cells that over express too much of the HER2 gene can be a specific target for therapies such as Herceptin®. This is usually achieved by performing a special laboratory test on a small piece of you original tumour (from the time of your original surgery or biopsy).

Future perspectives – Conclusion

There are many exciting projects underway, as this is an exceptional time in genetic medicine with the sequenced human genome and a full toolbox to translate basic findings into clinical practice. Currently, efforts are focused on various human diseases, specifically, studies to identify their causative or predisposing genes, understand their pathogenesis and develop new therapies. Research faculty

ranges from basic genetic studies of human cancer predisposition, a new morbid obesity gene, new methods to prolong human egg and embryo viability, microRNAs and immunologic disorders, and the role of copy number variation (CNV) in various diseases, through to clinical trials evaluating new treatments for genetic disorders, including the clinical validation of pharmacogenetic guided-dosing for various drugs.

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ΣΥΝΤΟΜΗ ΕΠΙΣΚΟΠΗΣΗ SHORT REVIEW
ΦΑΡΜΑΚΕΥΤΙΚΗ 24, III, 68-73, 2012 PHARMAKEFTIKI 24, III, 68-73, 2012

The Acid-Base Balance and the Effect of Cannabinoids in Subarachnoid Hemorrhage

Adanela Musara[1], Tahsin Kelliçi[2], Gezim Boçari[3]
[1.] Department of Medicine; University "Alexander Moisiu", Durres.
[2.] Department of Chemistry; University of Athens,
[3.] Molecular Diagnostic Center, Obstetric Gynecologic University Hospital Center, Tirana;

Summary

The use of the triple H therapy (hypervolemic, hypertensive, hemodilutional therapy) is widely accepted in the clinical management of patients with subarachnoidal hemorrhage (SAH). The clinical efficacy of triple H therapy is lacking. Since cannabinoids (CB) are involved in different functions as nociception, control of appetite and energy balance, cognitive processes or even the regulation of emotional states, the therapeutic potential of putative receptor-specific ligands have always aroused great interest in the industry. At a time when there is much talk of the efficacy of rimonabant - the researchers found that it preferentially binds to CB1, thereby blocking endocannabinoid action at that receptor but not at CB2 - in the treatment of smoking and obesity (and associated metabolic disorders) it is necessary to investigate the therapeutic potential of CB1 antagonists in a field relatively unexplored: the aneurisms derived from the subarchnoidal hemorrhage, resulting in a possible therapy instead of the triple H therapy.

Introduction

The human brain represents approximately 2% of total body weight, yet it receives approximately 20% of cardiac output and uses 20% of total body oxygen consumed under normal conditions. In this situation, most of the energy of the brain is obtained exclusively from aerobic metabolic process[1].Impairment in the supply of nutrients and oxygen to the brain can cause cellular damage[2].

Respiratory acid-base disturbances have a profound effect on Central Nervous System (CNS). This phenomenon stems from the fact that CNS must respond to changes in systemic carbon dioxide partial pressure, pCO_2, which are immediately reflected in the CNS as a result of the permeability of the Blood Brain Barrier to CO_2, as well as to changes in the peripheral concentration of the hydrogen ions[3]. More to the point, the almost instantaneous effect of acute respiratory acidosis on the Cerebrospinal fluid (CSF) pH and the intracellular pH of brain cells is explained by the above mentioned ability of CO_2 to pass through the cellular barriers[4].

Acid-Base Balance Disturbances

Acid base balance is one of the factors that affect cerebral blood flow (CBF) and its disturbances, associated with abnormal metabolism, head trauma or stroke, lead to secondary brain injuries, consequently worsening the clinical outcome[5,6] CBF varies directly with the alterations in the cerebral perfusion pressure (CPP), which is defined as the difference between mean arterial and intracranial pressures, and inversely with cerebrovascular resistance (the sum of vascular resistance to flow, particularly at the level of the small pial arteries and penetrating pre-capillary arterioles). The contribution of any given cerebral vessel to overall CBF is defined by factors, such as its radius and length, and both blood viscosity and pressure. Tissue perfusion in the brain, a measure of the exchange of

* *Corresponding author Musaraj A., e-mail: adanela.musaraj@gmail.com*

oxygen and carbon dioxide is approximately 50 to 55 mL/100 g/min. As blood perfusion is progressively reduced, oxygen extraction from hemoglobin, which is indicated by arteriovenous difference in oxygen, increases without clinical manifestation. When blood perfusion reaches 25 to 30 mL/100 g/min, electroencephalographic (EEG) abnormalities and consciousness alterations may occur. As blood perfusion falls further below 20 mL/100 g/min approximately, EEG becomes isoelectric and neurons increasingly switch to anaerobic metabolism, with concomitant increased production of lactate and hydrogen ions. Once perfusion reaches 10 to 12 mL/100 g/min, neurotransmission is lost, sodium-potassium pumps fail[7] and cytotoxic edema ensues[8]. In the absence of cerebral hypothermia, perfusion of less than 6 to 10 mL/100 g/min triggers tissue death cascade mediated by calcium and glutamate[9].

