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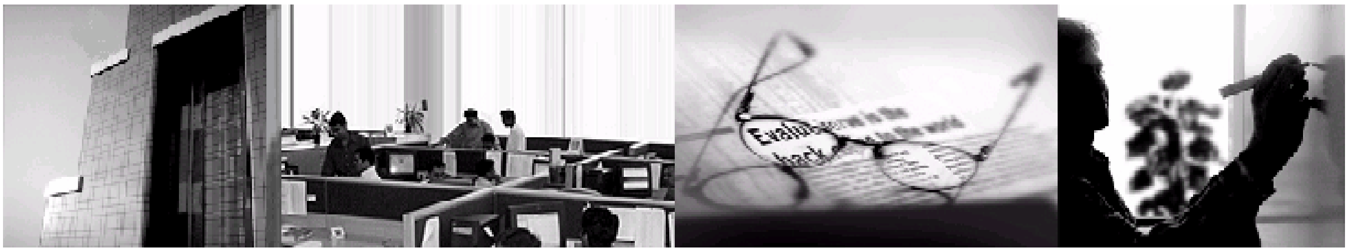

Developments in Microwave Chemistry

3/30/2005

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Contents

Evalueserve

Mike Taylor
Mike.Taylor@Evalueserve.com
Tel: +44 7713 065 946
UK

Bhuwan Singh Atri
Bhuwan.Atri@Evalueserve.com
Tel: +91 124 256 1770
Fax: +91 124 256 2393
India

Sonal Minhas
Sonal/Minhas@Evalueserve.com
Tel: +91 124 515 4140
Fax: +91 124 256 2393
India

India Team
Dr. Priyal Bisht

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1 Executive Summary

Microwave chemistry has an edge over conventional heating methods for conducting chemical reactions, and it will soon emerge as the preferred technology for performing chemical synthesis relating to lead development in pharmaceutical and biotechnology companies. Moreover, the use of microwave chemistry for industrial production holds promise, since research has already been initiated to scale up microwave chemistry reactions from milligrams to kilograms.

Over the past three decades, microwave chemistry has evolved as an established field of science, due to intensified research in the area. In the future, microwave chemistry is likely to become a preferred method for conducting analytical and synthetic reactions in laboratories. This is validated by the increasing number of publications in the field, from about 500 in 1997, to over 2000 up to 2004[1]. At present, about 25,000-30,000[2] chemists use microwave technology to conduct chemical reactions worldwide.

Initially, microwave chemistry was primarily used to carry out analytical processes such as ashing, digestion, extraction, fat analysis and protein hydrolysis. As microwave chemical synthesis has advanced, its applications have been extended to include the synthesis of fine chemicals, organometallic, coordination, intercalation compounds, and nanoparticles. Microwave technology also enables chemists to achieve cleaner and more efficient chemical reactions with higher yields, compared to conventional heating methods.

The microwave chemistry equipment market was estimated to be $ 89m in 2003. Although the market size is relatively small at present, in view of current growth trends, it is expected to reach $145.8m by 2008. This growth will be driven by advancement in equipment technology and growing awareness of technology, its success, and the advantages.

The equipment market is divided into two parts, i.e., chemical analytics and chemical synthesis. Though the analytical segment currently holds a larger share of the market, this may change in the future, since the chemical synthesis segment is expected to grow at a much faster rate. The key players in the microwave chemistry market are CEM Corporation, Biotage AB and Milestone s.r.l, with CEM Corporation holding the largest market share.

Two categories of equipment used in microwave chemistry, based on design requirements: single-mode and multi-mode microwave ovens. Both types cater to a specific market segment. Single-mode microwave equipment is primarily used for chemical synthesis, whereas multi-mode microwave equipment is mainly used for chemical analysis.

This equipment has been limited to laboratories due to lack of scalability of the technology. Presently, the manufacturers are directing their research to develop products that can increase the yield volume substantially. These new products have been successful in augmenting the scale of reactions from the level of 0.2 mL to 500 mL. However, scalability to the level of industrial production has still not been achieved, which questions the commercial viability of microwave chemistry.

In addition, there is a demand for a further increase in the rate of reaction. Consequently, instrument manufacturers are developing prototypes that will be able to achieve high-pressure conditions inside the reaction vessel, resulting in an

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1Reference: Evalueserve Analysis

[2] Source: Robert England, Director, Personal Chemistry

increased rate of reaction. Other areas of research include design modifications in the existing equipment, to provide safer reaction conditions; and development of equipment that can be used for chemical analysis as well as chemical synthesis.

In light of the limited research that has taken place in microwave chemistry till date, it offers researchers enormous scope for research and development. This is evident from the small number of patent publications (94) granted in this field over the past 30 years of research. Of these, about 68 were granted in the area of chemical analysis in the last two decades, and 48 in the field of chemical synthesis in the last six years. This indicates that the focus of research and development in microwave chemistry is shifting from chemical analysis to chemical synthesis.

2 Scope and Methodology

This section lays down the scope of the report and presents the methodology used by the authors to conduct their research. It also discusses the key limitations faced by them while preparing the report.

2.1 Scope of the Study

The following document proposes to study key developments in the field of microwave chemistry. Since microwave chemistry pertains to the use of microwaves in chemical reactions only, application areas that use microwaves for processes such as industrial drying and heating, etc., have been excluded from the scope of this study. In effect, only applications that use microwave as a source of heating for chemical analysis and chemical synthesis have been studied. The study encompasses a description of the main application areas of microwave chemistry, its current market size and structure, major research advances in the sphere, and key developments in intellectual property in this area.

This report serves as basic reference material for those who intend to gain an insight into microwave chemistry. It may be useful for undergraduate and graduate chemistry students, researchers, product development managers and industrial chemists.

Since the purpose of this report is to serve as elementary text pertaining to microwave chemistry, the authors have attempted to organise the information in breadth rather than in depth. Wherever necessary, specific details have been elaborated as footnotes. Detailed references have also been provided at the end of the report, for those interested in studying the topic in greater detail.

2.2 Methodology

The methodology used in the research carried out for this report includes:

1. Data collection
2. Data analysis

2.2.1 Data Collection

The information used in this report has been collected from various publicly available secondary and primary research sources.

The secondary sources of information include industry publications, research papers, association websites, educational institutions' websites, and the websites of various players in the industry (e.g.,CEM Corporation, Milestone s.r.l and Biotage AB). In addition, patent publications in this field have also been studied in depth. Information pertaining to patent publications granted until 2004 was obtained from the website of the United States Patents and Trademarks Office (USPTO) and the patent search engine, Thompson Delphion.

The primary research procedure comprised interviews conducted with experts in industries, academic institutions and manufacturing companies, to get their expert opinion. The authors would particularly like to thank Dr. Gavin Whittaker (Professor, Edinburgh University, UK) and Dr. Robert England (former Director, Personal Chemistry[3]) for providing valuable inputs to the study.

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[3] Now Biotage AB

2.2.2 Data Analysis

The data analysis exercise was conducted, using the qualitative analysis and quantitative analysis methods.

2.2.2.1 Qualitative Analysis Method

Qualitative analysis techniques were used to gain a fundamental understanding of the field of microwave chemistry. Basic inferences have been drawn by studying the conceptual framework of microwave chemistry, the applications and key advances that have taken place and future trends in the field.

2.2.2.2 Quantitative Analysis Method

Quantitative analysis techniques were used to understand the microwave chemistry market and the development of intellectual property. Inferences were drawn from various findings obtained from primary and secondary research sources, and a data-analysis exercise was specifically conducted to estimate the size of the microwave chemistry market. Estimates pertaining to the size of the market were obtained by undertaking a basic modelling exercise, using data relating to specific variables that could impact market size and growth.

2.3 Key Limitations

The key limitations of this study:

- Information on market statistics pertaining to microwave equipment is not available freely, because of which it was not possible to make a comprehensive analysis of the microwave chemistry market. This also limited the research to freely available online sources.
- The research, which was conducted to study intellectual property relating to microwave chemistry, is primarily based on patent publications in the public domain. Patent publications that have still not been published, containing information about recent developments in the field, could not be included in the report.
- Certain key information, deemed necessary for a comprehensive analysis of the microwave chemistry market, could not be obtained through primary research. This was because some respondents did not want to reveal this information due to confidentiality issues.
- Personal Chemistry, which is a major manufacturer of chemical synthesis equipment was acquired by Pyrosequencing in 2003. The organization has now been named as Biotage AB. Therefore the sales of the chemical synthesis equipment of Biotage AB (for 2003) could not be attained.

3 Introduction to Microwave Chemistry

Microwave chemistry involves the use of microwave radiation to conduct chemical reactions, and essentially pertains to chemical analysis and chemical synthesis. Microwave radiation has been successfully applied to numerous industrial applications (drying, heating, sintering, etc.).

This section provides a basic overview of microwave chemistry. It starts with an insight into the scientific principle governing the function of microwave radiation and its use in chemical analysis and synthesis. It also discusses the mechanism of microwave heating and provides a background to the evolution of microwave chemistry, enumerating its benefits and limitations, while briefly delving into the controversy pertaining to the 'microwave effect'.

Microwaves lie in the electromagnetic spectrum between infrared waves and radio waves. They have wavelengths between 0.01 and 1 metre, and operate in a frequency range between 0.3 and 30 GHz. However, for their use in laboratory reactions, a frequency of 2.45 GHz is preferred, since this frequency has the right penetration depth for laboratory reaction conditions. Beyond 30 GHz, the microwave frequency range overlaps with the radio frequency range. The microwave electromagnetic spectrum is divided into sub-bands comprising the following frequency ranges (Table 1):

Table 1: Microwave Frequency Bands

BANDS	FREQUENCY
L	1-2 GHz
S	2-4 GHz
C	4-8 GHz
X	8-12 GHz
Ku	12-18 GHz
K	18-26 GHz
Ka	26-40 GHz
Q	30-50 GHz
U	40-60 GHz
V	46-56 GHz
W	56-100 GHz

Source: www.wikipedia.com

While the lower microwave frequency ranges (L band) are used for the purpose of communication, the higher frequency ranges (W band) in the spectrum are used for analytical techniques such as spectroscopy. Microwave RADAR equipment that operate at lower wavelengths (0.01-0.25 m) are used for communication.

3.1 Fundamentals of Microwave Technology

The fundamental mechanism of microwave heating involves agitation of polar molecules or ions that oscillate under the effect of an oscillating electric or magnetic field. In the presence of an oscillating field, particles try to orient themselves or be in phase with the field. However, the motion of these particles is restricted by resisting forces (inter-particle interaction and electric resistance), which restrict the motion of particles and generate random motion, producing heat.

