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Pollutants Generated from Pharmaceutical Processes and Microwave Assisted Synthesis as Possible Solution for Their Reduction - A Mini Review

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ABSTRACT

In this review article we have briefly summarized the pharmaceutical processes and the pollutants i.e., VOCs and other air emissions from reactors and distillation assemblies, polluted solvents released in water and solid wastes etc. generated due to conventional processes involved in preparation of pharmaceuticals. Medicines are prepared for the better health and to decrease the mortality rate in human beings but the conventional processes involved in preparation of these pharmaceuticals generate chemical and thermal pollution in environment, thus, giving rise to some other severe health impacts and ultimately increase the disease and mortality rate in human beings. Thus, we have discussed the sustainable technology of microwave as possible solution for the preparation of pharmaceuticals without the generation of pollutants. Some practical examples for the preparation of pharmaceuticals via microwave and conventional processes are also discussed and compared herein showing the benefits of using microwave technology over conventional process in terms of better yield and ecofriendly approach without using hazardous solvents.

INTRODUCTION

Importance of Pharmaceutical Medicines

Clinically evident diseases including minor infections to those causing mortality are mostly due to the presence of pathogenic microbial agents including viruses, bacteria, fungi, protozoa, multicellular organisms and hazardous contamination in environment. Medicines used for the treatment of these clinically important infections are intermediate input combined with some other inputs to produce better health. Day to day progress in medicines for the treatment of different diseases provide value for money, in terms of both delivering higher-quality health care and reducing the costs of other health care inputs (Cutler & McClellan 2001).

Medicines contribute enormously towards the public health problems. The discovery, development and effective use of drugs have improved quality of life. This not only reduced the need for surgical intervention but also the length of time spent in hospital and saved many lives. Consumption of drugs is so vast that more than 650 million prescriptions are written each year only by GPs (House of Commons Health Committee 2005).

Pharmaceutical medicine is the medical scientific discipline dealing with the discovery, development, evaluation, registration, monitoring and medical aspects of marketing of medicines for the benefit of patients and public health (Stonier et al. 2007, Goldberg & Smith 1985).

The basics of these pharmaceutical medicines (used to fight against different diseases) are based on the knowledge and understanding of how drugs function, the limitations and variability of response to therapies, and how therapies can be used optimally in clinical practice (Stonier & Baber 2000). Day to day development is strongly needed in the field of pharmaceutical medicines due to different resistances which badly affects the efficiency of known many medicines.

Pharmaceutical Processes

Major steps of pharmaceutical process are research and development, conversion of organic and natural substances into bulk pharmaceutical substances or ingredients by means of fermentation, extraction, and/or chemical synthesis and the formulation of prepared pharmaceutical product (Encyclopedia of Poly. Sci. & Eng. 1986). In pharmaceutical industry medicines are produced by different means like chemical synthesis, fermentation and extraction and finally the formulation and packing of medicines obtained by these processes.

Chemical synthesis: Majority of the pharmaceutical medicines are prepared by means of chemical synthesis, generally by a batch process. Cardiovascular agents, central nervous system agents, vitamins, antibiotics, antifungal compounds, antihistamines and antihypertensive drugs are just a few examples of the bulk pharmaceutical substances prepared by means of the process of chemical synthesis (Watthey & Reinhold 1992).

Fermentation: Commonly known pharmaceuticals such as steroids, antibiotics and some food additives are produced by fermentation. Main steps of fermentation are inoculum and seed preparation, fermentation and product recovery (US

Environmental Protection Agency 1991). In fermentation, microorganisms (e.g., bacteria, yeast or fungi) are used to produce the desired medicines as a by-product of normal metabolism.

Extraction: This pharmaceutical process involves the extraction of organic compounds for their use as medicines from plant materials or animal tissues. Extraction is used to separate liquid mixtures by taking advantage of differences in the solubility of the mixture components. A solvent that preferentially combines with only one of the components is added to the mixture. The resulting mixture consists of an extract (containing the preferentially combined material) and a raffinate (containing the residual phase) (Buonicore & Davis 1992).