Hypocapnia, on the other hand, is a state of reduced carbon dioxide, Even when marked, hypocapnia is normally well tolerated, often with few apparent effects. Transient induction of hypocapnia can lead to lifesaving physiological changes in patients with severe intracranial hypertension or neonatal pulmonary-artery hypertension, but hypocapnia of longer duration in critically ill patients may have a negative outcome[10,11] (**Figure 1**).

In patients with traumatic brain injury, prophylactic hyperventilation is actually associated with worse outcomes[12], which may be explained in part by the reduced cerebral oxygenation[13]. Thus, although intracranial pressure may decrease transiently, it may do so at the expense of cerebral perfusion[14]. In addition, hypocapnia may exacerbate secondary brain injury, since increased cerebral vascular reactivity and vasoconstriction can result in decrease in regional cerebral blood flow[15]. Therefore, hypocapnia may result in a disproportionate (regional) decrease in cerebral blood flow, without a further decrease in intracranial pressure[16]. Because of these possibilities, a panel of experts has recommended against the prophylactic use of hyperventilation[17].

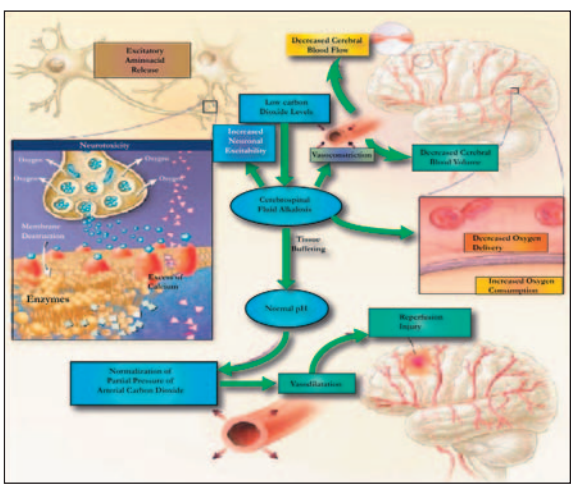

Figure 1: *Neurologic Effects of Hypocapnia. Systemic hypocapnia results in cerebrospinal fluid alkalosis, which decreases cerebral blood flow, cerebral oxygen delivery, and to a lesser extent, cerebral blood volume. Reproduced with permission from Arieff and Laffey [14]*

The above mentioned acid base disturbances, pH changes and changes in oxygen and carbon dioxide levels are associated with acute cerebrovascular diseases, such as subarachnoidhemorrhage (SAH)

Triple-H therapy

Triple-H therapy consists of three separate components: *hypervolemic, hypertensive, hemodilutional therapy,* Thus, Triple H theraphy elevates blood pressure, increases blood volume, and thins the blood. It is used to prevent and treat cerebral vasospasm after aneurysmal subarachnoid hemorrhage (SAH) by driving blood flow through and around blocked arteries However Triple H therapy has many known complications. These include pulmonary edema, dilutional hyponatremia, and complications related to the Swanz-Ganz catheter. Intracranial complications include exacerbation of cerebral edema, increased ICP, hemorrhagic infarction, and risk of rebleeding of unsecured aneurysm. It has been reported that among 323 patients with SAH, 112 patients developed a delayed ischemic deficit, 94 of whom underwent hypervolemic therapy. Infarction caused by vasospasm was found ultimately in 43 of these 94 patients. Twenty-six patients (28%) developed an intracranial complication during hypervolemic therapy: cerebral edema was aggravated in 18, and a hemorrhagic infarction developed in 8. In 13 of 18 patients with aggravation of edema, delayed ischemic deficit developed within 6 days after the SAH. After hypervolemic therapy, the 18 patients with aggravation of edema deteriorated rapidly, and 14 of them died. Hemorrhagic infarction developed as the delayed ischemic deficit resolved. Thus, to avoid hemorrhagic infarction, it is important to discontinue hypervolemic therapy as soon as the delayed ischemic deficit resolves[18,19,20].