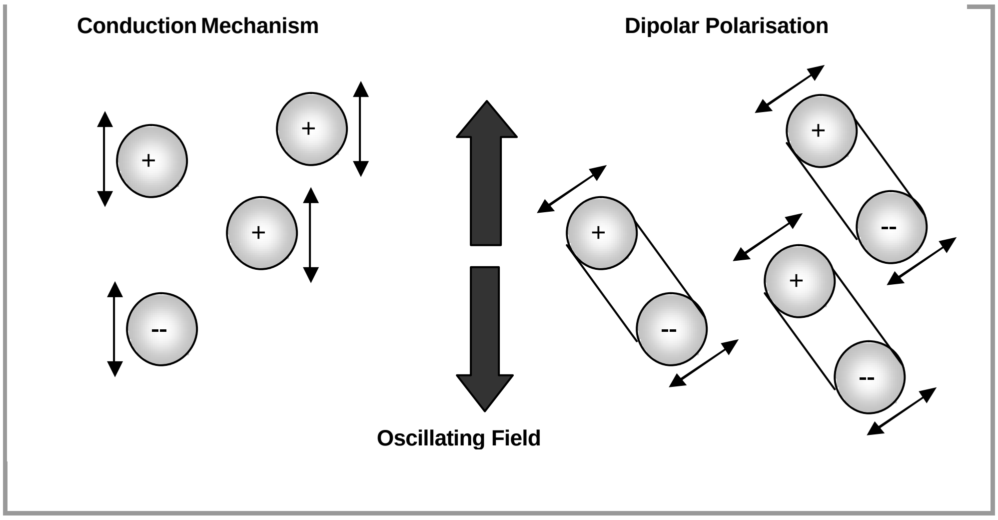
Since the response of various materials to microwave radiation is diverse, not all materials are amenable to microwave heating. Based on their response to microwaves, materials can be broadly classified as follows:

- Materials that are transparent to microwaves, e.g., sulphur
- Materials that reflect microwaves, e.g., copper
- Materials that absorb microwaves, e.g., water

Only materials that absorb microwave radiation are relevant to microwave chemistry. These materials can be categorised according to the three main mechanisms of heating (Figure 1), namely:

1. Dipolar polarisation
2. Conduction mechanism
3. Interfacial polarisation

Figure 1: Methods of Heating by Microwave Radiation



Source: Pueschner GmBH website (www.pueschner.com/engl/basics/index.html)

3.1.1 Dipolar Polarisation

Dipolar polarisation is a process by which heat is generated in polar molecules. On exposure to an oscillating electromagnetic field of appropriate frequency, polar molecules try to follow the field and align themselves in phase with the field. However, owing to inter-molecular forces, polar molecules experience inertia and are unable to follow the field. This results in the random motion of particles, and this random interaction generates heat. Dipolar polarisation can generate heat by either one or both the following mechanisms:

1. Interaction between polar solvent molecules such as water, methanol and ethanol
2. Interaction between polar solute molecules such as ammonia and formic acid

The key requirement for dipolar polarisation is that the frequency range of the oscillating field should be appropriate to enable adequate inter-particle interaction. If the frequency range is very high, inter-molecular forces will stop the motion of a polar molecule before it tries to follow the field, resulting in inadequate inter-particle interaction. On the other hand, if the frequency range is low, the polar molecule gets sufficient time to align itself in phase with the field. Hence, no random interaction takes place between the adjoining particles. Microwave radiation has the appropriate frequency (0.3-30 GHz) to oscillate polar particles and enable enough inter-particle interaction. This makes it an ideal choice for heating polar solutions.

In addition, the energy in a microwave photon (0.037 kcal/mol) is very low, relative to the typical energy required to break a molecular bond (80-120 kcal/mol). Therefore, microwave excitation of molecules does not affect the structure of an organic molecule, and the interaction is purely kinetic.

3.1.2 Conduction Mechanism

The conduction mechanism generates heat through resistance to an electric current. The oscillating electromagnetic field generates an oscillation of electrons or ions in a conductor, resulting in an electric current. This current faces internal resistance, which heats the conductor.

The main limitation of this method is that it is not applicable for materials that have high conductivity, since such materials reflect most of the energy that falls on them.

3.1.3 Interfacial Polarisation

The interfacial polarisation method can be considered as a combination of the conduction and dipolar polarisation mechanisms. It is important for heating systems that comprise a conducting material dispersed in a non-conducting material. For example, consider the dispersion of metal particles in sulphur. Sulphur does not respond to microwaves, and metals reflect most of the microwave energy they are exposed to, but combining the two makes them a good microwave-absorbing material. However, for this to take place, metals have to be used in powder form. This is because, unlike a metal surface, metal powder is a good absorber of microwave radiation. It absorbs radiation and is heated by a mechanism that is similar to dipolar polarisation. The environment of the metal powder acts as a solvent for polar molecules and restricts the motion of ions by forces that are equivalent to inter-particle interactions in polar solvents. These restricting forces, under the effect of an oscillating field, induce a phase lag in the motion of ions. The phase lag generates a random motion of ions and results in the heating of the system[4].

3.2 Evolution of Microwave Chemistry

The use of microwave radiation as a method of heating is over five decades old. Microwave technology originated in 1946, when Dr. Percy Le Baron Spencer, while conducting laboratory tests for a new vacuum tube called a magnetron[5], accidentally discovered that a candy bar in his pocket melted on exposure to microwave radiation. Dr. Spencer developed the idea further and established that microwaves could be used as a method of heating. Subsequently, he designed the first microwave oven for domestic use in 1947[6]. Since then, the development of microwave radiation as a source of heating has been very gradual (Table 2).

Table 2: Evolution of Microwave Chemistry

1946	Microwave radiation was discovered as a method of heating
1947	First commercial domestic microwave oven was introduced
1978	First microwave laboratory instrument was developed by CEM Corporation to analyse moisture in solids
1980-82	Microwave radiation was developed to dry organic materials
1983-85	Microwave radiation was used for chemical analysis processes such as ashing, digestion and extraction
1986	Robert Gedye, Laurentian University, Canada; George Majetich, University of Georgia, USA; and Raymond Giguere of Mercer University, USA, published papers relating to microwave radiation in chemical synthesis

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[4] Reference: http://homepages.ed.ac.uk/ah05/microwave.html

[5] A device that generates an electromagnetic field

[6] Reference: http://www.gallawa.com/microtech/history.html

1990s	Microwave chemistry emerged and developed as a field of study for its applications in chemical reactions
1990	Milestone s.r.l. generated the first high pressure vessel (HPV 80) for performing complete digestion of difficult to digest materials like oxides, oils and pharmaceutical compounds
1992-1996	CEM developed a batch system (MDS 200) reactor, and a single mode cavity system (Star 2) that were used for performing chemical synthesis
1997	Milestone s.r.l and Prof. H.M (Skip) Kingston of Duquesne University culminated a reference book titled “Microwave-Enhanced Chemistry – Fundamentals, Sample Preparation, and Applications”, and edited by H. M. Kingston and S. J. Haswell
2000	First commercial microwave synthesiser was introduced to conduct chemical synthesis

Source: Evalueserve Analysis

The application of microwave technology in industrial usage occurred much later, when, in 1978, Michael J. Collins designed and produced the first microwave laboratory instrument, a moisture/solids analyser. Subsequently, in the early 1980s, microwave irradiation was developed as a method of heating dry organic materials such as agricultural products, oils, etc., at an industrial scale.

By the mid-1980s, the use of microwave radiation further evolved to encompass the field of chemical analysis, and its application was extended to analytical processes such as ashing, extraction and digestion of chemicals.

For nearly a decade, developments in microwave chemistry were driven by chemical analysis, and it was only in 1986 that two groups, one led by Robert Gedye and his associates at the Laurentian University in Ontario, Canada, and the other by George Majetich of the University of Georgia, USA, and Raymond Giguere of Mercer University, USA, made the first attempt to use microwaves in chemical synthesis. It was discovered that certain reactions could work a thousand times faster when microwave radiation replaced the usual heating source. A report was then published on the use of microwave heating for synthetic organic transformations, and it was established that performing organic synthesis under microwave radiation had significant advantages compared to conventional heating techniques.

In the decade of 1990s, advancements were made in the products developed by companies in the filed of microwave chemistry equipment. In 1990, Milestone s.r.l. introduced the first high pressure digestion vessel, HPV 80 in 1990. The system helped in complete digestion of difficult to digest materials such as oxides, oils, and pharmaceutical compounds. Between 1992 and 1996, CEM Corporation introduced a microwave digestion system (MDS 2000) with a batch reactor. This increased the number of tests that could be performed simultaneously in the microwave digestion system. During the same period, CEM Corporation also introduced a single mode cavity system (Star 2) that controlled digestion reactions in a better way.

During the same period, researchers conducted reactions, which were previous performed using conventional heating methods, using microwave radiations. In 1992, Mike Mingos and David Baghurst of Oxford University, UK, discovered that microwaves heat up solvents above their normal boiling points (a phenomenon called superheating) -- for instance, water boils at 119 °C instead of 100 °C on exposure to 500 watts of microwave radiation[7]. Later, in 1993, Didier Stuerga of the University of Bourgogne in Dijon, France, observed the selectivity pattern when the sulphonic acid group was added to naphthalene in the presence of microwaves. The bonding of the group could be controlled, to determine which part of the chemical group predominated.

However, due to lack of microwave ovens that were specifically designed for chemical synthesis, some researchers attempted chemical synthesis, using domestic microwave ovens in the initial years. This resulted in unpredictable chemical reactions[8], which led to the belief that microwave heating was ineffective for conducting chemical synthesis.

The first custom-built commercial microwave synthesiser, to conduct chemical synthesis, was introduced in 2000. It was designed to produce a uniform microwave field, regardless of the content of the vessel, and was equipped with additional functions such as temperature control of the chemical reaction and safety mechanisms[9]. Since then, the development of equipment for microwave chemical synthesis has become a major field of research in microwave chemistry.

3.3 Microwave Chemistry Apparatus

Most pioneering experiments in chemical synthesis using microwaves were carried out in domestic microwave ovens. However, developments in microwave equipment technology have enabled researchers to use dedicated apparatus for organic reactions. The following are the two categories into which microwave chemistry apparatus are classified:

- Single-mode apparatus
- Multi-mode apparatus

3.3.1 Single-mode Apparatus

The differentiating feature of a single-mode apparatus is its ability to create a standing wave pattern, which is generated by the interference of fields that have the same amplitude but different oscillating directions. This interface generates an array of nodes where microwave energy intensity is zero, and an array of antinodes where the magnitude of microwave energy is at its highest (Figure 2).

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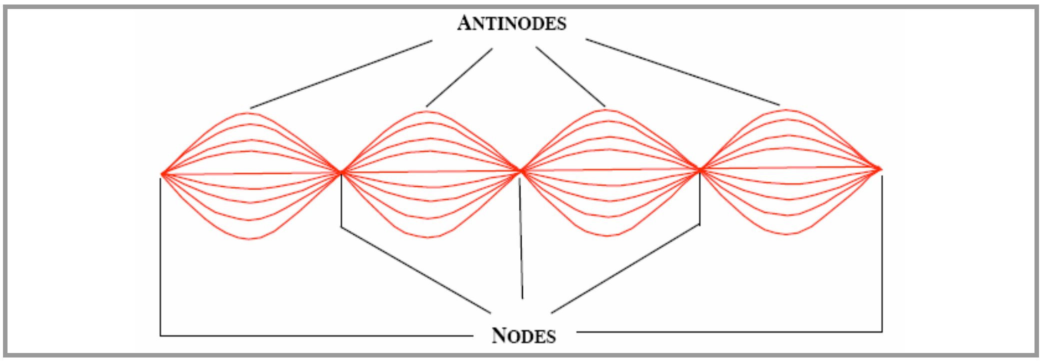
[7] This is because microwaves heat the solvent in a container directly, allowing it to reach a higher than usual temperature before bubbles can form and it boils.

