WORLD JOURNAL OF PHARMACEUTICAL RESEARCH
SJIF Impact factor 8.084
Volume 12, Issue 4, 1299-1319. Research Article ISSN 2277– 7105

PV SIGNAL DETECTION USING STATISTICAL DATA MINING METHODS

***Atharva Bharat Karale and Dr. M. D. Game**

Vidyabharati College of Pharmacy, C. K. Naidu Road, Camp, Amravati.

Article Received on
02 Jan. 2023,

Revised on 23 Jan. 2023,
Accepted on 12 Feb. 2023

DOI: 10.20959/wjpr20234-27277

***Corresponding Author**
Atharva Bharat Karale
Vidyabharati College of Pharmacy, C. K. Naidu Road, Camp, Amravati.

ABSTRACT

Pharmacovigilance programmes monitor and help safeguarding the use of medicines which is grave to the success of public health programmes. Identifying new possible risks and developing risk minimization action plans to prevent or ease these risks is at the heart of allpharmacovigilance activities throughout the product lifecycle. In this paper we examine the use of data mining algorithms to identify signals from adverse events reported. The capabilities include screening, data mining and frequency tabulation for potential signals, including signal estimation using established statistical signal detection methods. We have standard processes, algorithms andfollow current requirements for signal detection and risk management activities. The Safety Evaluators, who are familiar with the current labeling, known adverse events, and mechanism of actions of their drugs, read the reports, look for particular abnormalities or issues relative to the normal product safety profile, and check the validity of the report. If the collection of reports is regarded important due to abnormalities or issues after this process, the drug and adverse event relationship is investigated more thoroughly and regulatory action may be taken. In this paper various statistical data mining algorithms and statistical analyses used to find patterns within sets of data at the FDA. With data mining, the FDA can improve its report analysis processby automatically selecting the most significant reports for review as well as allowing reviewers to view the information from all the reports received in an organized manner, instead of having to manually consider each one. The reports that may contain serious and unexpected adverse events.

KEYWORDS: Adverse drug reactions, pharmacovigilance, safety signals, statistical methods.

1 THEORY

1.1 Introduction[1-4]

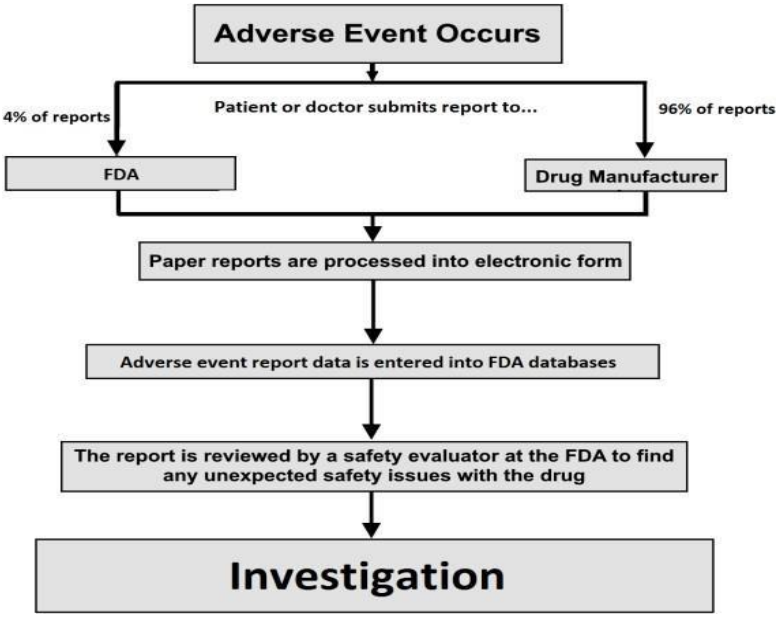
An important challenge for medical industry in developing new drug is the Adverse Drug Reaction (ADR). The study of the adverse drug reactions of the newly released drugs is called Pharmacovigilance which educate the people on the benefit and risk of drugs and warn them. Thequintillion of reports about adverse drug events received by the FDA every year by doctors, general public, manufacturers. As of 2016, FAERS contains over 12 million reports, and year by year over a million are added. After being recorded, the reports are inspected by individual reviewers, called Safety Evaluators, who are responsible for a defined class of drugs. Processing and analyzing this amount of data is difficult to accomplish, as the number of reports outweigh the number of report reviewers. Every month, each individual Safety Evaluator has to attempt to read and carry out an average of 3,417 adverse event reports. To support with the analysis of the enormous amounts of data, the FDA has begun deploying data mining techniques. The Safety Evaluators, who are familiar with the current labeling, known adverse events, and mechanism of actions of their drugs, read the reports, look for particular abnormalities or issues relative to the normal product safety profile, and check the validity of the report. If the collection of reports is regarded important due to abnormalities or issues after this process, the drug and adverse event relationship is investigated more thoroughly and regulatory action may be taken. In this paper various statistical data mining algorithms and statistical analyses used to find patterns within sets of data at the FDA. With data mining, the FDA can improve its report analysis process by automatically selecting the most significant reports for review as well as allowing reviewers to view the information from all the reports received in an organized manner, instead of having to manually consider each one. The reports that may contain serious and unexpected adverse events. Although not yet in routine use for most applications, data mining algorithms has been successfully applied by the FDA in past years. e.g. in 2010 and 2011, data mining was used to identify warning signs that associated Fluzone with febrile seizures in young children.

Researchers calculated an Empirical Bayesian Geometric Mean for each event, which is a value used to determine relevance of reports. This value was adjusted according to the various traits of each report. Next, values fitting within a specific confidence interval were marked for further investigation by reviewers, which may have led to the identification of the safety issue. Due to data mining's uniqueness in pharmacovigilance, the results of data mining are not depended on stand-alone; instead they are compared to the pharmaceutical

knowledge of the FDA Safety Evaluators. As part of the process of testing and moving toward data mining, the FDA has applied its new data mining strategies to existing data, to demonstrate the earlier identification of safety.