As invasive hemodynamic monitoring has become standard in the management of aneurysmal SAH, there have been complications related also to the Swanz-Ganz catheters used in this therapy. In a retrospective analysis of 630 Swan-Ganz catheters placed in 184 patients with aneurysmal SAH, there was a 13% incidence of catheter-related sepsis (81

of 630 catheters), a 2% incidence of congestive heart failure (13 of 630 catheters), a 1.3% incidence of subclavian vein thrombosis (8 of 630 catheters), a 1% incidence of pneumothorax (6 of 630 catheters), and a 0% incidence of pulmonary artery rupture [21]

To avoid complications associated with the use of "the triple H" therapy for cerebral vasospasm following subarachnoid hemorrhage an alternative therapy is gaining increasing interest, which however still needs further investigations on human patients with SAH. This therapy includes the adiministation of cannabinoids.

Cannabinoids and their potential therapeutic role

Since the discovery in the early 1990s, of specific membrane receptors of the main endogenous cannabinoid 9-tetrahydrocannabinol, the interest on this topic has not stopped growing. In light of recent work, the role of endocannabinoid system is particularly becoming a hot issue in the neurological pharmacology[22].

Endocannabinoids participate in the mechanism of preconditioning and neurological exogenous administration of cannabinoids in hemorrhage[23] and would benefit the damage associated with ischemia-reperfusion sequence[24]. Concerning their vascular effects, the situation appears more complex. According to studies, impact constrictors or dilators of cannabinoids are described[25]. Finally, pathophysiological conditions including cerebral ischemia, hemorrhagic shock or endotoxic shock might be connected with the physiological functions of endocannabinoids[26].

There are promising recent studies that suggest a possible neuroprotective role of the cannabinoid agonists [29-32]. Experiments in adult rat models show that a synthetic cannabinoid agonist, R (+)-WIN 55212-2 (1 mg / kg) administered after hypoxic-ischemic episodes, have neuroprotective effects both in vitro and in vivo[27]. Possible effects mediated by specific CB1 receptors have suggested that cannabinoids also reduce the neurotoxicity mediated by NMDA, AMPA or kainate[28], and inhibit the induction of the iNOS[29] (nitric oxide synthase), at least mediated by lipopolysaccharide. Moreover, cannabinoids have pharmacological effect of hypothermia[30], but may also have cardiorespiratory effect. Also, cannabinoid agonists have shown some effects on brain arteriolar vasodilator, an effect that seems to be mediated by the endothelium-derived hyperpolarizing factor (EDHF)[25].

This is a crucial point, because the EDHF is the guarantor of arterial vasodilation in deficit situations of nitrogen oxide (NO) and has a very important role on autoregulatory response ofcerebral arteries of newborn animals (rats)[31]. The neuroprotective effect of cannabinoids appears to be selective, i.e. it depends on the specific region of the brain that is damaged [30]. These studies on neuroprotection have been performed in adults. In newborn animals there are no studies on cannabinoids neuroprotection effect, but it has been shown that the depressant effects on motor activity, which are typical of cannabinoids, are practically absent in immature animals[32]. Furthermore, it has been suggested that cannabinoids may serve as growth factors and their receptors CB1 seem to be involved in events proliferation and migration of neurons and glial cells, synaptogenesis and axonal elongation, and myelin formation [33] (**Figure 2**).

As far as we know, cannabinoids have hypothermic pharmacological effects[34], influence the cardiorespiratory system[32] and also have vasodilator effects on the cerebral arterioles, an effect that seems mediated by the endothelium-derived hyperpolarizing factor (EDHF) [35].

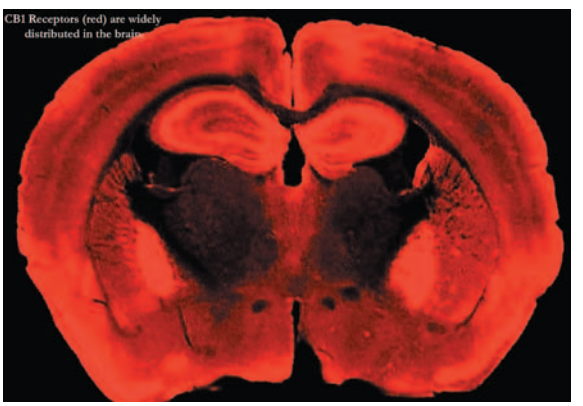

Figure 2: *CB1 receptors are so widely distributed throughout both the brain and body periphery that activating them indiscriminately could cause a host of undesired side effects. Reproduced with permission from Weckesser M.*[15]

There are also studies made in human patients treated with cannabinoids as Dexabinol, in secondary brain damage.