[8] Note: This is owing to the fact that domestic microwave ovens use a multi-mode heating mechanism, which provides an uneven microwave field density and is inadequate for chemical synthesis.

[9] Source: Microwave Synthesis: A New Wave of Synthetic Organic Chemistry by Robert England, Personal Chemistry

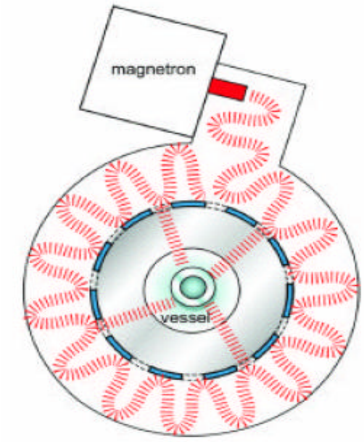
Figure 2: Generation of a Standing Wave Pattern



Source: Chapter on Standing Waves and Musical Instruments at www.tufts.edu

The factor that governs the design of a single-mode apparatus is the distance of the sample from the magnetron. This distance should be appropriate to ensure that the sample is placed at the antinodes of the standing electromagnetic wave pattern (Figure 3).

Figure 3: Single-mode Heating Apparatus



Source: Self-turning Single-mode cavity in Discoverer^{TM} system by CEM Corporation

One of the limitations of single-mode apparatus is that only one vessel can be irradiated at a time. However, after the completion of the reaction period, the reaction mixture can be rapidly cooled by using compressed air – this is a built-in cooling feature of the apparatus. As a result, the apparatus becomes more user-friendly. These apparatus can process volumes ranging from 0.2 to about 50 mL under sealed-vessel conditions (250 °C, ca. 20 bar), and volumes around 150 mL under open-vessel reflux conditions[10]. Single-mode microwave heating equipment are currently used for small-scale drug discovery, automation and combinatorial chemical applications. An advantage of single-mode apparatus is their high rate of heating. This is because the sample is always placed at the antinodes of the field, where the intensity of microwave radiation is the highest. In contrast, the heating effect is averaged out in a multi-mode apparatus.

3.3.2 Multi-mode Apparatus

An essential feature of a multi-mode apparatus is the deliberate avoidance of generating a standing wave pattern inside it (Figure 4).

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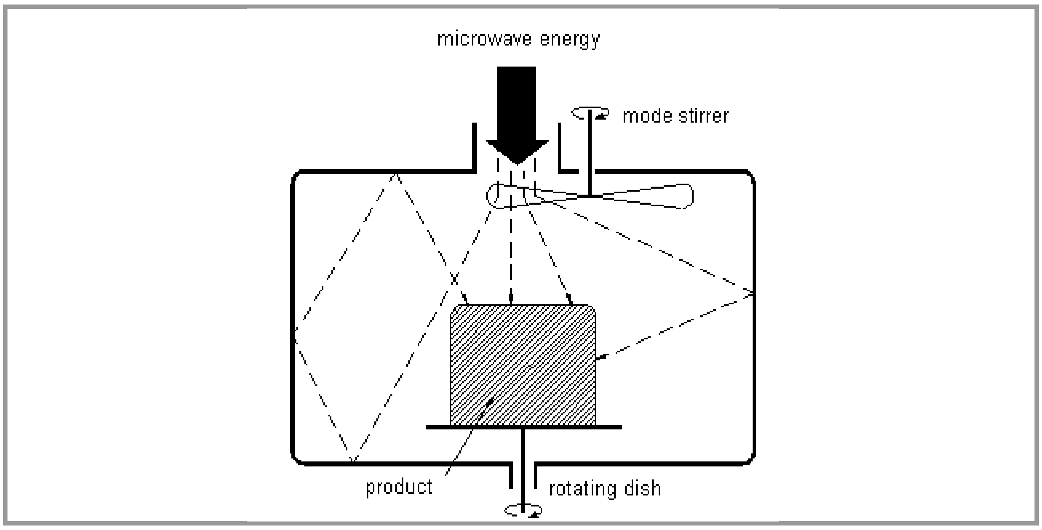
[10] Reference: http://www3.interscience.wiley.com/cgi-bin/fulltext/109799813/HTMLSTART

Figure 4: Multi-mode Heating Apparatus



Source: http://www.pueschner.com/engl/basics/index.html

The goal is to generate as much chaos as possible inside the apparatus. The greater the chaos, the higher is the dispersion of radiation, which increases the area that can cause effective heating inside the apparatus. As a result, a multi-mode microwave heating apparatus can accommodate a number of samples simultaneously for heating, unlike single-mode apparatus where only one sample can be irradiated at a time. Owing to this characteristic, a multi-mode heating apparatus is used for bulk heating and carrying out chemical analysis processes such as ashing, extraction, etc. In large multi-mode apparatus, several litres of reaction mixture can be processed in both open and closed-vessel conditions. Recent research has resulted in the development of continuous-flow reactors for single- and multi-mode cavities that enable preparation of materials in kilograms.[11]

A major limitation of multi-mode apparatus is that even with radiation distributed around them, heating samples cannot be controlled efficiently. This is largely due to the chaos generated, which makes it difficult to create equal heating conditions for samples that are heated simultaneously.

3.4 Benefits of Microwave Chemistry

Microwave radiation has proved to be a highly effective heating source in chemical reactions. Microwaves can accelerate the reaction rate, provide better yields and uniform and selective heating, achieve greater reproducibility of reactions, and help in developing cleaner and greener synthetic routes.

> ***"****Microwave-enhanced chemical reactions are safer, faster, cleaner and more economical than conventional reactions. The impact of microwave technology on laboratory instruction and research in academia can significantly improve educational programs at all levels and help attract students to chemistry, biochemistry and chemical biology.****"***
>
> - Professor Ajay K. Bose, Stevens Institute of Technology – Hoboken, New Jersey, USA

3.4.1 Increased Rate of Reactions

Compared to conventional heating, microwave heating enhances the rate of certain chemical reactions by 10 to 1,000 times. This is due to its ability to substantially increase the temperature of a reaction, for instance, synthesis of fluorescein, which usually takes about 10 hours by conventional heating methods, can be conducted in only 35 minutes by means of microwave heating (Table 3).

Table 3: Comparison of Reaction Duration (in minutes)

REACTION	CONVENTIONAL	MICROWAVE
Synthesis of fluorescein	600	35
Condensation of benzoine with urea	60	8
Biginelli reaction	360	35

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[11] Reference: http://www3.interscience.wiley.com/cgi-bin/fulltext/109799813/HTMLSTART

Synthesis of aspirin	130	1

Source: Milestone s.r.l

At present, there are two main theories that seek to explain the rate acceleration caused by microwaves. These theories are based on experiments conducted on the following set of reactions:

1. Liquid phase reactions
2. Catalytic reactions

3.4.1.1 Liquid Phase Reactions

The rate acceleration in liquid phase reaction, heated by microwave radiation, can be attributed to the superheating of solvents, for example, water, when heated by conventional methods, has a boiling point of 100 ºC. However, when a power input of 500 watts is employed for a minute in microwave equipment, the reaction can be performed at a temperature of 110 ºC. It has also been observed that the boiling point of water reaches 119 ºC at the reaction conditions mentioned above. This superheating of solvents enables the reaction to be performed at higher temperatures and results in an increase in the rate of the reaction.

3.4.1.2 Catalytic Reactions

The rate acceleration in solid-state catalytic reactions, on exposure to microwave radiation, is attributed to high temperatures on the surface of the catalyst. The increase in the local surface temperature of the catalyst results in enhancement of the catalytic action, leading to an enhanced rate of reaction[12]. It has been observed that when the catalyst is introduced in a solid granular form, the yield and rate of the heterogeneous oxidation, esterification and hydrolysis reactions increases with microwave heating, compared to conventional heating under the same conditions. Table 4 shows an increase in yield by 200% for oxidation and 150% for hydrolysis, when the reaction is conducted in the microwave batch reactor (Synthewave 402).

Table 4: Comparison of Yield under Microwave and Conventional Heating Methods

CHEMICAL REACTION	TEMPERATURE (^{0}C)	TIME (MINUTES)	MW YIELD (%)	CONVENTIONAL YIELD (%)
Hydrolysis of hexanenitrile	100	60	40	26
Oxidation of cyclohexene	80	60	26	12
Esterification of stearic acid	140	120	97	83

Source: http://www.mdpi.net/ecsoc-5/e0017/e0017.htm

3.4.2 Efficient Source of Heating

Heating by means of microwave radiation is a highly efficient process and results in significant energy saving. This is primarily because microwaves heat up just the sample and not the apparatus, and therefore energy consumption is less.

A typical example is the use of microwave radiation in the ashing process. As microwave ashing systems can reach temperatures of over 800 °C in 50 minutes[13],

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[12] Definition: A catalytic reaction is governed by the surface area and temperature of the reactants.

[13] Reference: www.milestone.com

they eliminate the lengthy heating-up periods associated with conventional electrical-resistance furnaces. This significantly lowers average energy costs.

3.4.3 Higher Yields

In certain chemical reactions, microwave radiation produces higher yields compared to conventional heating methods, for example, microwave synthesis of fluorescein results in an increase in the yield of the reaction, from 70% to 82% (Table 5).

Table 5: Comparison of Yields (%)

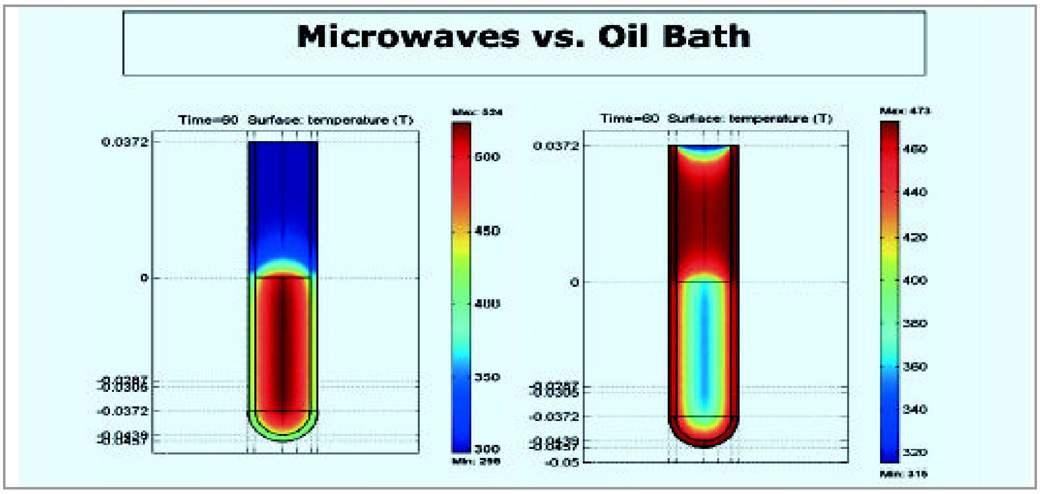
REACTION	CONVENTIONAL	MICROWAVE
Synthesis of fluorescein	70	82
Condensation of benzoine with urea	70	73
Biginelli reaction	70	75
Synthesis of aspirin	85	92

Source: Milestone s.r.l

3.4.4 Uniform Heating

Microwave radiation, unlike conventional heating methods, provides uniform heating throughout a reaction mixture (Figure 5).