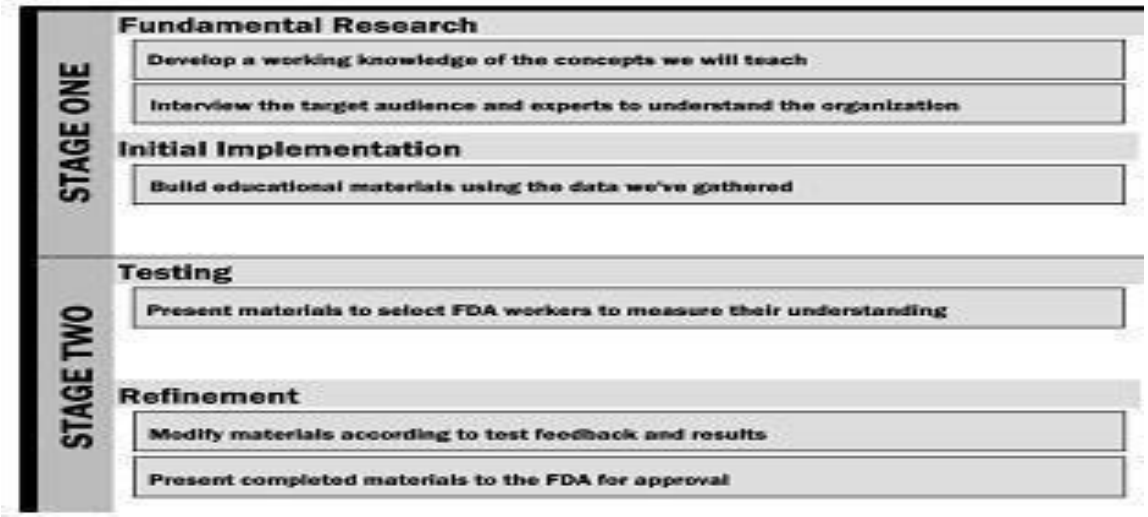
2 METHODOLOGY[5-6]

The overall goal was to support the FDA to conduct pharmacovigilance efforts more efficiently through the development of drug list on data mining concepts and applications, as well as providing a brief overview of suitable data mining tools to the FDA's work. The objectives are, study current pharmacovigilance strategies, assess the current data mining needs of the FDA. Thiswas accomplished in two stages.



2.1.1 FUNDAMENTAL RESEARCH

Stage one consists of interviewing with several domain experts and non-experts in the fields of data mining and pharmacovigilance. It began by establishing a foundation from generating initial prototypes of safety signals. The assessment was made up of semi-structured interviews with employees who are experienced in pharmacovigilance, data mining.



2.1.2 INITIAL IMPLIMENTATION

After gathering all of the information from fundamental research, this work began the initial implementation. To conclude stage one, it constructed a first draft of safety signals according to the information gathered during analysis.

2.1.1.1 STAGE TWO

Stage two consisted of presenting the first draft to a subset of FDA employees, the target audience, after administering a pre-test.

1.1.1.1 TESTING[7-8]

The second stage began with preliminary testing of the target audience, to evaluate what knowledge they had regarding data mining. With the pre-test, we established the extent of data mining knowledge already known by the target population. A post-test was administered to evaluate the efficiency. Test results for both pre- and post-test were evaluated using a standard percentage system.

1.1.1.2 REFINEMENT[9-10]

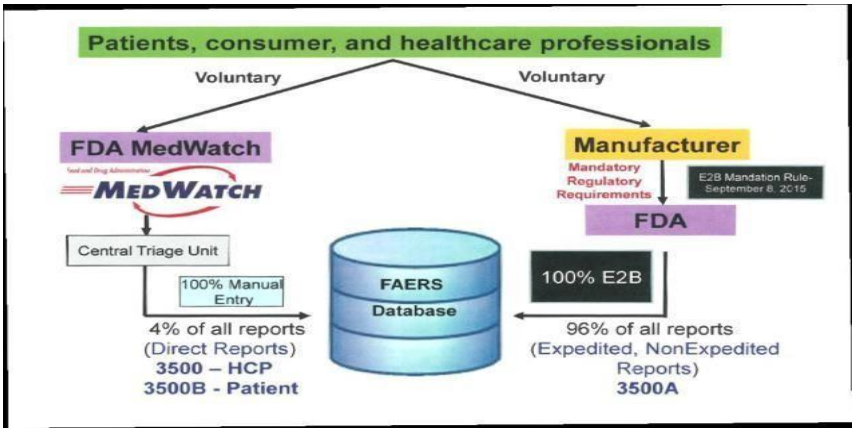
In this part of the process, the final draft was created about safety signals. Revisions were made based on the results from the posttest and the learners' feedback. A combined equipment 'microwave-hydrotherma treatment' has been frequently used in laboratories. The main advantageof the hydrothermal method is the possibility of the formation of crystalline phases, unstable atthe melting point of the desired compound; the main disadvantage is the necessity to haveexpensive equipment. Morphology control and crystallinity for the formed materials can be made by changing pressure, temperature, solvent, reaction time or

precursors' ratio. Hydrothermal reactions in water are considered as more suitable for green chemistry purposes, being environmentally friendly, and are widely applied to fabricate a variety of materials. This method allows minimum loss of reactants and frequently higher yields of products, being especially useful to obtain classic and less-common nanostructures with desired shape and size control products.

1.1.1.3 PROPOSED METHODOLOGY[11-12]

In pharmacovigilance, data mining is primarily used as a descriptive task to uncover links, patterns, and similarities, allowing for clear analysis. To demonstrate these utility, four main statistical data mining algorithms was useful in pharmacovigilance (PV): Proportional Reporting Ratio, Reporting Odds Ratio, Information Component, and Multi-item Gamma-Poisson Shrinker (Empirical Bayesian Geometric Mean) because they calculate signals of disproportional reporting (SDRs).

1.1.1.4 PROPORTIONAL REPORTING RATIO[14-15]

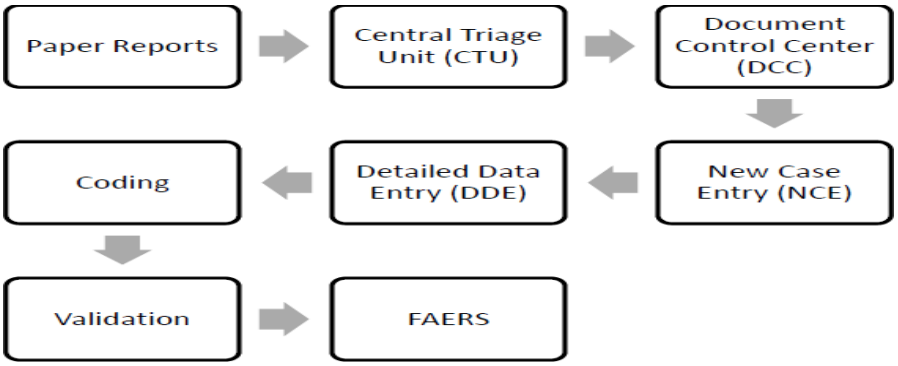


Fe3O4 can adopt different assisted morphologies with magnetic field; for example, it is possible to obtain complex Fe3O4 nanorods by the solvothermal technique. This is possible because, during the formation of nanorods, the growth of the crystals of the metal oxide is oriented in a specific orientation due to the magnetic field. If the magnetic field is applied in the Fe3O4 synthesis by thermal decomposition, it is possible to obtain nanotubes of 250 nm, which are not formed in the absence of the magnetic field; besides, it was observed that the speed in which these nanoparticles of Fe3O4 are heated by hyperthermia is considerably higher in the oxides synthesized in the presence of the magnetic field. Another example that can be mentioned of the synthesis of Fe3O4 with the assistance of magnetic fields is a series of chains prepared at a temperature of 90°C. These particles had an average size of 150 nm.