Secondary brain damage from traumatic brain injury involves several biochemical mechanisms including the release of excitatory amino acids (e.g., glutamate that overactivates their receptors andbrings about excitotoxicity [1]). Overproduction of oxygen free radicals and proinflammatory molecules (e.g., tumor necrosis factor- and bradykinin) have also been described in ischemic and traumatic brain injury in animals and man [2-4].

Glutamate antagonists, free radical scavengers, and anti-inflammatory agents have been shown to improve outcome in animal models of brain ischemia and traumatic brain injury. Knowledge prompted the clinical development of several glutamate antagonists, free radical scavengers, and anti-inflammatory agents as putative neuroprotective agents for head injury [5-8].However, the results of most of the clinical trials undertaken so far were disappointing [7, 8] (**Figure 3**).

Dexanabinol is a synthetic cannabinoid which acts as a non competitive inhibitor of NMDA receptors, an anti-oxidant and anti inflammation by inhibiting TNF.

According to a single existing study[36] dexanabinol, administered in humans within the first six hours after a trauma, reduced the incidence of intracranial hypertension very significantly leading to a faster recovery in the treated group. This molecule is currently the subject of a large multicenter study and we will soon know if its effect is only cosmetic pic or it can actually improve prognosis of severe traumatic brain injury. The demographic characteristics of the patients who were enrolled in the study are typical of the severe head trauma population, namely young males with the leading cause of injury being motor vehicle accidents. Thirty-seven patients received placebo (13 patients with low-dose vehicle and 24 with the high dose) and 30 were treated with the study drug (10 patients with 48 mg and 20 with 150 mg). The two dose groups were analyzed separately (each dose compared to its own placebo) as well as together (all drug treated vs. all vehicle controls). The four groups did not differ significantly in baseline demographics or risk factors and dexanabinol treatment effects were not different between the two doses (data not shown). Therefore, the results presented below show the comparison between all drug-treated and all vehicle-treated patients.

The effect of dexanabinol in the brain-injured patients appears to be similar to the edema-preventing effects previously observed in animal models of head trauma and stroke [12, 15, 22] and compatible with the proposed neuroprotective mechanisms of the drug [10,11].

Dexanabinol, in doses of 48 and 150 mg, was found to be safe and well tolerated in this group of patients with severe head trauma. Dose-limiting toxicity was not observed, suggesting a higher dose needs to be tested. A single administration of the drug resulted in significant improvement in ICP and CPP and a trend toward better neurologic outcome[36].

Recently a non selective CB1, CB2 cannabinoid analog WIN55212-2 was tested for the treatment of neonatal rat brain hypoxia–ischemia in Wistar rats

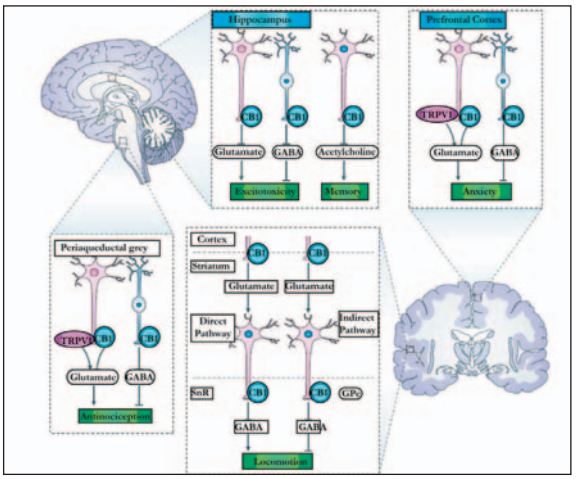

Figure 3: *Physiological roles of the endocannabinoids and the potential benefits or consequences of their dis-regulation. Reproduced with permission from Chin S.A.*

Results showed that admistration of WIN55212-2 promoted white and gray matter leadind to remyelination of the injured area.

However it is necessary to know all the mechanisms involved in the modulation of the endocannabinoid system before proposing such analogs as alternative therapeutic for hypothermia in the management of newborn-ischemic aneurysms, a prevalent and devastating condition for which no pharmacological treatments are yet available.[37].