Figure 5: Uniform Heating through Microwave Irradiation



Source: Biotage AB

In conventional heating, the walls of the oil bath get heated first, and then the solvent. As a result of this distributed heating in an oil bath, there is always a temperature difference between the walls and the solvent. In the case of microwave heating, only the solvent and the solute particles are excited, which results in uniform heating of the solvent. This feature allows the chemist to place reaction vessels at any location in the cavity of a microwave oven. It also proves vital in processing multiple reactions simultaneously, or in scaling up reactions that require identical heating conditions.

3.4.5 Selective Heating

Selective heating is based on the principle that different materials respond differently to microwaves. Some materials are transparent whereas others absorb microwaves. Therefore, microwaves can be used to heat a combination of such materials, for example, the production of metal sulphide with conventional heating requires weeks because of the volatility of sulphur vapours. Rapid heating of sulphur in a closed tube results in the generation of sulphur fumes, which can cause an explosion. However, in microwave heating, since sulphur is transparent to microwaves, only the metal gets heated. Therefore, reaction can be carried out at a much faster rate, with rapid heating, without the threat of an explosion.

3.4.6 Environmentally-friendly Chemistry[14]

Reactions conducted through microwaves are cleaner and more environmentally friendly than conventional heating methods. Microwaves heat the compounds directly; therefore, usage of solvents in the chemical reaction can be reduced or eliminated, for example, Hamelin developed an approach to carry out a solvent-free chemical reaction on a sponge-like material with the help of microwave heating. The reaction is conducted by heating a spongy material such as alumina. The chemical reactants are adsorbed to alumina, and on exposure to microwaves, react at a faster rate than conventional heating.

In most of our reactions, products are obtained which do not need further purification

- Rajender Varma of Sam Houston State University, Texas, US

The use of microwaves has also reduced the amount of purification required for the end products of chemical reactions involving toxic reagents.

3.4.7 Greater Reproducibility of Chemical Reactions

Reactions with microwave heating are more reproducible compared to conventional heating because of uniform heating and better control of process parameters. The temperature of chemical reactions can also be easily monitored. This is of particular relevance in the lead optimisation phase of the drug development process in pharmaceutical companies.

3.5 Limitations of Microwave Chemistry

The limitations of microwave chemistry are linked to its scalability, limited application, and the hazards involved in its use.

3.5.1 Lack of Scalability

The yield obtained by using microwave apparatus available in the market is limited to a few grams. Although there have been developments in the recent past, relating to the scalability[15] of microwave equipment, there is still a gap that needs to be spanned to make the technology scalable. This is particularly true for reactions at the industrial production level and for solid-state reactions.

3.5.2 Limited Applicability

The use of microwaves as a source of heating has limited applicability for materials that absorb them. Microwaves cannot heat materials such as sulphur, which are transparent to their radiation. In addition, although microwave heating increases the rate of reaction in certain reactions, it also results in yield reduction compared to conventional heating methods -- examples have been cited in the reference section[16].

3.5.3 Safety Hazards Relating to the Use of Microwave-heating Apparatus

Although manufacturers of microwave-heating apparatus have directed their research to make microwaves a safe source of heating, uncontrolled reaction conditions may result in undesirable results, for example, chemical reactions involving volatile reactants under superheated conditions may result in explosive conditions. Moreover, improper use of microwave heating for rate enhancement of

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[14] Reference: http://www.milestonesci.com/synth-Start-features.php

[15] Developments in the scaling up of microwave equipment yields are discussed in detail in Chapter 6.

[16] Reference: http://homepages.ed.ac.uk/ah05/microwave.html

chemical reactions involving radioisotopes may result in uncontrolled radioactive decay.

Certain problems, with dangerous end results, have also been observed while conducting polar acid-based reactions, for example, microwave irradiation of a reaction involving concentrated sulphuric acid may damage the polymer vessel used for heating. This is because sulphuric acid is a strong coupler of microwave energy and raises the reaction temperature to 300 °C within a very short time. As a result, the polymer microwave-heating container may melt, with hazardous[17] consequences. Conducting microwave reactions at high-pressure conditions may also result in uncontrolled reactions and cause explosions.

3.5.4 Health Hazards Relating to the Use of Microwave-heating Apparatus

Health hazards related to microwaves are caused by the penetration of microwaves. While microwaves operating at a low-frequency range are only able to penetrate the human skin, higher frequency-range microwaves can reach body organs. Research has proven that on prolonged exposure microwaves may result in the complete degeneration of body tissues and cells. It has also been established that constant exposure of DNA to high-frequency microwaves during a biochemical reaction may result in complete degeneration of the DNA strand.

Research has been carried out to understand this phenomenon, and two schools of thought have evolved. The first is based on the thermal degeneration of DNA by microwave radiation, and believe that microwaves have enough energy to disrupt the covalent bond of a DNA strand. The other school of thought is emphatic about the existence of a 'non-thermal microwave effect'. Kakita et al[18] have proved that in identical temperature conditions, microwave-irradiated DNA strands were different from those heated under conventional heating methods. Microwave-irradiated DNA strands were usually destroyed, which does not occur in conventional heating. This discovery has restricted the use of microwave heating to only abiological reactions.

3.6 The Microwave Effect Controversy

Researchers have developed various theories pertaining to microwave rate acceleration. These opinions emanate from the varied response of chemical reactions under microwaves radiation. In some cases, researchers have tried to explain this phenomenon by means of the superheating theory related to microwaves. Some have been proved to be reaction-specific, whereas others have been disproved. The following text discusses these aspects in detail.

3.6.1 Atomic-level Excitation of Solid-state Reactions

Currently, no explanation exists for the thermal effect of microwaves in solid-state reactions. According to Dr. Gavin Whittaker of the Department of Chemistry at the University of Edinburgh, UK, the belief that microwave radiation affects a particle at the atomic level and causes excitation of the particles to higher energy levels seems to be the only valid explanation for rate acceleration in solid-state reactions at present[19]. Researchers have studied the heating of solid particles by microwaves and concluded that microwave radiation results in the generation of surface defects in solid particles. The generation of these surface defects enables increased ion motion, and hence helps in easy excitation of these ions to higher energy levels. Though theories have been propounded, to explain atomic excitation caused by microwaves, a complete explanation still remains an issue of contention.

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[17] Reference: http://www.sampleprep.duq.edu/dir/mwavechap16/mwave.htm

[18] Reference: http://www.engr.psu.edu/ae/iec/abe/mwaves.html

[19] Evalueserve Primary Research

3.6.2 Rate Acceleration in the Absence of Superheating

Researchers have tried to develop chemical reactions with specific microwave effects other than superheating. Reactions, where superheating has been suppressed, have still demonstrated microwave-specific effects, for example, Pagnotta[20] carried out the mutarotation of alpha-glucose to beta-glucose with both conventional heating and microwave radiation. Superheating was suppressed in the reaction by introducing a wooden stick. The reaction demonstrated a surprising increase in the alpha-glucose to beta-glucose concentration ratio at a specific reaction condition. The authors of the paper suggested a specific microwave effect. They proposed that specific activation of polar functionalities occurs in either the glucose or the surrounding solvent cage, and it is more effective for one form than the other.

3.6.3 Non-thermal Heating at Identical Temperature Conditions

Researchers have conducted experiments to disprove thermal-rate acceleration of microwaves. Such experiments demonstrated rate acceleration in reactions carried out in temperature conditions identical to conventional heating. However, an interesting fact that emerged from these experiments was that the reactions, for which the microwave-specific effect was observed, were performed under the action of catalysts in solid states. It was later observed that in microwave heating, though the bulk temperature of the reaction system remains the same, the surface temperature in the area local to the catalyst increases greatly. This increase in the surface temperature fastens the action of catalysts on the reactant surface, and therefore increases the rate of the reaction.

3.6.4 Change in the Kinetics of the Reaction

One of the most important aspects of microwave energy is the rate at which it heats. Microwaves will transfer energy in 10^{-9} seconds with each cycle of electromagnetic energy. The kinetic molecular relaxation from this energy is approximately 10^{-5} seconds. This means that energy transfers at a faster rate than the molecules can relax, which results in non-equilibrium conditions and high instantaneous temperatures that affect the kinetics of the system. This leads to enhancement in reaction rates and product yields.

In the Arrhenius reaction rate equation ($k = Ae^{-Ea/RT}$), the reaction rate constant is dependent on two factors: the frequency of collisions between molecules that have the correct geometry for a reaction to occur (A), and the fraction of those molecules with the minimum energy required to overcome the activation energy barrier ($e^{-Ea/RT}$). It would be worthwhile to note that microwaves neither influence the orientation of collisions nor the activation energy – activation energy remains constant for each particular reaction. However, microwave energy affects the temperature parameter in this equation. An increase in temperature causes greater movement of molecules, which leads to a greater number of energetic collisions. This occurs much faster with microwave energy due to high instantaneous heating of the substance(s) above the normal bulk temperature, and is the primary factor for observed rate enhancements. Microwave heating is extremely useful in slower reactions where high activation energy is required[21].

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[20] Reference: M. Pagnotta, C.L.F. Pooley, B. Gurland & M. Choi. *J Phys Org Chem* 6, 407-411 (1993)

[21] Reference: B. L. Hayes, Microwave Synthesis, Chemistry at the speed of light, CEM publishing, 2002, chapter 2, pp 29

Stuerga et al[22] discovered that when the reaction involving the addition of the sulphonic acid group to naphthalene was exposed to microwaves, the selectivity of the reaction for 1- naphthalene sulphonic acid (1- NSA) or 2- naphthalene sulphonic acid (2- NSA) could be controlled. It was observed that the rate at which the sample was heated determined the concentration of the products. An interesting fact that emerged from this reaction was that the effect of conventional heating and microwave radiation on the concentration of end products was identical. Therefore, it was concluded that microwave heating does not change the kinetics of the reaction.

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[22] Reference: D. Stuegra, K. Gonon & M. Lallemant. Tetrahdron 49, 6229-6234 (1993)

4 Applications of Microwave Chemistry

This section discusses applications of microwave chemistry in various industries and major applications that have been developed in the field of analytical chemistry and chemical synthesis.

4.1 Introduction

Due to the successful development of commercial instrumentation, microwave dielectric heating is now being increasingly applied in chemical reactions. It has been successfully applied in varied industries such as the biotechnology, pharmaceuticals, petroleum, plastics, chemicals, etc. However, most of these applications have been limited to small-scale use in laboratories and have not been extended to the production level.

The major industrial applications of microwave chemistry can be segmented as:

1. Applications in analytical chemistry
2. Applications in chemical synthesis

4.2 Applications in Analytical Chemistry

The various applications of microwave radiation in analytical chemistry encompass the following processes:

1. Ashing
2. Digestion
3. Extraction
4. Protein hydrolysis
5. Moisture/solids analysis
6. Spectroscopic analysis

4.2.1 Ashing

Ashing is used in various analytical laboratories to determine the ash content in a sample, for the purpose of process and quality control. Microwave heating is extensively used for ashing in the petroleum and fuels, plastics, pharmaceuticals and food industries. In most of these industries, microwave-powered muffle furnaces, which are specifically meant for laboratory use, are used for ashing. These microwave muffle furnaces[23] have proven to be more efficient (about 97%) compared to conventional muffle furnaces. They can reach high temperatures ranging between 1,000 °C and 1,200 °C, and can also process a large number of samples simultaneously.