This was achieved due to the growth of the particles of uniaxial way by the influence of the magnetic field, and it was observed that the intensity of the magnetic field during the synthesis had a significant effect on the anisotropy of the resulting material. The assisted syntheses with magnetic fields can also be applied to the synthesis of some composites, as long as they comply with the characteristics mentioned above. An example of this is the thin layers of reduced graphene oxide (rGO) with Fe_3O_4 nanocrystals. The synthesis of this composite is quite simple, based on taking advantage of the ferromagnetic characteristics of the nanocrystals of Fe_3O_4 that are adhered to the surface of sheets of rGO. When applying the magnetic field on this suspension, the particles agglomerate in one of the walls of the reactor and they adhere to each other by the electrostatic interactions. Biological methods, being compared with conventional chemical and physical methods, could be a preferable synthesis route due to environmentally friendly conditions, despite their lower speed of metal reduction. However, their studies are currently relatively limited, especially those establishing key factors of the biosynthesis, so this method is only developed in laboratory scale, although bacteria could be applied for industrial recovery of silver. The biological synthesis of nanoparticles does not require further stabilizing agents: the microorganisms or extracts themselves act as stabilizing and capping agents. Other advantages of the biological routes are no necessity of toxic chemicals and contaminants, possibility to control shapes and sizes, low cost, biocompatibility and numerous precursors (microorganisms and plants). So, biological methods perfectly fit to the green chemistry, in particular to nanochemistry, resulting in biologically produced nanoparticles, which are non-toxic, stable, environmentally friendly and cost effective. Frequently, the nanoparticles, prepared by biological methods, expose a higher antimicrobial activity (being compared with those synthesized by conventional chemical methods), related with the fact that the stabilization and capping by proteins in more effective. Main recent reviews in this area are described. Biology-based green chemistry methods consist of the use of bacteria, viruses, yeasts, plant extracts fungi and algae, among which we consider plant extracts as most frequent and popular green routes, as it will be shown below especially for the synthesis of nanoparticles, not only those of noble metals, but also carbon dots, metal sulfides, oxides, etc. This area, phytonanotechnology (use of plants) is scalable and medically applicable. Microorganisms represent natural nanofactories, capable to adsorb, accumulate and reduce toxicity of heavy metals, where enzymes are able to reduce metal ions to cero-valent nanoparticles. In the case of bacteria use for nanoparticle preparation, the techniques include the use of bacteria-

containing biomass, as well as supernatant and derived components. Mycosynthesis (use of fungi) allows an easy, stable and possibly scaled-up biosynthesis of nanoparticles. Viruses, whose feature is dense and highly reactive surface (for instance, the surface of tobacco mosaic virus contains 2130 capsid protein molecules), were used to produce several inorganic nanoparticles, such as CdS, ZnS, Fe_2O_3 and SiO_2, important for semiconductor and quantum dot (QD) applications. In addition to conventional 0D nanoparticles, the nanotubes and nanowires can also be produced by virus action. The use of yeasts led the preparation of CdS and PbS QDs, Au and other metal nanoparticles. The use of algae is rare, generally for Au, Pd and Pt nanoparticles. Thus, in the case of algae use, the tetrahedral, decahedral and icosahedral Aunanoparticles, as well as bimetallic Ag/Ag nanoparticles, can be formed due to the action of proteins as stabilizing agent, shape-control modifier and reductant at the same time. Inorganic micro- and nanosized materials can be prepared via intracellular- and extracellular microorganism-assisted synthesis. The formation of nanoparticle is considered (but not yet fully understood) as a bottom-up process due to redox processes with participation of metal ions and biological molecules (proteins, sugars and enzymes), provided by the microorganism, whose interaction with metal ions depends on its type and can vary, also depending on temperature and pH (environmental factors), as well as metal salt concentration, leading to a particular morphology and size of nanoparticles. In the intracellular methods, several additional stages are needed, such as ultrasonication to destroy cell wall, washing, centrifugation, etc. which are absent in the extracellular techniques. Biosynthesis processes of fabrication of homogeneous-size nanoparticles with certain reproducible morphology is carried out by size and shape control of critical factors, such as temperature (maximum possible for fast growth of microorganisms), pH (one of the most important factors, ranged generally from 3 to 10; acidic pH contributes to the agglomeration of nanoparticles due to the higher ion binding), salt concentration, choice ofbiological source, temperature, redox conditions, synthesis duration and incubation period, irradiation and aeration. As it was noted, the use of plant extracts are common preparation procedures for a variety of nanoparticles of metals, non-metals and several of their compounds. Plant extracts contain polyphenols, terpenoids, proteins, enzymes, peptides, sugars, phenolic acids, bioactive alkaloids as a driving force for nanoparticle formation. Using plant extracts, the following nanoparticles have been obtained: Au, Ag (a host of reports), Cu, CuO, TiO_2, ZnO, In_2O_3, Fe, Fe_2O_3, Pb and Se. A large number of their final morphologies have been reported: spheres, triangles, cubes, pentagons, hexagons, wires, rods, etc., for example, Au

triangles (reduction of HAuCl4 with Aloe vera), and Ag nanowires (reduction of Ag+ with Cassia fistula leaf). Nanoparticle sizes can vary considerably, for example, CdS (from ultra-small 2–5 nmto large 200 nm), Ag (5–400 nm), Au (5–85 nm) or magnetite (20–50 nm). Factors influencing their size and shape are as follows: plant extract and metal salt concentrations, temperature (25–95°C), pH (lower pH—larger particles), reaction time (normally from minutes to several hours). Different metals have distinct capacity to be reduced by plant extracts; easiest processes correspond tonoble metals, especially silver. Typical disadvantages in plant-assisted reduction of metals are difficulties in separation of formed metal nanoparticles from the biomass and accompanying putrification processes in reaction systems in the case of long-term reduction. So, the low or practically no cost of plant extracts can cause an imagination about apparent scalabilityfor these processes.