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Η επίδραση της οξεοβασικής ισορροπίας και των κανναβινοειδών στην υποαραχνοειδή αιμορραγία

Adanela Musara[1], Tahsin Kelliçi[2], Gezim Boçari[3]
[1.] Τμήμα Ιατρικής, Πανεπιστήμιο του Δυρραχίου «Aleksander Moisiu»
[2.] Εργαστήριο Οργανικής Χημείας, Τμήμα Χημείας, Πανεπιστήμιο Αθηνών
[3.] Μοριακό Διαγνωστικό Κέντρο, Πανεπιστημιακή Γυναικολογική Κλινική, Τίρανα

Περίληψη

Η εφαρμογή της θεραπείας «Triple H» (hypertension: υπέρταση, hypervolemia: υπερογκαιμία, hemodilution: αιμοαραίωση) έχει αποδεχθεί ευρέως ως ο κύριος τρόπος της κλινικής διαχείρισης των ασθενών με υποαραχνοειδή αιμορραγία (SAH). Παρόλα αυτά η κλινική αποτελεσματικότητα της θεραπείας αυτής παρουσιάζει κενά. Εφόσον τα κανναβινοειδή εμπλέκονται σε σημαντικές λειτουργίες του οργανισμού όπως στους υποδοχείς ερεθισμάτων πόνου, τον έλεγχο της όρεξης, τις ενεργειακές απαιτήσεις του σώματος, τη νοητική ανάπτυξη, καθώς και τη ρύθμιση της διάθεσης, οι θεραπευτικές ιδιότητες των υποκαταστατών που δεσμεύονται στους κανναβινοειδείς υποδοχείς έχουν προκαλέσει μεγάλο ενδιαφέρον στη βιομηχανία φαρμάκων. Ιδιαίτερα τώρα που η επιστημονική κοινότητα συζητά έντονα την δραστικότητα του rimonabant – υποκαταστάτης που δεσμεύεται εκλεκτικά στον υποδοχέα CB1, εμποδίζοντας τη δράση των ενδοκανναβινοειδών στο συγκεκριμένο υποδοχέα αλλά όχι και στο CB2- στη θεραπεία της παχυσαρκίας και κατά του καπνίσματος είναι απαραίτητη η διερεύνηση των θεραπευτικών ιδιοτήτων των ανταγωνιστών του υποδοχέα CB1 σε ένα σχετικά ανεξερεύνητο πεδίο: τα ανευρύσματα που προκαλούνται από την υποαραχνοειδή αιμορραγία, αποτελώντας έτσι μια εναλλακτική θεραπεία στο τριπλό Η.

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Αθήνα, 13 Ιουνίου 2012

Συγκρότηση σε σώμα του νέου Δ.Σ. της Ελληνικής Φαρμακευτικής Εταιρείας (Ε.Φ.Ε.)

Την 13η Ιουνίου 2012 συγκροτήθηκε σε σώμα το νέο Διοικητικό Συμβούλιο της Ε.Φ.Ε. που προήλθε από τις εκλογές της 30ης Μαΐου 2012

Η σύνθεση του νέου ΔΣ μετά από ψηφοφορία μεταξύ των εκλεγέντων συμβούλων είναι η παρακάτω:

Πρόεδρος:	Κωνσταντίνος Δεμέτζος	Καθηγητής, Τμ. Φαρμακευτικής, Ε.Κ.Πανεπιστήμιο Αθηνών
Α΄ Αντιπρόεδρος:	Άννα Τσαντίλη - Κακουλίδου	Καθηγήτρια, Τμ. Φαρμακευτικής, Ε.Κ.Πανεπιστήμιο Αθηνών
Β΄ Αντιπρόεδρος:	Τζούλια Άττα - Πολίτου	Αν. Καθηγήτρια, Τμ. Χημείας, Ε.Κ.Πανεπιστήμιο Αθηνών
Γενικός Γραμματέας:	Ιωάννα Χήνου	Αν. Καθηγήτρια, Τμ. Φαρμακευτικής, Ε.Κ.Πανεπιστήμιο Αθηνών
Ταμίας:	Ελένη Σκαλτσά	Αν. Καθηγήτρια, Τμ. Φαρμακευτικής, Ε.Κ.Πανεπιστήμιο Αθηνών
Ειδικός Γραμματέας:	Σοφία Χατζηαντωνίου	Επικ. Καθηγήτρια, Τμ. Φαρμακευτικής, Πανεπιστήμιο Πατρών
Μέλη:	Μαρία Καπετανίδου	Φαρμακοποιός, Προϊσταμένη Αξιολόγησης Λοιπών Προϊόντων, ΕΟΦ
	Γρηγόρης - Πάρης Μποσκόπουλος	Φαρμακοποιός Σύμβουλος Επιχειρήσεων
	Ιωάννης Παπαδόπουλος	Φαρμακοποιός, Οικονομολόγος Υγείας Υπ. Διδάκτωρ Πανεπιστημίου Αθηνών
Αναπλ. μέλος	Σταυρούλα Καντούνα	Φαρμακοποιός
Εξελεγκτική Επιτροπή:	Ιωάννα Ανδρεάδου	Επικ. Καθηγήτρια, Τμ. Φαρμακευτικής, Ε.Κ.Πανεπιστήμιο Αθηνών
	Όλγα Τζάκου	Αν. Καθηγήτρια, Τμ. Φαρμακευτικής, Ε.Κ.Πανεπιστήμιο Αθηνών