4.2.1.1 Pyrolysis (Ashing in Vacuum)

Microwave radiation is also used as a heating source to accelerate the process of pyrolysis, which is the ashing of organic material in the absence of air. Pyrolysis entails the thermal degradation of solid organic material in the absence of air, to produce char, pyrolysis oil and syngas (a mixture of carbon monoxide and hydrogen). Since microwaves cause uniform heating in the pyrolysis reaction vessel, the waste management industry utilises microwave pyrolysis for the thermal degradation of complex organic compounds such as cellulose and starch. In addition, microwaves are an environment-friendly source of heating, since unlike conventional heating methods, they do not use fuel to heat the vessel.
Another innovative use of microwave radiation in pyrolysis is the 'cracking' of benzene over a Ni-Zeolite catalyst, with a high level of selectivity and efficiency. This

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[23] Reference: http://www.cem.com/pages/ash.htm

is of particular importance for industries producing aromatic hydrocarbons as a by-product of their processes, which need to dispose the toxic industrial waste.

4.2.2 Digestion

Digestion is the process by which samples are broken down to their basic constituents for chemical analysis. Microwave digestion systems are used in analytical laboratories for sample decomposition and preparation. Microwave digesters heat microwave-absorbing reagents containing a sample inside a pressurised, microwave-transparent container, in contrast to conventional open-vessel digestion. Pressurisation allows higher temperatures to be achieved, and increases the speed of digestion.

Microwave digestion cuts down sample preparation time because of closed vessels and rapid heating. Rapid heating accelerates the reaction rate exponentially and results in an approximately 100-fold decrease in the time required for the process of digestion at 175 °C, compared to such a process conducted at 95 °C.

Microwave radiation has now become the technology of choice for sample-preparation trace and ultra-trace metals analysis and is being used in the digestion of even the toughest organic or inorganic samples in diverse industries.

4.2.3 Extraction

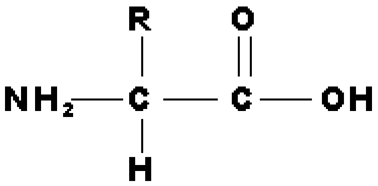
Microwave extraction has proved to be more effective and efficient than its conventional counterpart, the Soxhlet extraction method. The Soxhlet extraction, which is a standard technique, is a continuous solvent extraction method. Extraction systems are used to conduct routine solvent extractions of soils, sediments, sludge, polymers and plastics, pulp and paper, biological tissues, textiles and food samples.

Experiments have proved that microwaves, in comparison with the Soxhlet extraction, use a lesser volume of solvent and sample and perform extraction at a much faster rate. For example, it has been observed that about 500 microwave extractions can be performed for a given solvent, compared to just 32 Soxhlet extractions.

4.2.4 Protein Hydrolysis

Microwave radiation has been found to be very useful in protein hydrolysis, to achieve precision in amino acid analysis. The general structure of an amino acid is a chemical structure in which a primary amine and a carboxyl group are tied to the same carbon atom (Figure 6).

Figure 6: Amino Acid



Source: http://www.milestonesci.com/hydr-fund.php

A protein molecule consists of about 20 such amino acids that are linked through peptide bonds. To facilitate the analysis of the amino acid present in a protein molecule, the peptide bond needs to be hydrolysed. Conventional hydrolysis methods take hours to break the peptides, whereas microwave protein hydrolysis reduces this to 10-30 minutes by processing samples at elevated temperatures (up

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to 200 °C). The microwave heating apparatus is also able to generate high precision in breaking the peptide structure without causing any damage to the amino acid.

Microwave systems are used for protein sequencing/ structure studies, biomedical research, quality assurance of peptide hormones, protein therapeutic agents, dietary formulations, etc.

4.2.5 Moisture Analysis

Microwave radiation is being used to analyse the moisture level in many solid compounds, for example, solids, powders or slurries (0.1% - 99.9% moisture), and has been found to be highly effective in reducing testing time.

Microwave moisture analysis is specifically applied at product development stages such as process and quality control, and to test raw materials, intermediate and finished products. The food and beverage, chemical, environmental, organic and pharmaceutical industries use microwaves for moisture analysis.

4.2.6 Spectroscopic Analysis

Spectroscopic analysis involves the measurement of the emission and absorption of different wavelengths (spectra) of visible and non-visible light by the material being studied, to identify its constituents. Microwave spectroscopy is conducted by comparing the pattern of atomic or molecular resonance in the microwave spectrum, and comparison of the resonance pattern with pre-established patterns.

4.3 Applications in Chemical Synthesis

Application of microwave radiation in chemical synthesis encompasses its use in the acceleration of chemical synthesis. Microwave-enhanced synthesis allows organic chemists to work faster, generate higher yields, and increase product purity. In addition, due to the availability of high-capacity microwave apparatus, the yields of the experiments have now easily scaled up from milligrams to kilograms, without the need to alter reaction parameters.

Microwave organic synthesis is the main component of microwave-assisted chemical synthesis.

4.3.1 Organic Synthesis

Organic synthesis is the preparation of a desired organic compound from available starting materials. Microwave-assisted organic synthesis has been the foremost and one of the most researched applications of microwaves in chemical reactions. The earliest of such reactions was conducted by Richard Gedye and his co-workers, in the hydrolysis of benzamide to benzoic acid under acidic conditions. They reported rate enhancements up to 5-1000 times in comparison to conventional heating methods.

Since then, chemists have successfully conducted a large range of organic reactions. These include the following:

1. The Diels-Alder reaction
2. Racemisation of large organic molecules thorough Diels-Alder cyclo-reversions
3. The Ene reaction
4. Heck reaction
5. Suzuki reaction
6. Mannich reaction
7. Hydrogenation of [beta]-lactams
8. Hydrolysis

9. Dehydration
10. Esterification
11. Cycloaddition reaction
12. Epoxidation
13. Reductions
14. Condensations
15. Protection and deprotection
16. Cyclisation reactions, etc.[24]

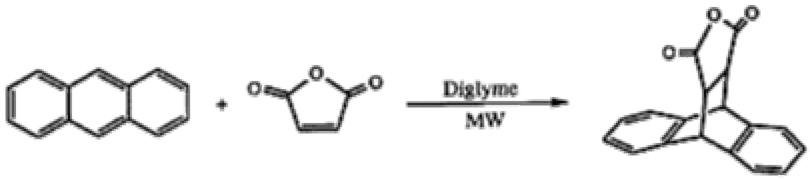
Microwave-assisted organic synthesis is being widely applied in the pharmaceuticals industry, particularly for developing compounds in the lead optimisation[25] phase of drug development. In this phase, chemists use diverse synthetic techniques to develop candidate drugs from lead compounds.

Based on reaction conditions, organic synthesis reactions can be conducted in the following ways:
1. Organic synthesis at atmospheric pressure
2. Organic synthesis at elevated pressure
3. Organic synthesis in dry media

4.3.1.1 Organic Synthesis at Atmospheric Pressure

Microwave-assisted organic reactions can be most conveniently conducted at atmospheric pressure in reflux conditions[26]. A good example of microwave-assisted organic synthesis at atmospheric pressure is the Diels-Alder reaction of maleic anhydride with anthracene (Figure 7). In the presence of diglyme (boiling point 162 °C), this reaction can be completed in a minute, with a 90% yield. However, the conventional synthetic route, which uses benzene, requires 90 minutes[27]. It is extremely important to use dipolar solvents for reactions in such conditions. Solvent systems with higher boiling points are preferred in microwave-assisted organic synthetic reactions.

Figure 7: The Diels-Alder Reaction with Microwave Radiation



Source: Dr. Gavin Whittaker, Edinburgh University, http://homepages.ed.ac.uk/ah05/ch1/c1org.htm

4.3.1.2 Organic Synthesis at Elevated Pressure

Microwaves can be used to directly heat the solvent in sealed microwave-transparent containers. The sealed container helps in increasing the pressure in the reactor, which facilitates the reaction that will take place at much higher temperatures. This results in a substantial increase in the reaction rate of microwave-assisted organic

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[24] Reference: http://homepages.ed.ac.uk/ah05/microw ave.html

[25] Definition: The process of chemically modifying and subsequently testing lead compounds so that desirable characteristics can be introduced into the molecules

[26] Definition: Boiling a liquid in a vessel attached to a condenser so that the vapours continuously condense for re-boiling

[27] Reference: http://homepages.ed.ac.uk/ah05/microwave.html

synthesis. However, increase in the reaction rate of any chemical synthesis depends on three factors: volume of the vessel, the solvent to space ratio, and the solvent boiling point[28].

4.3.1.3 Organic Synthesis in Dry Media

Microwaves have been applied to organic synthesis in dry media, using solid supports[29]. Microwave radiation, based on solid supports, has been highly successful in reducing the reaction time for condensation, acetylation and deacetylation reactions, for example, deacetylation of a protected compound such as alcoholic acetate held on a support material. The microwave-assisted reaction could be completed within two to three minutes, compared to conventional oil-bath heating at 75 °C for 40 hours.

4.3.2 Microwave-assisted Synthesis of Organometallic and Coordination Compounds

Microwave radiation has been successful in accelerating the reaction rate for the generation of organometallic and coordination compounds, which are produced by generating covalent bonds between organic compounds and metals.

In case of organometallic compounds, it has been observed that the use of microwaves in the synthesis of organo-B-metal compounds has resulted in a 40-fold[30] increase in the rate of reaction. This enhanced rate of reaction was achieved under conditions identical to high-pressure organic synthesis[31] in 100 mL Teflon pressure vessels, containing relatively small quantities of solvent (~12 mL).

In addition, the synthesis of a variety of transition metal coordination compounds, under atmospheric conditions, has been successfully carried out under microwave radiation, for example, the reaction of hydrated rhodium chloride ($RhCl_3.xH_2O$) and cycloocta-diene C_8H_{12}, to produce $[Rh(cod)Cl]_2$ in the presence of $EtOH/H_2O$, in microwave radiation, increased the rate of the reaction more than 1200-fold for the same yield[32].

Improved syntheses of $[Fe([eta]-C_5H_5)([eta]-arene)][PF_6]$ and $[Fe([eta]-arene)_2][PF_6]$ salts, using the microwave-heating properties of metal powders, have also been reported[33].

Organometallic compounds are an important constituent of vitamins such as vitamin B-12. Their applications range from their use in the production of display screens and the manufacture of computer chips to their usage in electrolytic solutions for batteries.

Like organometallic compounds, coordination compounds have a large variety of applications, for example, in the dye industry, in medical science and in the preparation of catalysts.

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[28] Reference: http://homepages.ed.ac.uk/ah05/microwave.html

[29] The solid supports include alumina, montmorillonite clay, alkali metal fluoride doped alumina and silica.

[30] Reference: http://homepages.ed.ac.uk/ah05/microwave.html

[31] M. Ali, S.P. Bond, S.A. Mbogo, W.R. McWhinnie & P.M. Watts. *J. Organometallic Chem.* 371, 11 (1989).

[32] Reference: http://homepages.ed.ac.uk/ah05/ch1/c1orgmet.htm

[33] Reference: Q. Dabirmanesh & R.M.G. Roberts. J. Organomet. Chem. 460, C28-C29 (1993).