1.2 INFORMATIONS COMPONENT (IC)[19-20]

THEORY[21-22]

Data play the most fundamental role in synthesis. The ideology of Data Mining calls for the development of new chemical relativities and reaction conditions that can potentially provide benefits for chemical syntheses in terms of resource and energy efficiency, product selectivity, operational simplicity, and health and environmental safety.

1.2.1.1 CALCULATION FORMULA

$IC= log2\ (A\times(A+B+C+D)/(A+D)\times(A+B))$, By using a ruthenium-catalyzed redox isomerization of propargyl alcohols into enones in lieu of the traditional twostep stoichiometric reduction and oxidation sequence, a catalytic enantioselective total synthesis of adociacetylene B can be realizedefficiently. Isomerization of an alkynyl vinylcyclopropene to a fused 5- to 7-ring structure converts classical atom inefficient synthetic strategies to ones of ideal atom, economy.

1.2.1.2 MULTI ITEM GAMMA POINTER SHRINKER

Bayesian "shrinkage" can be summarized as the improving of an estimate by combining the estimate with other information. Stratification is a procedure for mitigating effects of confoundingby adjusting for associations between a drug and a variable and an event and the same variable, in which primary alcohols were added stereoselectively to alkenes, which provides an atom economic version of the classical reaction where a Grignard reagent is added to an aldehyde.

1.2.1.3 HYPOTHESIS GENERATION[21-22]

Data mining is needed in pharmacovigilance to analyze the increasing number of reports received, speed up the identification of potential safety issues, aid in hypothesis generation, and time to in-depth. Because the number of reports is growing exponentially, it is challenging for Safety Evaluators to view all of the reports within the time constraints. Since not all of the reports are able to be read, reports that point out a potential safety signal might not be found. With data mining, these unviewed reports can be analyzed and used to form a basis that aids evaluators in creating a hypothesis of potential safety signals. Additionally, by easing the amount of manual review that has to be conducted, data mining can give Safety Evaluators more time to focus their efforts on other time sensitive tasks.

1.2.1.4 DATA COLLECTION[23-24]

Because of the nature of classical chemical reactivity, organic synthesis extensively utilizes protection–deprotection of functional groups, which increases the number of steps in synthesizing the desired target compounds. Novel chemistry is needed to perform organic synthesis without protection and deprotection. Recently, progress has been made on this subject. For example, Baran et al. have re-ported a total synthesis of a natural product without any protecting groups. Another instance is the efficient synthesis of ()-3-deoxy-D-glycero-D-galacto- nonulosonic acid (KDN) by using the indium-mediated allylation reaction in water reported by Chan and Li. The Knoevenagel condensation of the diketone with hemiacetalic sugar gave-C-glucosidic ketone in water directly. The Click chemistry developed by Sharpless tolerates a wide range of functionalities and allows the direct modification of biological compounds. The archetypical example of Click chemistry is the Huisgen 1, 3-dipolar cycloaddition of alkynes to azides to form 1, 4-disubsituted 1, 2, 3-triazoles catalyzed by Cu (I). The reaction is mild and highly efficient, and does not require protecting groups.

1.2.1.5 SAFETY SIGNAL INDUCTION[25-26]

Also of fundamental importance to greener syntheses is the development of tandem and cascade reaction processes that incorporate as many reactions as possible to give the final product in one operation. For example, a palladium-catalyzed tandem reaction resulted in multirings in one step. Another example is Jamison's synthesis of the core piece of ''ladder'' polyether marine natural products through a biomimetic cascade cyclization in neutral water. An alternative way to simplify organic syntheses into a single operation is to perform sequential reactions in a flow reactor. Ley and colleaques reported that a multistep synthesis of the alkaloid natural product (-)- oxomaritidine can be accomplished by using microfluidic pumping systems that pass material through various packed columns containing immobilized reagents, catalysts, scavengers, or catch- and-release agents, combining seven separate synthetic steps linked into one continuous sequence. DATA PROCESSING.[34-35]

In the case of using alkaline and alkaline-earth metal complexes as final products or reactants, high-purity, highly thermally stable, crystalline and blue photoluminescent bis (8-hydroxyquinoline) calcium (CaQ2) was prepared with high yields from 8-hydroxyquinoline and Ca (OH) 2 (2: 1 molar ratio) in water by stirring at 90°C for 4 h, being proposed for use as organic electroluminescent materials. Another example is an improved method for transformation of meseylates or glycidyl tosylates to allyl alcohol derivatives, applying excess amount of reducing agent rongalite (approx. 3 mol equivalent, sodium hydroxymethanesulfinate dihydrate Na+ HOCH2SO2 – · 2H2O) with catalytic amount of tellurium (0.1 mol equivalent) as catalyst material. The purpose was to avoid difficulties in elimination of elemental tellurium, formed from telluride anion, during this conversion, resulting in excellent yields (up to 92%). This process can be considered as greener due to the recyclability of tellurium and its use in small catalytic amount, conversion of rongalite (commercially available, inexpensive and powerful reagent for organic synthesis) to bisulfite derivative, which is non-toxic and water-soluble, and use of water as principal solvent with addition of small volume of tetrahydrofuran (THF). For metal phthalocyanines as important compounds with a host of applications, new sustainable synthesis methods are in a permanent search. In general, industrial production of phthalocyanines requires relatively high temperatures (above 180°C) and hazardous solvents. Phthalocyanines in a crystalline form are of especial interest. Thus, prism-shaped crystals of cobalt phthalocyanine (CoPc, more than 1 mm in size, stable up to 430°C) and zinc phthalocyanine (ZnPc, up to 8 mmin size, stable up to 550°C, prepared at 160°C from o-phthalodinitrile and metal acetates as

precursors for 6 h in one-stage solvothermal process, using EtOH, pentanol or benzyl alcohol as reaction media. Change of solvent led to different length of phthalocyanine needles. This greener technique does not require any additional substances, in particular surfactants, or recrystallization with the use of concentrated sulfuric acid. Since MPc single crystals are important materials for construction of devices, among other applications, the search for appropriate environmentally friendly methods for their synthesis and growth contributes to rapid development of organic semiconductor devices. Greener synthesis of MOFs is also underway in several laboratories worldwide. In relation to green chemistry, the crucial parameters in the MOF synthesis consist of.