Ο Πρόεδρος
Καθηγητής Κωνσταντίνος Δεμέτζος

Η Γραμματέας
Αν. Καθηγήτρια Ιωάννα Χήνου

Αθήνα, 13 Ιουνίου 2012

Ανακοίνωση του νέου Δ.Σ. της Ε.Φ.Ε

Αγαπητοί συνάδελφοι,

Με την ευκαιρία της συγκρότησης σε σώμα του Δ.Σ. της Ελληνικής Φαρμακευτικής Εταιρείας (Ε.Φ.Ε), παρουσιάζουμε τις αρχές και τις κατευθύνσεις που θεωρούμε ότι εκφράζουν την επιστημονική μας εταιρεία.

Η **Ε.Φ.Ε**. είναι ιστορικά η Επιστημονική Εταιρεία όλων των Ελλήνων Φαρμακοποιών, ανεξαρτήτως επαγγελματικής δραστηριότητας, με μόνους σκοπούς την προαγωγή της Φαρμακευτικής επιστήμης και την επιστημονική της συμβολή σε θέματα που σχετίζονται με το φάρμακο και την ανθρώπινη υγεία.

Η **Ε.Φ.Ε**. ιδρύθηκε το **1932** και η ιστορική της πορεία είναι παράλληλη με την εξέλιξη της Φαρμακευτικής επιστήμης στην Ελλάδα.

Βασικός σκοπός της **Ε.Φ.Ε** είναι:

1. η ανάδειξη του επιστημονικού ρόλου του Έλληνα Φαρμακοποιού και η συμβολή του στη σωστή ενημέρωση των πολιτών για θέματα υγείας που σχετίζονται με το φάρμακο, θεωρώντας ότι το φάρμακο αποτελεί αποκλειστικά κοινωνικό αγαθό..

2. Η συμβολή της στην ανάπτυξη διαύλου επικοινωνίας με τους θεσμικούς φορείς της υγείας, ώστε να καταστήσει δυνατή τη λειτουργία της και ως σύμβουλου της πολιτείας σε θέματα που αφορούν το φάρμακο.

3. Η συμμετοχή της στα Διεθνή και Ευρωπαϊκά δρώμενα (EUFEPS, FIP), που αφορούν στο φάρμακο και η ουσιαστική της παρέμβαση στις αντίστοιχες επιστημονικές εξελίξεις.

Η εκπλήρωση των παραπάνω σκοπών της **Ε.Φ.Ε**. θα υλοποιηθεί με την ουσιαστική συμμετοχή όλων των Φαρμακοποιών, αξιοποιώντας την εμπειρία που έχουν αποκτήσει από την άσκηση της επιστήμης τους στους διάφορους επί μέρους χώρους απασχόλησης τους.

Ευελπιστούμε η **Ε.Φ.Ε**. μέσω των δραστηριοτήτων της να δημιουργήσει τον πυρήνα επιστημονικής γνώσης και προβληματισμού σε θέματα που αφορούν στην εξέλιξη της επιστήμης μας, στην ορθή χρήση και να συμβάλλει στην καλύτερη ενημέρωση των Ελλήνων πολιτών σε θέματα υγείας.

Ο Πρόεδρος
Καθηγητής Κωνσταντίνος Δεμέτζος

Η Γραμματέας
Αν. Καθηγήτρια Ιωάννα Χήνου

1ο Συνέδριο Φαρμακευτικών Επιστημών

Με μεγάλη επιτυχία ολοκλήρωσε τις εργασίες του το Πρώτο Συνέδριο φαρμακευτικών Επιστημών, που έλαβε χώρα στις εγκαταστάσεις του Πανεπιστημίου Αθηνών, στην Πανεπιστημιούπολη Ζωγράφου.