4.3.3 Microwave-assisted Synthesis of Intercalation Compounds

Applications of microwave chemistry for intercalation compounds have been tested recently. Intercalation compounds comprise organic or organometallic compounds that are incorporated between layers of oxides and sulphides.

Conventional heating methods for the preparation of intercalation compounds, such as the intercalation of pyridine or its derivative into the layered compound a-VO(PO$_4$), are slow and have their stoichiometric limitations with respect to the yield obtained. The maximum stoichiometry obtained for this reaction, even after 64 hours, has been VO(PO$_4$).py$_{0.85}$. The use of microwaves in this process has reduced the reaction time to 2-5 minutes, and has resulted in the attainment of complete stoichiometric results.

Intercalation compounds have found their applications in fields such as energy storage devices, impurity extraction from bauxite ore, etc.

4.3.4 Microwave-assisted Synthesis of Ceramic Products

Microwave processing of ceramic materials has reached a high degree of maturity. In the ceramic production industry, the removal of solvent or moisture is a critical step in the generation of ceramic products. Initially, the use of microwaves in this industry was limited to the effective removal of solvents from solid samples. It is estimated that for materials with a water content below 5%, microwave drying is more energy-efficient than conventional drying methods. However, over the past few years, the utility of microwaves has increased due to the other advantages they provide. It has been proven that microwave heating provides better uniform heating than conventional heating methods. This has increased their utility over conventional methods, which provide non-uniform heating, and may generate solids with uneven properties. Ceramics are widely used in electrical components, sanitary-ware industries, and in many other industries.

Microwaves have also found application in the sintering process. Sintering is the process of welding together the powdered particles of a substance or mixture by heating it to a temperature below the melting point of the components. The particles stick together and form a sinter. Initial studies[34] in microwave-aided sintering were carried out by using a 400W microwave-tuned waveguide applicator, to effect the sintering of alumina and silica rods at >1700 °C. Since then, a wide range of materials has been processed with microwaves. A frequency range of 28 GHZ is used to facilitate the generation of homogeneous profiles of the materials sintered. However, microwave sintering has not become an economically viable replacement for conventional methods. In the near future, improved product and process simplification may lead to an economically viable microwave-sintering operation.

4.3.5 Microwave-assisted Synthesis of Polymer Products

Polymer chemistry, including ceramic processing, forms the single-largest application area of microwave chemistry. The use of polar reactants in polymerisation reaction results in controlled synthesis, and a combination of this with direct heating of reactants makes microwave heating an economically viable option. Economic analyses suggest that the cost of curing polymers may be reduced from 4-11MJKg^{-1} to 0.3-0.5 MJKg^{-1} by switching over to the use of microwaves[35].

Curing is a polymerisation process, which transforms a liquid resin to a solid, creating the maximum physical properties attainable from the materials. Using microwave radiation in curing has greatly increased the rate of the reactions. It has

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[34] Reference: A.J. Berteaud & J.C. Badot, *J. Microwave Power*, (1976)

[35] Reference: C. Akyel & E. Bilgen. *Energy* 14, 839 (1989)

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been found that the rate of a curing reaction, using microwaves, is not dependent on the power applied but on the way the pulse is applied, for example, curing of diglycidyl ester of bisphenol A (DGEBA) with diaminophenolsulphone (DDS) is carried out with short high power pulses with a low time-averaged power (2x10^{-3} sec, average power 700 watts). The results were found to be comparable to those of longer pulses with high time-averaged power (2x10^{-2} sec, 1500 watts). This property makes microwave-enabled curing a more economic option since less power is applied for a shorter period of time time.

4.3.6 Solid-state Chemical Synthesis

The microwave dielectric losses of many solid compounds have been used to provide sufficient heat to drive a chemical reaction, for example, the high energy-loss factor of copper oxide has been used to synthesise the high transition temperature (T_c) superconductor $YBa_2Cu_3O_x$. A number of other materials also display excellent heating properties, for example, boron and carbon have adequate heating characteristics and can be used as the only significant microwave absorber material for a solid-state reaction. Work relating to the use of microwaves in solid-state reactions has been cited as a reference[36].

4.3.7 Processing of Radiopharmaceuticals

Microwave-assisted organic synthesis at an elevated pressure has been used in the pharmaceutical industry for the synthesis of radiolabelled chemicals or radiopharmaceuticals. Radiopharmaceuticals are a genre of chemical compounds that have a radioisotope of an element used in drug making. During pre-clinical trials, these radiopharmaceuticals are used as tracers to generate a nuclear medical image. Positron Emission Tomography (PET) is a common technique used for the generation of nuclear medical images. The most critical aspect relating to radioisotopes is their decay time. The decay time of commonly used radioisotopes is given in Table 6:

Table 6: Half Life of the Isotopes of Some Common Elements Used in Radiopharmaceuticals

Element	Half Life (in minutes)
Oxygen-15	2
Nitrogen-13	10
Carbon-11	20
Fluorine-18	110

Source: Microwave Applications in Radiolabelling with Short-lived Positron-Emitting Radionuclides

With so little decay time, radiopharmacists are always on the lookout for a method that can squeeze their production time. Microwave chemistry provides a solution to the radiopharmaceutical generation issue. A multi-mode microwave oven was used in the first trial of this kind and it was observed that the rate of reaction increased substantially. This has resulted in the enhanced use of microwaves to produce radiopharmaceuticals. Examples of rate acceleration caused by the use of microwaves are cited in the reference paper[37].

Other advantages of microwaves include the high yield of the reaction. This can be attributed to the short half-life of reactants, for example, saving five minutes in a synthesis with carbon-11 resulted in an enhanced production rate of 15%. It has also

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[36] Reference: http://homepages.ed.ac.uk/ah05/ch1/c1solids.htm

[37] Reference: Microwave Applications in Radiolabelling with Short-lived Positron-Emitting Radionuclides, Sharon Stone-Elander¸ Karolinska Pharmacy, Karolinska Hospital, SE-17176 Stockholm, Sweden, and Department of Clinical Neuroscience, Section for Clinical Neurophysiology and Nils Elander, Karolinska Hospital and Institute, SE -17176 Stockholm, Sweden

been observed that several reactions could only be achieved by using microwaves[38,39].

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[38] Reference: Zijlstra S, de Groot TJ, Kok LP, Visser GM, Vaalburg W. J Org Chem 1993; 58: 1643-1645.
[39] Reference: Hwang D-R, Moerlein SM, Welch MJ. J Nucl Med 1989; 30: 1757.

5 Market Overview

This section relates to the market scenario for instruments related to microwave chemistry. It deals with the market size and structure, key segments in the market, types of products being offered, primary growth drivers, key trends, major suppliers of microwave instrumentation, and main buyers of such products.

5.1 Introduction

Microwave chemistry came into existence in the early 1980s, and it was the use of microwave chemistry apparatus for heating that led the way in the beginning. However, in the1990s, with the advent microwave usage in synthesising chemical reactions, the market for chemical synthesis equipments has also grown. It is expected that the market for apparatus for chemical synthesis will overtake the chemical analysis market.

CEM Corporation, Biotage AB[40] and Milestone s.r.l are the three leading players in the microwave chemistry instrumentation market. These players manufacture products that are suitable for laboratory use. Their target customers are academic laboratories and laboratories in the chemical, pharmaceutical and biochemical industries.

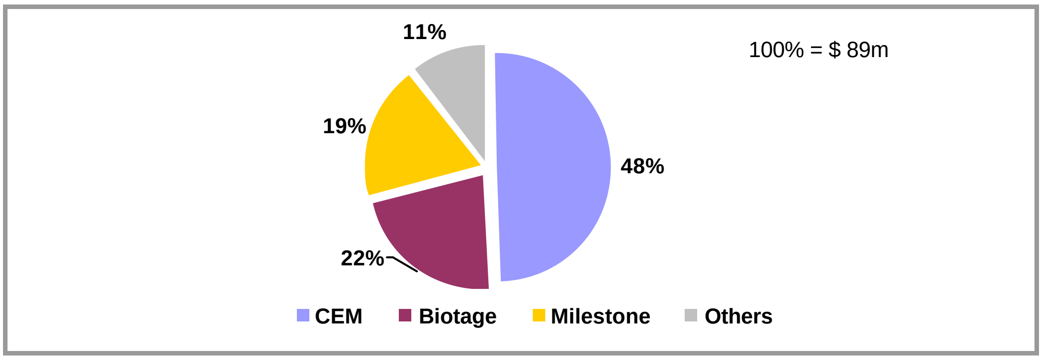
5.2 Market Size and Structure

The market for instruments used in microwave chemistry was estimated at $ 89m in 2003. (The calculation of market size estimates is included in the Appendix.) The small size of the market can be attributed to the following reasons:

- Limited awareness of industrial applications of microwave chemistry
- Difficult commercial scalability

At present, there are three main producers of microwave chemistry instruments -- CEM Corporation, Milestone s.r.l and Biotage AB. CEM Corporation is the market leader, with a market share of about 49%[41], followed by Biotage AB and Milestone s.r.l. The market for microwave chemistry products is highly concentrated, with the top three players monopolising around 90%[42] of the market (Figure 8).

Figure 8: Market Share (by revenues in $ m) of Manufacturers in 2003



Source: Evalueserve Analysis

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[40] Previously Personal Chemistry

[41] Source: Evalueserve Analysis

[42] Source: Evalueserve Analysis

5.3 Major Segments of the Market

The microwave chemistry instrumentation market is split as follows:

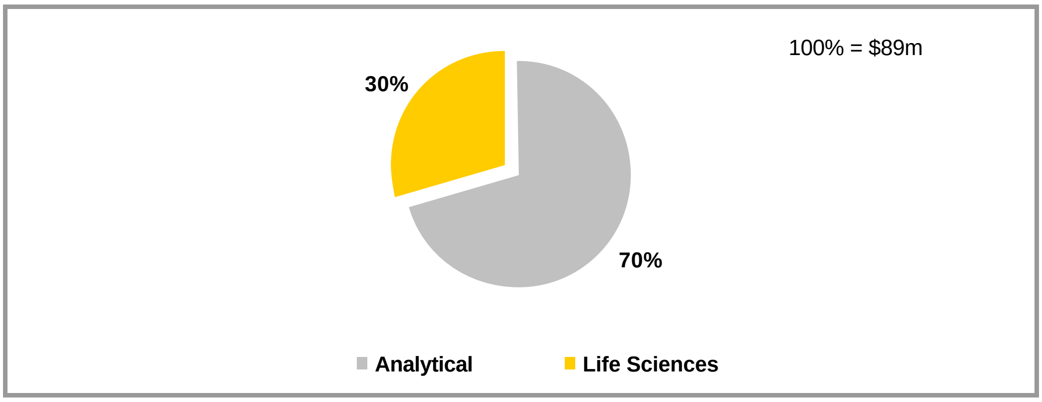
- Distribution by application areas
- Product-wise distribution
- Geographic distribution

5.3.1 Distribution by Application Areas

On the basis of application areas, this market can be segmented into the analytical and synthesis segments. In 2003, the analytical segment had a market share of about 70%[43], whereas chemical synthesis had a market share of 30%[44] (Figure 9). The chemical synthesis segment is still in its nascent stage while the analytical segment has reached its pinnacle and has been in existence for over 20 years.