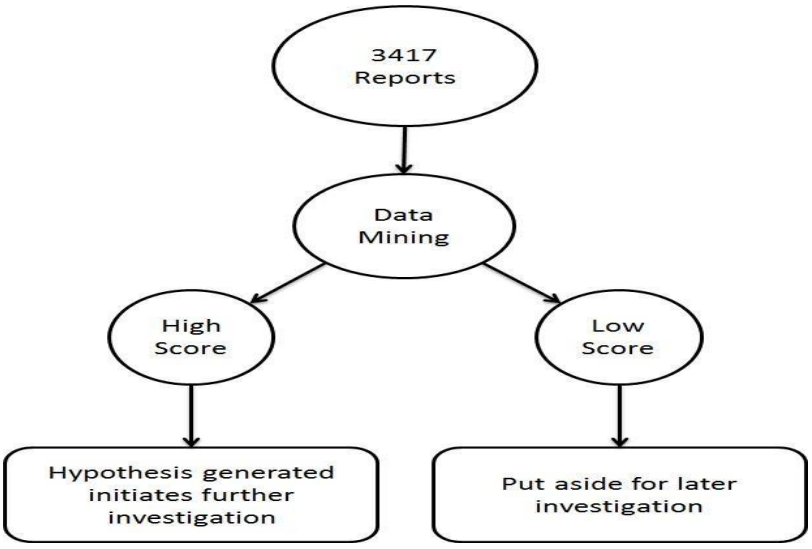
(i) solvent, (ii) cation source (inorganic part), (iii) linker molecules (organic part), and (iv) synthesis conditions (pressure, temperature, reactor). In the case of wastes in MOF syntheses,their big amounts are formed as a result of solvent use both in the synthesis and for purification purposes; therefore, greener solvents are needed, for instance, ethanol or acetic acid. Maximum use of all precursors should be taken into account: any waste or side product should be re- elaborated that leads to the loss of time and energy. Metal oxides or hydroxides (lesser sulfates) are recommended to be used as metal source, thusavoiding loss of toxic anions (perchlorates, nitrates or chlorides) due to water formation from O atoms of oxides and protons from acidic linkers. Solvent-less and energy-minimized methods are preferable, routes for synthesis and purification of crude MOFs. Organic linker molecules from renewable natural products (biomass) are desirable, for example, cellulose or starch (the same for solvents: water or ethanol). All additional unnecessary steps should be avoided, for example, temporary modification of processes. Aniline along with Zinc and acetic acid is the key reaction as it gives the part of Oxides.

1.2.1.6 ACTING ON SAFETY SIGNAL[33-34]

Preparation of nanoparticles, first of all those of elemental metals, has been the central point of green synthesis processes (together with organic reactions discussed above) for the past 15 years. As general approaches for the nanoparticles synthesis, the following aspects are useful in these processes inorder to make them greener. Thus, capping agents are used in the majority of syntheses for stabilization, shape control and prevention of aggregation of formed nanoparticles. Classic capping agents in the nanochemistry are long-chain hydrocarbons, functionalized with a heteroatom (oleyamine, trioctylphosphine, oleic acid, and dodecanthiol), polymers (polyvinyl alcohol, PEG) and block copolymers (poly (acrylic acid)-block-polystyrene), dendrimers, etc. For green chemistry purposes, the following agents are

considered as greener in the synthesis procedures for nanoparticles formation: (i) polysaccharides (like starch or dextran) exhibiting mild capping ability and water solubility (sometimes reduction properties), avoiding toxic solvents and allowing easy separation of nanoparticles from reaction media; (ii) biomolecules (proteins and peptides) possessing high biocompatibility; and (iii) small molecules (i.e. CO) together with organic capping agents. The natural products, used in the synthesis of nanoparticles and nanomaterials, can be applied not only as capping agents, surfactants, solvents and reactants, but also as carriers, catalysts and templates. The use of ligands can passivate and coat nanoparticle surfaces, thus stabilizing them, preventing agglomeration and influencing their chemical properties. Typical ligands in the nanoparticle synthesis are phosphines, thiols, amines, selenols, carbenes and alkynyls, being classified by their molecular structures and 'head group'. Classic reducing agents in nanoparticle synthesis are normally N2H4, HCOH and NaBH4. Ascorbic acid as an organic reductant can be also used. The following greener reductants are recommended for safer obtaining nanoparticles: (i) molecular H2 (disadvantage: combustibility); and (ii) polysaccharides (used also as capping agents, see above) like b-D-glucose, starch or amylose, possessing water solubility and avoiding hazardous organic solvents. NaAlH4 and other strong reductants contribute to the formation of small nanoparticles, whereas plant extracts result in polydisperse products and larger particles. Their use is directly or indirectly related with toxicity, since non-toxic (green) reductants are not so strong in order to be able to form metal nanoparticles of sufficiently high quality, where a much faster kinetics is needed. On the other hand, strong reductants are frequently toxic and expensive. So, one of the main purposes of green synthesis of high-quality nanoparticles is the search for or creation of green (non-toxic) and simultaneously strong reductants. In the case of solvents, whose consumption in some manufactures, for example, pharmaceutical industry, is over 80%, their correct selection is highly important, taking into account the high amount of used solvent wastes and their toxicity. Solvents are applied for dissolution of raw materials/ reactants, heat transfer, dispersion and solubilization of formed nanoparticles. So, the following solvents are recommended as greener media fornanoparticle low- and large-scale synthesis: (i) obviously water as preferred solvent (if, for any reasons, it is impossible to carry out a solvent-less synthesis as the best option), always available at low cost and non-flammable (disadvantage: high heat capacity, inhibiting energy-saving production), and (ii) SC fluids (CO_2, H_2O and ILs). In the cas of SC water (critical pressure 22.1 MPa, critical temperature 646 K), the SC hydrothermal synthesis is controllable and economicallypreferable; in addition, SC water is

able to dissolve organic substances and to obtain nanoparticles, highly dispersible in organic media. In the case of SC CO2 (SC pressure 74 bar, SC temperature 304 K), it is also promising, being non-flammable, non-toxic, compatible with the environment, chemically inert and inexpensive. ILs, consisting of charged organic and inorganic ion pairs, can substitute toxic and volatile organic solvents; in this case, capping agents are generally unnecessary. The use of ILs can be united with microwave (due to high dielectric constants, high polarities and high ionic charges) and ultrasonic treatment. Among greener synthesis strategies for nanoparticle synthesis, in addition to correct selection of solvents, capping agents and reductants, the selection of heating method is also important to avoid high energy consumption. Furnace, oil/water bath and heating mantle are classic heating sources, which can be replaced by microwaves, whose aid has already led to preparation of a series of nanoparticles (metals, metal chalcogenides, phosphates, oxides, etc.). Solvent-less MW-assisted route is preferable or, in the case of impossibility, the use of DMF or DMSO (sometimes, additional small IL amounts are useful), possessing high dielectric constants, is recommended. Larger nanoparticles are normally synthesized at prolonged MW-irradiation time. Ultrasound-assisted synthesis of nanoparticles is also considered as green method, where the heating is produced fromacoustic cavitation and not directly from ultrasound itself. Ultrasonic treatment allows also maintaining formed nanoparticles to remain small without fast further agglomeration. After preparation, nanoparticles are normally separated from reaction medium by precipitation and washed by their redissolving and precipitation. Post-processing can include size sorting. Greener syntheses of nanoparticles, in particular, are carried out by biological methods, where reducing agents are organic compounds and biomolecules.