Formulation and packaging: Primary objective of formulation and packing is to convert the manufactured bulk substances into a final, usable form. It involves the formulation of bulk pharmaceuticals into various dosage forms such as tablets, capsules, injectable solutions, ointments, etc. that can be taken by the patient immediately and in accurate amount (US Environmental Protection Agency 1995).

From the above described processes, most pharmaceutical manufacturing plants are preparing medicines using the method of chemical synthesis involving the use of organic chemicals as raw materials and as solvents. Nearly all products are made using batch operations (Daughton 2003).

Production of a synthesized drug consists of one or more chemical reactions followed by a series of purifying operations. Production lines may contain reactors, filters, centrifuges, stills, dryers, process tanks, and crystallizers piped together in a specific arrangement. Arrangements can be varied in some instances to accommodate production of several compounds. Small plant may have only a few pieces of process equipment but a large plant can contain literally hundreds of pieces (Metry 1980).

POLLUTANTS GENERATED FROM PHARMACEUTICAL PROCESSES

During the last three decades, chemical pollution due to synthesis of pharmaceutical medicines by conventional ways exclusively increased at an alarming rate (Daughton & Ternes 1999). The occurrence of pharmaceutical pollutants in the environment has gained increased attention since the 1980s; however, their occurrence has increased at an alarming rate since the 1990s because of the process of chemical synthesis involving a series of reactions and recovery processes in the pharmaceutical industry (Daughton 2003, Inanc et al. 2002). Plants synthesizing pharmaceutical products emit many volatile organic compounds (VOCs) and other pollutants in the environment via air emissions and wastewater and solid wastes.

Wastewater

Another issue is that due to purity concerns, most of the solvents used in pharmaceutical manufacturing activities are not recycled for reuse. As a result, pharmaceutical wastewater contains many hazardous chemicals including varying concentrations of organic solvents (Enright 2005). Pharmaceutical wastes also contain chemicals which are priority pollutants such as isopropanol, acetic acid, ethyl acetate, ethanol, n-heptane, tetrahydrofuran, methanol, toluene, dichloromethane and acetonitrile, etc. (Constable 2007). Biological treatment of the pharmaceutical wastewater containing recalcitrant chlorinated compounds, including common solvents such as perchloroethylene (PCE), trichloroethylene (TCE), chloroform (CF) and carbon tetrachloride (CT) is not an easy task (Van Eekert et al. 1999, Middeldorp et al. 1999, Zou et al. 2000, Koons et al. 2001, Assaf & Lin 2002, Bradley 2003, Chen 2004, Raynal et al. 2010). However, anaerobic treatment of chlorinated VOC emissions from pharmaceutical industry is not feasible because the flue gas contains large quantity of oxygen. Hence, there is an urgent need to explore the methods to control such pollutants (Morono et al. 2006).

Air Emissions

Solvents constitute the predominant VOC (acid gases, halogen acids, sulphur oxides and nitrous oxides, etc.) emission from production plant causing pollution. Plants differ in the amount and type of organic chemicals and solvents used resulting in emission of different VOCs. Depending upon the type and quantity of reactants and solvents some plants may be negligible sources of VOCs while others are responsible for high source of pollution due to VOCs. In addition, all types of equipment used have the potential to emit air pollutants. Reactors and distillation operations are major sources of pollution due to air emission.

Reactors: Reactor emissions of conventional pharmaceutical processes are badly affecting the environment due to emission of air containing VOCs during reactor charging, hazardous solvent evaporation during the reaction as by-product gases, overhead condenser venting, uncondensed VOCs during refluxing, purging, vaporized VOCs remaining from a solvent wash, and opening reactors during a reaction cycle to take samples to monitor reaction progress.

Distillation operations: Volatile organic compounds during conventional heating are emitted from the distillation condensers. The magnitude of polluted VOCs depends on the operating parameters of the condenser, the type and quantity of organics being condensed, and the quantity of inerts involved in the reaction.

Solid Wastes

Both nonhazardous and hazardous wastes are generated during all three stages of pharmaceutical manufacturing by conventional ways. These wastes include raw materials or products, used solvents, reaction residues, filtered media, filter cakes, used chemical reagents, dust particles from filtration or air pollution control equipment, raw material from packaging wastes, laboratory wastes and spills and the waste material generated during packaging of the formulated product.