Το Συνέδριο διήρκησε 4 μέρες, από τις 27 έως και τις 30 Απριλίου 2012 και η διοργάνωση του αποτέλεσε πρωτοβουλία των τρίων Φαρμακευτικών Τμημάτων των Πανεπιστημίων της χώρας μας, με στόχο να αποτελέσει θεμέλιο λίθο για τη δημιουργία ενός κύκλου συνεδρίων του ίδιου αντικειμένου.

Το πλούσιο και ιδιαίτερα ενδιαφέρον επιστημονικό πρόγραμμα και η επιλογή καταξιωμένων ομιλητών του χώρου συντέλεσαν σε μία πολύ εντατική συμμετοχή και ανταπόκριση από πλευράς φαρμακοποιών, υπαλλήλων στις φαρμακευτικές βιομηχανίες και ιδιαίτερα φοιτητών της Φαρμακευτικής στο συνέδριο, με αποτέλεσμα το συνέδριο να ξεπεράσει κάθε προσδοκία συμμετοχών φτάνοντας συνολικά τους 900 συνέδρους.

Παράλληλα, στο συνέδριο συμμετείχαν επιστήμονες και ερευνητές από όλο το φάσμα των φαρμακευτικών επιστημών.

Στο πλαίσιο του Συνεδρίου πραγματοποιήθηκε Επίσημη Τελετή Έναρξης την Παρασκευή 27 Απριλίου 2010 και ώρα 19:30. Στην τελετή του συνεδρίου απεύθυναν χαιρετισμό ο Αντιπρύτανης του Πανεπιστημίου Αθηνών, κ. Θωμάς Σφηκόπουλος, ο Αν. Πρόεδρος Τμήματος Φαρμακευτικής του Πανεπιστημίου Αθηνών, κ. Παναγιώτης Μαράκος, ο Αν. Πρόεδρος Τμήματος Φαρμακευτικής του Πανεπιστημίου Θεσσαλονίκης, κ. Χρήστος Παναγιωτίδης και ο Πρόεδρος του Τμήματος Φαρμακευτικής του Πανεπιστημίου Πατρών, κ. Σωτήρης Νικολαρόπουλος. Η τελετή ολοκληρώθηκε με την Επίσημη Έναρξη του Συνεδρίου από τον Πρόεδρο της Οργανωτικής Επιτροπής, καθηγητή κ. Παναγιώτη Μαχαίρα.

Στη συνάντηση των μελών ΔΕΠ των 3 Φαρμακευτικών Τμημάτων αποφασίστηκε το επόμενο συνέδριο να πραγματοποιηθεί σε 2 χρόνια στη Θεσσαλονίκη.

15ο Πανελλήνιο Συμπόσιο Φαρμακοχημείας

Στις 25-27 Μαΐου 2012 πραγματοποιήθηκε με μεγάλη επιτυχία το 15ο Πανελλήνιο Συμπόσιο Φαρμακοχημείας. Το Συμπόσιο έλαβε χώρα στην Αθήνα, στην αίθουσα 'Λεωνίδας Ζέρβας' του Εθνικού Ιδρύματος Ερευνών. Οργανώθηκε από την Ελληνική Εταιρεία Φαρμακοχημείας και το Τμήμα Οργανικής και Φαρμακευτικής Χημείας της Ένωσης Ελλήνων Χημικών και τελούσε υπό την αιγίδα της European Federation of Medicinal Chemistry (EFMC).

Η επίσημη γλώσσα του Συμποσίου ήταν η αγγλική. Το Συμπόσιο παρακολούθησαν 250 σύνεδροι - μεταξύ των οποίων 98 προπτυχιακοί φοιτητές- από πανεπιστήμια και ερευνητικά κέντρα, από όλη την Ελλάδα, καθώς και το εξωτερικού (Αλγερία, Βουλγαρία, Κύπρος, Δανία, Γαλλία, ΠΓΔΜ, Ιταλία, Ρουμανία, Ταϊλάνδη, Τουρκία, Σερβία, Ηνωμένο Βασίλειο).