1.2.1.7 FAERS[35-36]

Nanoparticles of metallic silver and gold have been prepared by green methods much more in comparison with other noble and other metals with aid of bacteria, fungi, plant extracts, yeasts, viruses and algae. In the synthesis of Ag nanoparticles, a variety of the following physical methods (accompanied by chemical reduction of Ag+ ion to convert it to Ag0) have been applied: UV- and sunlight photo reduction (leading mainly to large nanoparticles and nanocrystals; long-term acting stabilizing agents required), ultrasound-assisted processes (temperature control is needed), laser ablation (leading to nanoparticles with perfect shapes and sizes), microwave-assisted reactions (stabilizing agents required), radiolysis, electrochemical reduction and high-pressure (autoclave) technique. Physical methods, used for preparation of silver nanoparticles, have the following disadvantages: tube furnace (large space, heating environment), ceramic heater (fast cooling needed), laser ablation (depends of laser characteristics) and arc discharge (use of Agwires as electrodes). Also, Ag0 nanoparticles were prepared by chemical routes using the following reductants, among others: NaBH4, sodium citrate, ascorbic acid, curcumin, heparin, polyblock polymers and polysaccharides, as well as thermal decomposition of AgNO3 via spray pyrolysis. These reactions are different in respect ofnanoparticles. As example of green synthesis of noble metal nanoparticles, a simple use of ascorbic acid as a reducing agent and sodium carboxymethylcellulose as a structure-directing agent, one-dimensional Ag nanobelts (lengths of 50 μm) and other nanostructures (brick-like, pie-like and three- dimensional hierarchical ones) were prepared from AgNO3 at large scale in mild conditions at 30°C and used for catalytic purposes. As a result of classic action of polyphenol- type compounds, Au nanoparticles (16.6 nm, diverse shapes) were prepared with the aid of catechin (a polyphenol compound, belonging to flavonoids) as a reducing and capping agent .In the case of algae as green medium], both microalgae (Chlorella vulgaris, Chaetoceros calcitrans, Spirulina platensis, Oscillatoria willel, Plectonema boryanum) and macroalgae (Sargassum cinereum, Padina pavonica, Caulerpa racemosa, Ulva lactuca) were used for Ag0 nanoparticles synthesis. Plant extracts have been extensively used for fabrication of Au and especially Ag nanoparticles (interest caused by the antibacterial properties of Ag nanoparticles). In some reactions, Phoenix dactylifera seeds (as waste product), Taraxacum officinale, Cassia tora L. roots, C. longa tuber, soya bean leaf (Glycine max) and Hippophae rhamnoides (Pd nanoparticles) extracts were applied, among many others. In addition, Ag nanoparticles (from $AgNO_3$) and TiO_2 nanoparticles (from $TiO(OH)_2$) were prepared using aqueous leaf extract

of Euphorbia prostrata. Also, spherical Ag (12 nm) and hexagonal and triangular Au (11 nm) nanoparticles were obtained with the aid of leaf extract of Rosa rugs in water for 10 min].

1.2.1.8 REPORTING BODIES[37-38]

The FDA advances data input from different bodies that may be affected by the activities such as public, consumers, nurses, sponsors, pharmacists/pharmacies, physicians, and third party payer. The reporting bodies are encouraged by the agency to use trained health care experts to assist in reporting adverse events. Varieties of these combinations are especially well seen in the example of carbon dots/QDs, additionally providing their water- solubility properties. Thus, fluorescent carbon nanorods (CNDs, red emission peak at 615 nm, quantum yield 15%) were synthesized by microwave treatment of a non-fluorescent p-phenylenediamine in EtOH-H2O solution leading to its carbonization and formation of CNDs. These CNDs serve as chemo sensors for glutathione (GSH) detection and temperature sensor at a molecular level. As examples of using other plant extracts, fluorescent water-soluble N/P co- doped CQDs were hydrothermally prepared at 90–150°C from edible Eleocharis delis, resulting in easily scalable CQDs serving as sensors for Fe3+ ions and having potential applications in an anti-counterfeit area. The Pontiac ficus-indica extract, having hydrophilic properties, was used for ultrasound-assisted preparation of laminar carbon from commercial graphite as a precursor for 30 min. Small QDs were obtained from the same precursor by stirring for 30 min at 50°C and further ultrasonic treatment for 30 min more. In addition, water-soluble photoluminescent CQDs (size 1–3 nm, quantum yield 14%) were hydrothermally obtained from lemon peel waste and applied for Cr6+ detection (limit 73 NM). This fabrication method can be scaled up. The composite of these CQDs with TiO2 is capable to carry out photo. Stakeholders in the PvPI system include healthcare bodies and professionals, manufacturers of drugs (i.e. Market Authorization Holders/MAHs), Adverse Drug Reaction (ADR) Monitoring Centers (AMCs), regulatory bodies such as the Central Drugs Standard Control Organization (CDSCO). ADR reporting-cum-analysis bodies.

2 RESULTS

Though method comparison at the individual level is inconclusive, progress has been made in identifying the advantages, disadvantages and differences between the frequentist methods and the Bayesian methods. The group of frequentist methods consists of Proportional Reporting Ratio (PRR), Reporting Odds Ratio (ROR), and Relative Reporting Ratio (RRR).