However, this may change in future as the demand for chemical synthesis equipments is expected to increase. The chemical synthesis segment is expected to grow at an average annual rate of 15%-20%[45], while the analytical segment is expected to grow at only 5%[46].

Figure 9: Market Share (by revenues in $ m) by Application Areas in 2003



Source: Evalueserve Analysis

5.3.1.1 Analytical Segment

The analytical segment uses microwave technology for the rapid analysis of various chemical substances. Microwave-assisted methods are now well accepted for completing the various processes of chemical analysis, such as digestion, extraction, ashing, hydrolysis, etc.

Microwave-assisted chemical analysis has become a popular application in the petroleum, the food and beverages, and the chemical industries. CEM Corporation and Milestone s.r.l are the leading manufacturers of microwave equipments for chemical analysis.

5.3.1.2 Chemical Synthesis Segment

Microwave-assisted chemical synthesis has been successfully used in the field of drug research and development. In the chemical synthesis segment, microwave technology is used to perform rapid synthesis, to make new compounds for drug

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[43] Evalueserve Analysis, Company Reports

[44] Evalueserve Analysis, Company Reports

[45] Source: Michael J. Collins, CEO, CEM – Interview: The Wall Street Transcript

[46] Source: Michael J. Collins, CEO, CEM – Interview: The Wall Street Transcript

discovery, protenomics and genomics. Biotage AB, CEM Corporation, and Milestone s.r.l are the leading manufacturers of microwave synthesisers.

5.3.2 Product-wise Distribution

The two types of microwave ovens available in the market, for industrial purposes, are the following:

1. Single-mode microwave ovens
2. Multi-mode microwave ovens

5.3.2.1 Single-mode Microwave Ovens

Microwave ovens, which take one sample at a time for heating, are called single-mode microwave ovens. These ovens are mainly used to conduct chemical synthesis. They are currently used for small-scale drug discovery, automation and combinatorial chemical applications.

5.3.2.2 Multi-mode Microwave Ovens

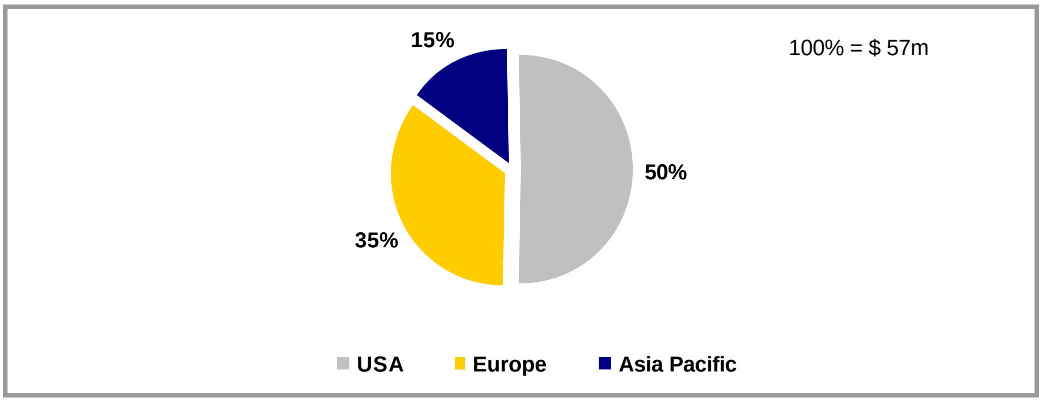
Microwave ovens capable of heating multiple samples anywhere inside the oven are known as multi-mode microwave ovens. These ovens provide an uneven microwave field density, and therefore have been proven unfit for chemical synthesis. Consequently, these instruments are only used in chemical analysis. However, manufacturers such as Milestone s.r.l and CEM Corporation have introduced a range of multi-mode microwave ovens to conduct chemical synthesis.

5.3.3 Geographic Distribution

The microwave chemistry market can be divided into three segments, on the basis of geography -- the US, Europe and the Asia Pacific. In 2002, the US held the largest market share, of 50% (Figure 10), which was primarily due to the vast level of awareness in the US pertaining to the applications of microwave chemistry.

Europe had the second-largest market share of 35%, while the Asia Pacific held 15%. The Asia Pacific market was dominated by Japan.

Figure 10: Geographic Distribution of the Microwave Chemistry Market in 2002



Source: Robert England, Director, Personal Chemistry

5.4 Growth Drivers of the Microwave Chemistry Market

The size of the microwave chemistry market is increasing with the growing level of research and innovation being conducted by instrument manufacturers, and increasing awareness amongst the scientific community about the technology and the benefits therein. It is expected that the large amount of published literature, patent publications (refer to Chapter 6 for information on patent publications) and

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research will create greater awareness about the applications of microwave chemistry, and will contribute to further development in the field of applications.

The key growth drivers for the microwave chemistry market are the following:

1. Proven success of the technology
2. Increasing awareness of the technology

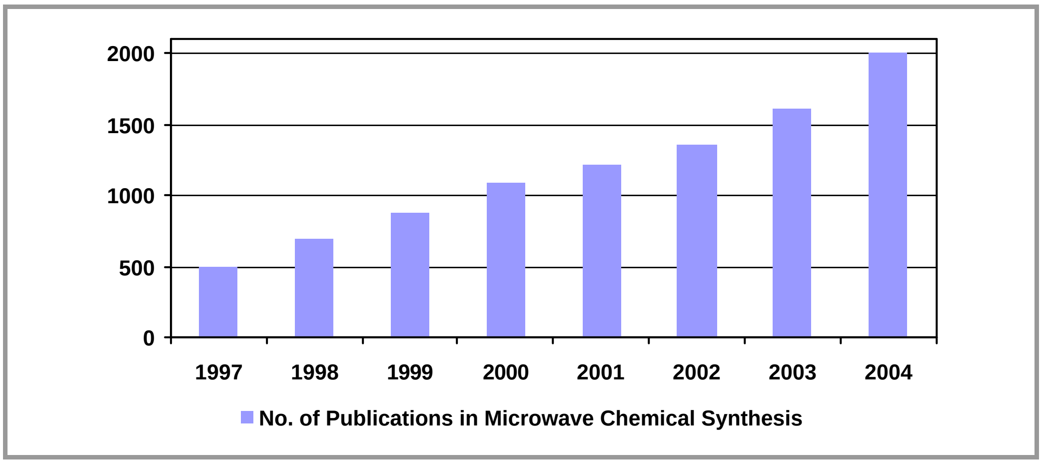
5.4.1 Proven Success of Technology

Use of microwaves in chemical synthesis has lead to enhanced reaction rates, higher yields, and cleaner reactions. Better temperature and pressure control of reaction parameters can be achieved in modern microwave reactor, which results in easier reproducibility. Microwave radiation has been successfully applied to a large range of applications, ranging from drying and heating of ceramics to synthesis of organometallic compounds. At present, more than 25,000-30,000[47] chemists worldwide use microwave technology for chemical applications. Moreover, around 40%[48] of all explorative chemistry is conducted, using microwave synthesisers.

5.4.2 Increasing Awareness of Technology

The level of awareness regarding the application of microwave radiation for conducting synthetic and analytical chemistries has been growing. This is particularly true in the case of microwave-assisted chemical synthesis. There has been a rapid growth in the number of publications from about 500 in 1997 to over 2000 up to 2004[49] (Figure 11).

Figure 11: Number of Publications in Microwave Chemical Synthesis from 1997-2004



Source: Evalueserve Analysis

5.5 Recent Trends

The following are some of the recent trends in the microwave chemistry instrument market:

5.5.1 High Growth in the Chemical Synthesis Segment

The chemical synthesis segment continues to be the highest growing segment in the market. It is estimated that it will show a healthy growth rate of 15%-20% till 2008[50]. This segment will derive its growth from two main factors -- firstly, an increase in the use of microwave chemical synthesis equipments in the R&D laboratories, and

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[47] Source: Robert England, Director, Personal Chemistry

[48] Estimates of Personal Chemistry

[49] Reference: http://www3.interscience.wiley.com/cgi-bin/fulltext/109799813/HTMLSTART

[50] Source: Evalueserve Analysis, Company reports

secondly, an increasing number of reactions that can be conducted efficiently by microwave radiation.

5.5.2 Increased Research on Scalability

The major players in the market are conducting research to develop microwave instrumentation that addresses the problem of the non-scalability of reactions in microwave synthesisers. CEM Corporation and Milestone s.r.l have already developed new products, such as the Flow-through Reactor and Batch Reactor, to address this problem.

5.5.3 Customers are Becoming Increasingly Sensitive about Price

A major trend emerging in the chemical synthesis segment of the market is the increasing price-sensitivity of buyers. Whereas pharmaceutical and biotech companies previously bought relatively expensive instruments in the range of $ 100,000- $ 300,000, they have now become more price-conscious and are targeting instruments at around $ 50,000.

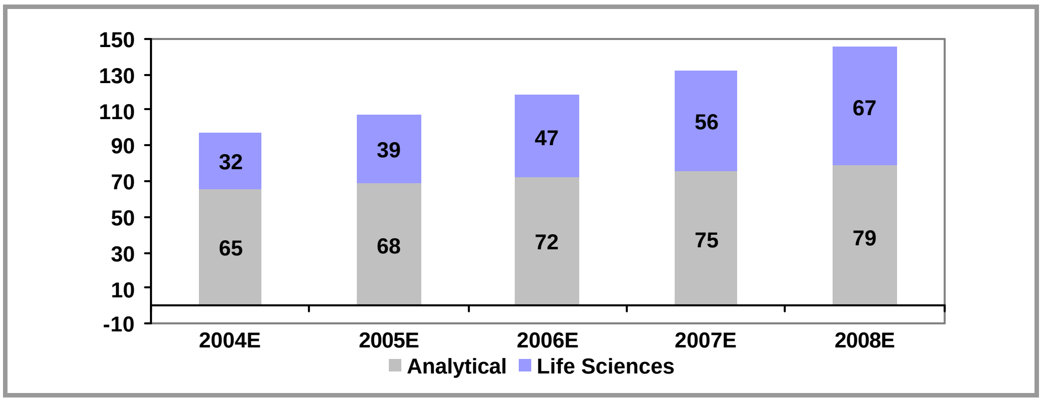
5.6 Microwave Chemistry Market Forecast

Over the next five years, the market for microwave instruments for chemical analysis and chemical synthesis is predicted to grow at a CAGR of 9.6[51]% per annum, to reach $ 145.8m by 2008 (Figure 12) (The forecast estimate calculation is given in the Appendix).

The chemical synthesis market will give a major thrust to the microwave chemistry market, which is expected to grow at a CAGR of 20% per year, to $ 67.2m by 2008. As the analytical segment has matured, it is predicted to show a stable CAGR of about 5% per year, reaching $ 78.6m during the same period.

In the next five to six years, the chemical synthesis segment is expected to overtake the analytical segment in terms of market share. This is primarily due to the increasingly successful implementation of microwave instruments in chemical synthesis. Another contributor will be growing research and intellectual property activity in the segment, such as research on the scaling up of reactions.

Figure 12: Market Size Forecast for Microwave Chemistry from 2004-2008 (in $ m)



Source: Evalueserve Analysis

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[51] Source: Evalueserve Analysis

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5.7 Buyers and Suppliers

5.7.1 Key Users

Since current technology limits the large scalability of microwave chemistry applications, the use of industrial instruments is restricted to laboratories. Therefore, users of products related to microwave chemistry are restricted to corporate R&D laboratories and various educational and research institutions involved in microwave chemistry research.