Other prominent wastes include reaction residues and filtrates from chemical synthesis processes. Typically, solid wastes are shipped off-site for disposal or incineration. Industries have to bear big cost in a number of practices to reduce waste generation and material losses. Typical practices include process optimization, production scheduling, materials tracking and inventory control, special material handling and storage procedures, preventive maintenance programs, and waste stream segregation **(**US Environmental Protection Agency 1991).

Health Impacts

Public health problems caused by environmental contamination due to chemical synthesis in pharmaceutical plants are a growing concern worldwide. Exposure to pollutants released into the environment as a result of conventional pharmaceutical processes are potential risks to human health and ecosystems**.** Researchers are working to prioritize that which pharmaceutical chemicals could potentially pose the highest risk to consumers and the environment **(**Rodriguez-Mozaz 2010, Andrews et al. 1990**).** Exposure to solvents in the form of vapours, mists or liquid form has adverse effects on human health. They can enter the body by inhalation, swallowing and through skin pores. The way that solvents may enter the body depends on the volatility and fat-solubility of the solvent, and the resulting severe health effects attributed to each solvent. Effects on human health due to solvents include narcotic effect causing fatigue and dizziness. Exposure to high dose of solvent may lead to unconsciousness and ultimately leading to death. Release of pharmaceutical pollutants in environment causes irritation of eyes and the respiratory tract, dermatitis and other skin disorders and severe damage to the liver, kidneys, heart, blood vessels, bone marrow and nervous system (e.g., chronic toxic encephalopathy). Solvents can penetrate the skin and enter the blood circulation causing mortality. The health risk of exposure to solvents depends on the specific solvent and on the level of exposure to the solvent. Solvents differ in their potency to harm health. Solvents also can pose a safety risk. Some solvents produce vapours, which are heavier than air. These vapours may flow to floor, or in worst cases to spaces where ignition by a spark from welding or static electricity may light them. Vapours of solvents can also accumulate in confined places and stay there for a long time, presenting risks for health and property (Odkvist et al. 1992).

The potential adverse ecological effects and the indirect human exposure to pharmaceutical chemicals warrant a multidisciplinary evaluation to establish a basis for appropriate risk assessment and potential environmental impact.

THE MICROWAVE TECHNOLOGY

According to the Environmental Protection Agency, green chemistry or sustainable chemistry is the design of chemical products that reduce or eliminate the use of hazardous substances. In recent years there is a greater societal expectation that chemists and chemical engineers should set up the trend to produce greener and more sustainable chemical processes. This review emphasized on the adaptation of green technology in place of conventional methods for the production of medicines in pharmaceutical processes to avoid pollution, ultimately as a measure to control risks to human health (Peter & Dunn 2012). Adaptation of microwave technology for the synthesis of medicines is the best possible solution.

Microwave irradiation produces efficient *in situ* heating, resulting in even heating throughout the sample in comparison to the wall heat transfer that occurs when an oil bath is applied as an energy source (conventional method). Thus, using microwaves the tendency towards the initiation of boiling is reduced, and superheating above the boiling point of the solvent is possible even at atmospheric pressure. Superheating can be generated rapidly in closed microwave-transparent vessels to the desired temperatures above the normal boiling point of a particular solvent (Lidstrom et al. 2001).

Microwave assisted medicine synthesis is one of the important tool to medicinal and environmental chemists for rapid organic synthesis. Over the last decades, researchers have developed wide number of applications of microwave technology in organic synthesis, which are well reported. Some quick advantages of the use of microwave technology include spectacular decrease in reaction time, improved conversions, clean product formation and wide scope for the development of new reaction conditions.

Researchers are also working to look for an expedited synthesis and purification strategy that would combine the use of microwave heating with polymer-assisted solution phase organic synthesis (Himanshu 2010).

APPLICATION OF MICROWAVE TECHNOLOGY IN PHARMACEUTICAL SCIENCE

Microwave Assisted Drug Extraction

Microwave-assisted organic synthesis (MAOS) is the novel technique that is set to revolutionize synthesis has recently moved to the forefront of medicinal research (Adam 2003, Tierney et al. 2003, Himanshu et al. 2010).