The frequentist methods use ratios to find and estimate associations and are typically accompanied by hypothesis tests for independence (e.g. chi squared test, Fisher's test) and these tests are used as extra precautionary measures that take into account the sample size used while computing the association. The group of Bayesian methods includes Gamma-Poisson Shrinker (GPS), Multi- item Gamma-Poisson Shrinker (MGPS) and Bayesian Confidence Propagation Neural Network (BCPNN). Methods are categorized as Bayesian if the data mining method incorporates both the disproportionality measure, the measure of how much the drug-event combination occurs "disproportionally" compared to if there was no association between the drug and event, and sample size to "shrink" the disproportionality measure toward the baseline case of no association by an amount proportional to the variability of the measure. Some general advantages and disadvantages of each group by cleaner processes as cement, ceramics and bioceramics, adsorbents, polymers, bioplastics, biodiesel and biocomposites. All methods from the abovediscussed set of greener laboratory techniques cannot be always considered as indeed green upon scaling up.As an example, ball milling in a larger scale could be a source of solid microsize pollution. In organic chemistry, the green chemistry reactions include several processes in the formation of C–C bonds (i.e. Suzuki and Glaser coupling, Knoevenagel condensation, McLurry, Wittig, Gewald, Michael, Reformatsky and Gringard reactions, arylaminomethylation, etc.), C–N bonds (synthesis of oximes, imines, azines, guanidines, (thio)semicarbazones, nitrones, N- arylation of amines, etc.), C–O, C–S, C- Hal, C–H and other bonds, cycloaddition reactions, reductions and oxidations, as well as for. Functionalization of nanocarbons (CNTs, graphene and C60) and in supramolecular chemistry. A range of nanosized materials and composites can be produced by greener routes, including nanoparticles of metals, non-metals, their oxides and salts, aerogels or QDs. At the same time, such classic materials can be improved or obtained by cleaner processes as cement, ceramics and bioceramics, adsorbents, polymers, bioplastics, biodiesel and biocomposites. Our future challenges in resource, environmental, economical, and societal sustainability demand more efficient and benign scientific technologies for. Working with chemical processes and products. Green chemistry addresses. Such challenges by inventing novel reactions that can maximize the desired products and minimize by-products, designing new synthetic schemes and apparatus that can simplify operations in. chemical productions, and seeking greener solvents that are inherently environmentally and ecologically benign. Together,such fundamental innovations in chemical sciences will lead us to a new generation of chemical syntheses. reporting issue by adjusting the

disproportionality measure to account for these low counts. The FDA's intake of reports has been exponentially increasing over the years while the number of Safety Evaluators has remained relatively constant. Tables illustrate the overwhelming number of reports that each Safety Evaluator must view.

	Frequentist Methods	Bayesian Methods
Tend to highlight a greater number of DEAs	X	
Tend to highlight a greater variety of DEAs	X	
Tend to highlight DEAs earlier	X	
More computationally intensive		X
More sensitive to low-frequency of reports	X	
More intuitive computations	X	
Ability to sort associations along one single dimension		X
Address reporting biases or confounding		
May result in loss of credible signals		X
Lower impact of random fluctuations of relative reporting ratio ("shrinkage")		X
Produce more false positives	X	
Produce more false negatives		X

Average Monthly SE's report				
Months	**Expedited**	**Non- Expedited**	**Direct**	**Total Average**
Nov-16	962	459	44	1465
Oct-16	2010	1492	107	3608
Sep-16	1918	2467	110	4495
Aug-16	1584	5656	118	7357
Jul-16	1759	1571	105	3436
Jun-16	1681	1103	107	2892
May-16	1588	1746	106	3441
Apr-16	1742	885	113	2740
Mar-16	1786	845	120	2750
Feb-16	1632	1216	83	2931
Jan-16	1454	944	77	2475
Total Average Over 11 Months	1647	1671	99	3417

4 CONCLUSION

Data mining algorithms are becoming more frequently used as a supplement to traditional expert reviews of reports and to rapidly analyze the large volume of accumulated data. New algorithms are constantly being researched to uncover new trends and associations in data or

to improve uponexisting algorithms. These algorithms could be routinely applied in order to monitor, prioritize, and identify undiscovered safety signals of adverse drug events that warrant further attention. In choosing an algorithm, the most important question is not which algorithm to use but what is the correct threshold value. The benefit of using multiple algorithms is that one may catch a signal that the other does not. To summarize the differences between the algorithms, the algorithms that are frequently detected a higher number of safety signals than the Bayesian based algorithms. This comparison is only relative to a specific comparison of signals detected from handpicked drugs.

ACKNOWLEDGEMENT

I am extremely grateful to **Dr. S. D. Pande**, Principal, Vidyabharati College of Pharmacy, and Amravati for providing all the required resources for the successful completion of my Project.

My heartfelt gratitude to my Project guide Dr. M. D. Game, for valuable suggestions And guidance in the preparation of the Project report.

I express my thanks to all staff members and friends for all the help and co-ordination extended in bringing out this Project successfully in time.

I will be failing in duty if I do not acknowledge with grateful thanks to the authors ofthe references and other literatures referred to in this Project.

Last but not the least; I am very much thankful to my parents who guided me in everystep which I took.

5 REFERENCES

1. Meyboom RH, Hekster YA, Egberts AC, Gribnau FW & Edwards IR, "Causal or casual? The role of causality assessment in pharmacovigilance", Drug Saf, 1997; 17: 374-389.
2. Ribera MGTC, Costa DA, Machado AASC, Ribera MGTC, Costa DA, Machado AASC. 2010 Green Chemistry letters and reviews 'Green Star': a holistic Green Chemistry metric for evaluation of teaching laboratory experiments. Green Chem. Lett. Rev, 3: s 149–159. (Doe: 10.1080/17518251003623376)
3. Anastasia PT, Warner JC. 1998 Principles ofgreen chemistry. In Green chemistry: theory and practice (ends P Anastasia, J Warner), pp. 29– 56. Oxford, UK: Oxford University Press.
4. Firkin M. 2018 Principles of Green Chemistry's-Education Inst. See https://www.e-

education.psu.edu/eme807/node/534 (accessed 5 May2019).