Το επιστημονικό πρόγραμμα περιελάμβανε 6 κεντρικές διαλέξεις, 11 κύριες διαλέξεις, 15 προφορικές ανακοινώσεις και 124 ανηρτημένες ανακοινώσεις. Κατά τη διάρκεια του Συμποσίου αναπτύχθηκαν και συζητήθηκαν διαφορετικές πτυχές των σύγχρονων εξελίξεων στην επιστήμη της Φαρμακοχημείας από τον σχεδιασμό νέων φαρμακομορίων αξιοποιώντας τις δυνατότητες της τεχνολογίας in silico, τη σύνθεση και βιολογική αξιολόγηση νέων υποψηφίων φαρμακομορίων, τη σημασία των φυσικών προϊόντων ως πηγής ανακάλυψη νέων δραστικών ουσιών φαρμάκων, έως το ρόλο της επιγενετικής (επιγονιδιωματικής) καθώς κα της ανακάλυψης νέων βιοδεικτών.

Μεταξύ των ανηρτημένων ανακοινώσεων, επιλέχθηκαν τρεις για σύντομη προφορική παρουσίαση πριν το κλείσιμο του Συμποσίου.

Πριν την έναρξη του Συμποσίου διοργανώθηκε επιτυχημένο σεμινάριο της εταιρείας λογισμικών Schrödinger, το οποίο παρακολούθησαν 40 μεταπτυχιακοί και προπτυχιακοί φοιτητές.

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1st Announcement

ΦΑΡΜΑΚΕΥΤΙΚΗ 24, ΙΙΙ, 78, 2012 PHARMAKEFTIKI 24, III, 78, 2012

Στη μνήμη του Καθηγητή Σκεύου Φιλιάνου

Στις 24 Σεπτεμβρίου 2012 έφυγε από κοντά μας πλήρης ημερών ο αγαπημένος δάσκαλος μας, ο ομότιμος καθηγητής Σκεύος Φιλιάνος. Γυιός φαρμακοποιού, ο Σκευος Φιλιάνος γεννήθηκε στην Αλεξάνδρεια το 1923, σπούδασε στη Βηρυτό και το Κάιρο, άσκησε για 17 χρόνια το φαρμακευτικό επάγγελμα, ενώ από το 1959 ξεκινά την ακαδημαϊκή του σταδιοδρομία στο Εργαστήριο Φαρμακογνωσίας του Πανεπιστημίου Αθηνών, όπου και υπηρέτησε σε όλες τις βαθμίδες μέχρι τη βαθμίδα του τακτικού καθηγητή. Μέχρι το 1990 οπότε και συνταξιοδοτήθηκε υπήρξε δάσκαλος πολλών γενιών φαρμακοποιών στο αντικείμενο της Φαρμακογνωσίας, ασκώντας τους στα εργαστήρια ή μεταδίδοντας τις γνώσεις του στις αίθουσες διδασκαλίας, Τον θυμόμαστε ήρεμο, ευγενικό, υπομονετικό, με αγάπη για την επιστήμη του – κλασικός φαρμακογνώστης- αλλά και για τη Φαρμακευτική γενικότερα επιτελώντας παράλληλα με σεμνό και αθόρυβο τρόπο ευρύ κοινωνικό έργο ως μέλος του ανώτατου Υγειονομικού Συμβουλίου, μέλος της Ευρωπαϊκής Επιτροπής Φαρμακοποιίας και Πρόεδρος της Επιτροπής της Ελληνικής Φαρμακοποιίας, εμπειρογνώμων των ομάδων Φυτοχημείας Λιπαρών Ουσιών και Εντομοκτόνων της Ευρωπαϊκής Φαρμακοποιίας, εμπειρογνώμων της Π.Ο.Υ. σε θέματα φαρμακοποιών, μέλος κατά περιόδους του Δ.Σ. της Ε.Φ.Ε.. Βαθύς γνώστης της Φαρμακογνωσίας, Φυτοχημείας, της Φυτοθεραπευτικής και της Ιστορίας της Φαρμακευτικής, με ιδιαίτερο ενδιαφέρον για την Ομοιοπαθητική, ο Σκεύος Φιλιάνος εντυπωσίαζε με τις επιστημονικές του γνώσεις στα πεδία αυτά αλλά και με την ευρύτητα της μόρφωσής του. Οι φοιτητές του, οι μετέπειτα συνάδελφοί του, αλλά και όσοι είχαν την τύχη να γνωρίσουν το Σκεύο Φιλιάνο θα τον θυμούνται πάντα ως ένα γλυκύτατο, ήρεμο, σεμνό δάσκαλο και άνθρωπο που έκρυβε έναν θησαυρό γνώσεων και ήταν πρόθυμος πάντα να συνεργαστεί και να βοηθήσει τους νεώτερους. Καλό ταξίδι στο δάσκαλό μας...

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