As discussed earlier, conventional techniques i.e., extraction or chemical synthesis are not only time and solvent consuming and thermally unsafe rather they also produce large number of pollutants thus badly damaging the environment. High and fast extraction and synthesis ability with less or no solvent consumption and protection of environment from pollutants are the attractive features of this new promising microwave assisted extraction (MAE) or microwave assisted synthesis (MAS) technique (Mandal et al. 2007). Many pharmaceutical processes are optimized using microwave technology (Shrishailappa et al. 2009, Mattina et al. 1997).

Trend of Synthesis of Medicines in Microwave

The green technology of microwave has been used in chemistry since the late 1970s. But after 1990s research conducted in MAOS has dramatically increased and chemists have synthesized wide number of organic compounds including medicinal compounds via this technology (Himanshu et al. 2010, Larhed & Hallberg 2001). To date number of top pharmaceutical, agrochemical and biotechnology industries are using MAOS technology as a forefront methodology for the synthesis of many medicines especially life saving medicines, as this technology is not only speeds up chemical reactions but it is also known to reduce side reactions, increase yields, improve reproducibility and is eco-friendly.

One of the reasons of increasing use of microwave technology is that almost any type of organic reaction requiring heating or thermal conditions can be performed using microwave radiation depending on the ability of a solvent or matrix to absorb microwave energy and convert it into heat (Himanshu et al. 2010, Larhed & Hallberg 2001).

BENEFITS OF MAS OVER CONVENTIONAL WAYS OF SYNTHESIS OF MEDICINES

Pharmaceutical process of preparation of medicines via microwaves has many advantages over conventional ways of synthesis (Honda et al. 1998, Kripilani et al. 2006, Himanshu et al. 2010).

- Use of microwaves speeds up the chemical reaction by reducing reaction time from hours to minutes.
- Uniform heating occurs throughout the reactant materials in comparison to conventional heating process.
- Targeted products are produced with no side reactions.
- Better and more rapid process control is achieved.
- Final products prepared by microwave technology are more pure than obtained by conventional methods.
- Improve reproducibility and yield as compared to conventional ways.
- No release of VOCs in environment, thus, microwave process is environmental friendly than conventional ways of synthesis.
- In conventional ways of synthesis of medicines, water is used as coolant thus causing thermal pollution while in microwave methods there are no chances of thermal pollution.
- Reduce wastage of heating reaction vessel.
- In microwaves better yield is produced as compared to conventional ways of synthesis.
- Super heating: conventional heating is done from outside, therefore, the core of solvent may be as much as 5°C cooler than the edge, while in microwave, the core is 5°C hotter than the outside, because of surface cooling, therefore, in microwave we can raise the boiling point of solvent by as much as 5°C, an effect is known as super heating.

Complete comparison of two methods of preparation of pharmaceuticals is depicted in Table 1.

EXAMPLES OF SOME MEDICINAL COMPOUNDS PREPARED BY USING MICROWAVE TECHNOLOGY

Synthesis of 1,1',2,2'-Tetrahydro-4'-amino-7'-(4-fluorophenyl)-spiro[3H-indole-3,5'-(5H)pyrido(2,3-d) pyrimidine]-2,2'(1H)-diones (1) (Dwivedi et al. 2009)

Scaffold spiro [indole-pyridopyrimidines are known to be potential antibacterial and antifungal agents. They are prepared by microwave method which has many advantages over conventional ways of synthesis.

Microwave method: It was successfully synthesized in microwave using two synthetic strategies. First by using equimolar mixture of 2'-amino-3'-cyano-6'-(4-fluorophenyl)-1',4'-dihydro-spiro[3H-indole-3,4'(1-H)-pyridin]-2(1H)-one and urea, with DMF, and second was in basic alumina as solid support. For this purpose 2'-amino-3'-cyano-6'-(4-fluorophenyl)-1',4'-dihydro-spiro[3H-indole-3,4'(1-H)-pyridin]-2(1H)-one urea separately adsorbed on basic alumina was added and irradiated inside the microwave oven at a power output of 100% (1000 watt) to attain the desired product.