5. US Environmental Protection Agency. 2018 Green Chemistry. See http://www.epa.gov/greenchemistry (accessed 5 May 2019).
6. Praveen K, Banes V, Edwina L. 2016 Green synthesis of nanoparticles: their advantages anddisadvantages. AIP Conf. Proc. 1724, 20048. (doi:10.1063/1.4945168)
7. Hang W, Cue BW, Wiley J. 2012 Green techniques for organic synthesis and medicinalchemistry. Hoboken, NJ: John Wiley & Sons.
8. Sheldon RA, Isabel Amends UH. 2007 Green chemistry and catalysis. Wenham, Germany:Wiley-VCH.
9. Boohoo K, Harvey A. 2013 Process intensification technologies for green chemistry: engineering solutions for sustainable chemical processing. Hoboken, NJ: John Wiley & Sons.
10. Zhang L, Gong C, Bin D. 2018 Green chemistry and technologies. Berlin, Germany: Walter deGruyter GmbH & Co KG.
11. Malone SS, Niwadange SN. 2016 Green chemistry alternatives for sustainable development in organic synthesis. Green Chem., 3: 113–115. (doi:10.17148/IARJSET.2016.3621)
12. Orients IL, Matera EV. 2012 No applications of green chemistry methods in phosphorus-organic synthesis. Sup. Kham. 81: 221–238. (Doe: 10.1070/RC2012v081n03ABEH004248)
13. Hussein J, Ensue GL, Rashaan R-M, Thomas W.2018 A review of using green chemistry methods for biomaterials in tissue engineering. Int. J. Nano medicine, 13: 5953–5969. (doi:10.2147/IJN.S163399)
14. Do J. 2016 Mechanochemistry: a force of synthesis. ACS Cent. Sci, 3: 13–19. (doi:10.1021/acscentsci.6b00277)
15. Chudoba T, Wojnarowicz J. 2018 Current trendsin the development of microwave reactors forthe synthesis of nanomaterials in laboratoriesand industries: a review. Crystals, 8: 379. (Doe: 10.3390/cryst8100379)
16. Darer JA, Zhang J, Marwan NM, Wing X. 2017Continuous hydrothermal synthesis of inorganic nanoparticles: applications and future directions. Hem. Rev, 117: 11 125–11 238. (doi:10.1021/acs.chemrev.6b00417)
17. Ye N, Yan T, Jiang Z, Wu W, Fang T. 2018A review: conventional and supercritical hydro/solvothermal synthesis of ultra-fine particles as cathode in lithium battery. Ceram. Int, 44: 4521–4537. (doi:10.1016/j.ceramint.2017.12.236)

18. Babe SG, Neapolitan B, Ashokkumar M. 2015Ultrasound-assisted synthesis of nanoparticles for energy and environmental applications. In Handbook of ultrasonic and zoochemistry (deism Ashokkumar, F Cavalier, F Cheat, K Okitsu, A Samba dam, K Yaqui, B Zeus), 1–34. Singapore: Springer Science Business Media.(doi:10.1007/978-981-287-470-2)
19. Marci K. 2017 Magnetic-field-induced synthesis of magnetic wire-like micro- and nanostructures. Nano scale, 9: 16 511–16 545. (Doe: 10.1039/C7NR05823C).
20. Ran B, Stole A. 2016 Ball milling towards Green synthesis: applications, projects, challenges. Johnson Matthey Technol. Rev, 60: 148–150. (Doe: 10.1595/205651316X691375)
21. Marg etic D, Štrukil V. 2016 Mechanochemicalorganic synthesis, 1st edn. Amsterdam.
22. See https://www.sciencedirect.com/topics/chemistry/ (accessed 5 May 2019).
23. Ravichandran S, Karthikeyan E. 2011 Microwavesynthesis—a potential tool for Green chemistry.Int. J. ChemTech Res, 3: 466–470.
24. Kitchen HJ et al. 2013 Modern microwavemethods in solid-state inorganic materialschemistry: from fundamentals tomanufacturing. Chem. Rev, 114: 1170–1206. (Doe: 10.1021/cr4002353)
25. Dona Lab Kurt 2019 Mon wave 50. See http://dlu.com.ua/Monowave-50-1 (accessed 7 May 2019).
26. Glassing J, Champagne P, Cunningham MF. 2016 Current opinion in Green and sustainable chemistry graft modification of chitosan, Cellulose and alginate using reversible deactivation radical polymerization (RDRP). Cur.Open. Green Sustain. Chem, 2: 15–21. (doi:10.1016/j.cogsc.2016.09.002)
27. Radial Arias AN, Arreola E, Reyes Called J, Berrio Mesa E, Fuentes Zurita G. 2016 Mineralización de etilenglicol por foto-fentonasistido con ferrioxalato. Rev. Int. Contam. Ambient, 32: 213–226. (doi:10.20937/RICA.2016.32.02.07)
28. Feng S, Li G. 2017 Hydrothermal andsolvothermal syntheses. In Modern inorganicsynthetic chemistry, 73–104. Amsterdam, theNetherlands: Elsevier.
29. Taublaender AMJ, Glöcklhofer F, Marchetti-Deschmann M, UnterlassMM. 2018 Green andrapid hydrothermal crystallization and synthesisof fully conjugated aromatic compounds. Angew. Chem. Int. Ed, 57: 12 270–12 274.(doi:10.1002/ange.201801277)
30. Zada I, Yao L, Naz R, Zhang W, Mazhar ME, Zhang D, Ma D. 2019 Facilely green synthesis of 3D nano-pyramids Cu/carbon hybrid sensorelectrode materials for

simultaneous monitoringof phenolic compounds. Sens. Actuat. B. Chem, 282: 617–625. (doi:10.1016/j.snb.2018.11.114)

31. Xu Y, Ren B, Wang R, Zhang L, Jiao T. 2019Facile preparation of rod-like MnO nanomixturesvia hydrothermal approach and highly efficientremoval of methylene blue for wastewatertreatment. Nanomaterials, 9: 10. (Doe: 10.3390/nano9010010)
32. Mason TJ. 2000 Ultrasound in synthetic organic chemistry. Chem. Soc. Rev, 26: 443–451. (Doe: 10.1039/cs9972600443)
33. Ashokkumar M. 2016 Ultrasonic synthesis of functional materials. In Ultrasonic synthesis of functional materials (ed. M Ashokkumar), pp.17–40. Singapore: Springer. (Doe: 10.1007/978-3- 319-28974-8)
34. Pure S, Kaur B, Parmer A, Kumar H. 2013Applications of ultrasound in organic synthesis—a Green approach. Cur. Org. Chem, 17: 1790–1828. (Doe: 10.2174/13852728113179990018)
35. Manalapan S, Rajah U, Chen S, Elshikh MS.2019Sonochemical synthesis of bismuth (III) oxide decorated reduced grapheme oxidenanocomposite for detection of hormone (epinephrine) in human and rat serum.Ultrason. Sonochem, 51: 103–110. (doi:10.1016/j.ultsonch.2018.10.008)
36. Wang J, Wu Y, Zhu Y. 2007 Fabrication of complex of Fe3O4 Nano rods by magnetic-field- assisted solvothermal process. Mater. Chem. Phys, 106: 1–4. (doi:10.1016/j. matchemphys.2007.04.061).
37. Xiao W, Liu X, Hong X, Yang Y, Live Y, Fang Jading J. 2015 Magnetic-field-interacted synthesis Sheldon R (1994) Metaloporphyrins in Catalytic Oxidations (Marcel Dekker, New York).
38. Funabiki T (1997) Oxygenases and Model Systems (Kluwer, Dordrecht, the Netherlands).
39. Shiloh AE (1997) Metal Complexes in Biomimetic CChem.