Conventional method: In conventional way of synthesis, a mixture of urea and 2'-amino-3'-cyano-6'-(4-fluorophenyl)-1',4'-dihydro-spiro[3H-indole-3,4'(1-H)-pyridin]-2(1H)-one, was strongly heated on an oil bath. The temperature of reaction mixture was gradually raised to 180°C and it was heated up to the temperature of 220-230°C for 4 h. Final product was obtained after cooling with water and ethanol. **(**A comparison of microwave and conventional way of heating and their output is presented in Table 2).

Table 1: Comparison of microwave assisted technology vs. conventional methods of pharmaceuticals formation.

Conventional way of manufacture of pharmaceuticals	Microwave assisted synthesis of pharmaceuticals
Consistent thermal emissions to the environment. Conventional heating is done from outside, therefore the core of solvent may be as much as 5°C cooler than the edge. Material is not heated uniformly thus leading to the improper heating.	No environmental heat loss. In microwave, the core is 5ºC hotter than the outside, because of surface cooling, therefore in microwave, we can raise the boiling point of solvent by as much as 5ºC, an effect is known as super heating. Uniform heating occurs throughout the material and reaction.
A lot of side reactions occur during the processing.	Reduction in unwanted side reaction (reaction quenching), thus desirable chemical and physical effects are produced.
Thermal source is required for heating.	Electromagnetic waves are used as a source of heat.
Excessive amount of solvents other than reactants (methanol, ethylene, benzene, xylenes, toluene, hydrochloric acid, hexane). All these solvents are potential pollutants and cause many health problems.	So solvent free process, thus, no hazards to health and environment.
VOC emissions from material loading/unloading or from reactants. Fugitive emissions from sampling, tanks, etc. VOC emissions from filtering systems. Solvent vapours and fugitive emissions from purification tanks. VOC emissions from manual loading and unloading of dryers.	No air emissions.
Wastewater from wet scrubbers, with spent catalyst, pumps, equipment cleaning, etc. Use of water as coolent, thus, causing thermal pollution.	No wastewater production, neither use of water as coolent.
Wastages e.g., air emissions, wastewater generation or residual waste is mostly produced in a conventional way of manufacturance of pharmaceuticals.	No wastages.
All the compounds in a mixture are heated equally.	In microwave, specific component can be heated specifically, thus, increases the efficiency and reduced the operation cost.
Process speed or the rate of reaction is slow.	Reaction rate or speed is very high leading to the efficient results.
Mechanism applied for heating is conduction.	Dielectric polarization and ionic conduction based heating mechanisms are implemented.
Floor space requirement for reaction.	Limited space required.
Vessel should be in physical contact with surface source that is at higher temperature source.	No need of physical contact as everything is being done inside the microwave.
Final product is not pure.	Purity in final product is achieved with better results.

Synthesis of 1,1',2,2',3',4'-hexahydro-7'(4-fluorophenyl)-spiro[3H-indole-3,5'-(5H)pyrido(2,3-d) pyrimidine]-2',4'(1H, 3H)-dithione (2) (Dwivedi et al. 2009)

Microwave method: A mixture of 2'-amino-3'-cyano-6'-(4-fluorophenyl)-1',4'-dihydro-spiro[3H-indole-3,4'(1-H)-pyridin]-2(1H)-one, and carbon disulphide (15mL) with DMF was heated in microwave to obtain the targeted product. Same compound can also be prepared in basic media by irradiating a mixture of 2'-amino-3'-cyano-6'-(4-fluorophenyl)-1',4'-dihydro-spiro[3H-indole-3,4'(1-H)-pyridin]-2(1H)-one and carbon disulphide adsorbed on basic alumina in microwave.

Conventional method: A mixture of 2'-amino-3'-cyano-6'-(4-fluorophenyl)-1',4'-dihydro-spiro[3H-indole-3,4'(1-H)-pyridin]-2(1H)-one and carbon disulphide in presence of pyridine was refluxed for 15 h. After cooling, the excess pyridine was removed by distillation under reduced pressure and the residue was washed with water and cold ethanol to obtain targeted compound.

Synthesis of 2-phenyl benzothiazolo [3,2-α]-s-triazine-4-[3H] thiones (3)

Benzothiazole moiety are among those heterocyclic compounds which are known to possess strong fungicidal **(**Dandia et al. 2005), antituberculotic (Waisser et al. 1989),

Table 2: A comparison of microwave and conventional way of synthesis of some medicinal compounds.

Entry		Microwave Method			Conventional Method		
	Method	Reaction time (min)	Temperature ºC	Yield %	Reaction time (min)	Temperature ºC	Yield %
1	MW (DMF)	6 min	125	80%	420 min	reflux	62
	MW basic	3 min	182	89%	420 min	reflux	62
2	MW (DMF)	5	115	80	850	reflux	60
	MW basic	2	135	85	850	reflux	60
3	-	2		90	360	reflux	60
4	-	7		86.08	240	1000	67.45

antiallergic (Rousel et al. 1987) and anticancer (Wells et al. 2000) activities, while triazine derivatives are also famous to have broad spectrum antibacterial (Joshua et al. 2004), antifungal (Mohan et al. 2003) and antiviral activity (Poonian et al. 1976, Misra et al. 1976).

Microwave method (Kriplani et al. 2006): 2-phenyl benzothiazolo (3,2-α)-s-triazine-4-(3H) thiones are prepared in microwaves by irridiating a mixture of 2-benzylidenoimino-6-substitutedbenzothiazole and ammoniumthiocyanate in 1,4-dioxane at 160 Watt for 1.5 to 2 minutes.

Conventional method: While the synthesis of same compounds with conventional method utilized a mixture of 2-benzylidenoimino-6-substitutedbenzothiazole and ammoniumthiocyanate only provide 68% yield and also require 6 hour reflux (Velingkar & Dandekar 2009).

Synthesis of substituted acridone analogues (4) (Atwell et al. 1984)

Acridones are known to be the best anticancer agents and they are also prepared by microwave technology.

Microwave method: A mixture of N-(substituted phenyl) anthranilic acid and conc. sulfuric acid was subjected to microwave irradiation at 400W microwave intensity for 6-7 min to obtain substituted acridone.

Conventional method (Laoi et al. 2001): Conventional way of synthesis of substituted acridone involves heating of a mixture of N-(substituted phenyl) anthranilic acid and conc. sulfuric acid at 1000°C for about 4 hours. Reaction mixture is then cooled at room temperature and then poured into ice water. The precipitate formed was collected and washed with water. The solid precipitate was then boiled for 5 minutes with an aqueous solution of sodium carbonate and placed under high vacuum to obtain the desired product.

Synthesis of 3-bromocarbazole-N-acetic acid (Yamasaki et al. 1983)

Carbazole and its derivatives stand among those heterocyclic compounds, which acquired their place as emerging antibiotics (Baruth 1986) and are part of many medicines i.e., vetprofen (carprofen) (Ceuppens 1982, Schleimer 1981, Leung 1982, Veit 1982), carvedilol (used in chronic heart failure) (Doughty & White 2007) and ondansetron (Elz & Heil 1995), etc.

For the preparation of 3-bromocarbazole-N-acetic acid a mixture of 3-bromocarbazole, sodium hydroxide and the ethyl bromo-acetate in presence of DMF was heated in a domestic microwave oven in an open round-bottomed flask for 4 min. Then water was poured into the flask and the filtrate was acidified by adding hydrochloric acid until complete precipitation. The precipitate was filtered, washed with water, and dried in vacuum to obtain the crude product in 85% yield. The conventional way of synthesizing the same compound required long time, use of solvents and yield obtained is also very low.

CONCLUSION

From the current study, it can be concluded that use of sustainable technology of microwave in synthesis of medicinally important compounds is the best possible solution to avoid chemical and thermal pollution of environment. Use of medicines is vital for human beings to fight against diseases, thus, the processes involved in the preparation of these medicines should not be an initiative of some other disease by polluting human environment with hazardous materials. Thus, microwave technology should not only be adopted for preparation of new medicines, rather the processes involved in the preparation of already launched medicines should also be replaced by ecofriendly technique of microwave in laboratories as well as in industries.

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