The following are the key users of products related to microwave chemistry:

1. Pharmaceutical and biotechnology companies
2. Chemical companies
3. Educational and research institutions

5.7.1.1 Pharmaceutical and Biotechnology Companies

Pharmaceutical and biotechnology companies are increasingly turning to microwave chemistry. These companies have benefited from a cleaner, more efficient and convenient method, made possible by the use of microwaves, to conduct their drug development processes.

Pharmaceutical companies comprise the largest consumer segment in the market. They are using microwave synthesisers in their research laboratories to develop compounds for the lead optimisation phase in drug development. The reduced reaction time for chemical synthesis, using microwave radiation, gives chemists an ideal response period to apply diverse synthesis methods iteratively to new chemistries and develop proprietary compounds. Pharmaceutical companies such as GSK, Merck, Eli Lilly, and AstraZeneca are already using these instruments in their drug development processes.

5.7.1.2 Chemical Companies

Companies producing chemicals and chemical products, such as ChevronTexaco, have been using microwave technology to conduct various chemical analyses. This is because uniformity of heating and precise temperature control are two vital requirements. While, at present, most of these applications are concentrated on chemical analysis, microwave-accelerated organic synthesis is gaining popularity, especially in the case of companies that use fine chemicals.

The application of microwave chemistry in these companies has resulted in improved quality, higher yields and lower costs. In many processes, microwave heating has been found to be up to 50% more efficient, compared to conventional heating methods.

5.7.1.3 Educational and Research Institutions

Educational and research institutions are slowly shifting to microwave chemistry instrumentation from conventional techniques, to conduct their laboratory experiments. However, these institutions find it difficult to acquire microwave technology for their laboratories because of the high set-up costs involved. Some of the educational institutions that use microwave instruments include the Edinburgh University, UK; Imperial College, UK; The Commonwealth Scientific and Industrial Research Organisation, Australia; Cambridge Healthtech Institute, UK; Karl-Francis-University of Graz, Austria; University of Pittsburgh, USA; University of Connecticut, USA, and others.

Educational institutions find microwave chemistry useful, as multiple samples can be prepared with identical end results. Further, as microwave chemistry is a proven method for conducting green chemistry, it leads to a vast reduction in costs related to expensive reagents and their disposal.

5.7.2 Key Suppliers

There are three main suppliers providing dedicated instrumentation for microwave chemistry. They include:

1. CEM Corporation (the US)
2. Milestone s.r.l (Italy)
3. Biotage AB (Sweden)

5.7.2.1 CEM Corporation

5.7.2.1.1 Company Overview

CEM Corporation is a technology company based in the US. It designs, develops and markets microwave instruments used in laboratories, to perform various chemistries. These instruments are used by manufacturing companies for process and quality control. CEM Corporation currently caters to the analytical, process, quality control, and chemical synthesis markets.

5.7.2.1.2 Financials

The revenue of CEM Corporation stood at $ 43.8m in 2003, which was a growth of 16% over the previous year's revenue. During the same period, its operating income increased by 36% to $ 6.8 m. The chemical synthesis business unit of CEM Corporation contributed over $ 5.7 m to its total revenue in 2003.

5.7.2.1.3 Product Portfolio

CEM Corporation manufactures single-mode microwave synthesisers and multi-mode microwave synthesis systems. Its line of microwave instrumentation products includes the following:

1. Discover™ is the smallest instrument that is available for microwave synthesis in the market.
2. Explorer PLS™ integrates all the features of the Discover™ system, and has an automated reaction-handling module for maximum throughput and flexibility in a microwave-enhanced synthesis workstation.
3. Voyager™ is a flow-through system, designed to easily accommodate liquid, slurried and solid reactants.
4. MARS Synthesis™ is a flexible microwave system with a large capacity reaction chamber that is specially designed for combinatorial and parallel synthesis. It is capable of handling large reaction vessels when process development or scale-up is required.
5. Odyssey™ is a microwave peptide synthesiser system that reduces the time for peptide synthesis by 10-20 folds.
6. Discover CoolMate™ system is designed to carry temperature-sensitive reactions. The system provides a jacketed low-temperature vessel that helps in maintaining low reaction temperature. This ensures prevention of thermal degradation of the product.
7. Navigator™ system is ideal for laboratories that require automated high throughput. It offers flexibility in performing a variety of tasks with independent robotics and one or more Focused Microwave synthesis system(s).
8. Investigator™ is a system that allows real time analysis of the samples, using Raman-based spectroscopy technique, in the original reaction vessel.
9. SMART ProFat™ system analyses the meat and poultry raw materials and pre-blends for moisture, fat and protein content in less than 5 minutes.
10. Phoenix Airwave™ system is used for ashing
11. CleanSTAR™ system is useful in preparation of high purity materials for ultra-trace contamination detection.

5.7.2.1.4 Target Customer Segment

CEM Corporation currently caters to the analytical and chemical synthesis segments of the microwave chemistry market. With high-growth prospects in the chemical synthesis segment, it caters to companies involved in pharmaceuticals, biotechnology, genomics and protenomics.

5.7.2.1.5 Research and Development

CEM Corporation conducts extensive R&D activity for product innovation and the development of new products. It plans to invest about 9%-10% of its revenues in R&D, and intends to focus its research and development on the chemical synthesis segment[52].

5.7.2.1.6 Contact Information

Address: CEM Corporation
P.O. Box 200
Matthews, NC 28106-0200
Phone: 1 704 821 7015
E-mail: Doug.Ferguson@cem.com

5.7.2.2 Milestone s.r.l

5.7.2.2.1 Company Overview

Milestone s.r.l was founded in 1988 and provides advanced microwave platforms for various microwave chemistry applications. The company's microwave technology supports a broad range of techniques, including microwave-accelerated digestion, extraction, sample evaporation, ashing, synthetic chemistry, protein hydrolysis, as well as instrumentation for clean chemistry and mercury analysis. In 1998, Milestone s.r.l. commenced its activities in microwave laboratory instrumentation that were developed and manufactured by their German partners MLS Gmbh Mikrowellen-Laborsysteme. Milestone s.r.l has also pioneered the application of microwave radiation for histoprocessing procedures. Histoprocessing procedures help in reducing the sample turn around time from 24-48 hours to 60-80 minutes. The company holds a patent [53] for microwave histoprocessing.

5.7.2.2.2 Financials

The revenue of Milestone s.r.l stood at $ 16.5m in 2003. The chemical synthesis business unit of Milestone s.r.l contributed around $ 2.1m to its total revenue in 2003.

5.7.2.2.3 Product Portfolio

The product portfolio Milestone s.r.l includes the following:

1. MicroSYNTH is a multi-mode cavity system for microwave-enhanced chemical reactions.
2. FlowSYNTH is a continuous flow system that scales up yields from grams to kilograms level
3. Ethos MR is a microwave batch reactor for microwave-enhanced chemical reactions
4. START is a microwave organic synthesis labstation for academic research and teaching
5. MLS 1200 series systems are useful in high pressure digestion and for high temperature ashing.

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[52] Reference: www.cem.com/pages/News.html

[53] US 6042874

6. LAVIS 1000 microBASIC system is useful for batch reactions in organic synthesis
7. UltraCLAVE is a revolutionary autoclave for microwave enhanced reaction
8. HPV 80 is a high pressure digestion vessel. HPV 80 helps in complete digestion of difficult materials like oxides, oils an pharmaceutical compounds
9. SubPUR/duoPUR systems are high performance sub-boiling distillation units for preparing ultrapure acids
10. TraceCLEAN is an automated, closed acid reflux system that thoroughly and safely cleans accessories used in trace analysis work
11. PYRO systems include a rapid microwave ashing system and a sulphate ashing system
12. DMA-80 is a direct mercury analyzer system that determines the mercury concentration within 5 minutes without sample preparation

5.7.2.2.4 Target Customer Segment

Milestone s.r.l has installed more than 8,000 microwave systems in about 70% of the Fortune 500 companies. These include large and small research institutions, universities and laboratories. Some of its prominent customers include the following:

1. ChevronTexaco
2. Animal Health Services (the Netherlands)

5.7.2.2.5 Contact Information

Address: Milestone S.r.l.
Via Fatebenefratelli, 1/5
24010 Sorisole (BG)
Italy
Phone: 0039-035-573857

5.7.2.3 Biotage AB

5.7.2.3.1 Company Overview

Biotage AB is the largest manufacturer of products related to the instrumentation and knowledge management of microwave-assisted chemical synthesis. It was formed in 2003 by the acquisition of Personal Chemistry and Biotage LLC by Pyrosequencing. Biotage AB carries the Personal Chemistry product line, focusing specifically on products used in medicinal chemistry research and development in drug discovery. Personal Chemistry manufactured the first purpose-built microwave synthesiser, and since then has sold about 300 instruments worldwide. It has a market share of about 71% in the chemical synthesis microwave chemistry market[54].

5.7.2.3.2 Financials

The total pro-forma sales of Biotage AB are $ 44.6m (SEK 306m) in 2003. The total pro-forma sales of the drug discovery division of the company are $ 38.4m (SEK 265m) in 2003. The pro-forma turnover of the company from the microwave life science instruments segment of drug discovery division was recorded as $ 19.2m (SEK 132m) in 2003.

5.7.2.3.3 Product Portfolio

Biotage AB offers single-mode-cavity microwave synthesisers. Emrys™, a series of microwave synthesisers, is the company's flagship product. The Emrys™ series includes the following products:

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[54] Evalueserve Analysis

1. Emrys™ Creator is a personal microwave system for rapidly testing synthesis ideas
2. Emrys™ Optimizer is an automated microwave synthesiser for medicinal chemistry teams
3. Emrys™ Liberator is a system that applies all the benefits of microwave synthesis to the development and production of chemical libraries
4. Emrys™ PathFinder is a database for verified microwave synthesis reactions. Its synthesis methods are fast, reproducible and scalable
5. Emrys™ Knowledge Builder gives instant access to reproducible synthesis methods and enables sharing, execution and accumulation of an organisation's synthesis work
6. Emrys™ Advancer is a microwave synthesiser for synthesising compounds on the preparative (multi-gram) scale, safely, and in minutes
7. Initiator™ series are high-performance microwave systems for faster and easier chemical synthesis
8. Advancer™ is a batch microwave synthesiser for laboratory scale organic synthesis

Personal Chemistry had introduced Coherent Synthesis, which is an on-line knowledge-based microwave synthesis for lead compound development. At present, Coherent Synthesis has reached over 500,000 microwave synthesis reactions and is growing at the rate of 10,000 reactions per week[55].

5.7.2.3.4 Target Customer Segment

Biotage AB caters to the chemical synthesis segment of the microwave chemistry market. Its products are focused on the medicinal chemistry segment of the drug development process in pharmaceutical and biotech industries. Its customers include the top 20 pharmaceutical companies in the world.

5.7.2.3.5 Contact Information

Address: Kungsgatan 76
SE-753 18 Uppsala
Sweden
Phone: 46 18 489 9000
Fax: 46 18 489 9200
E-mail: info@personalchemistry.com

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[55] Personal Chemistry, press release, 3 September, 2003

6 Advances in Microwave Chemistry

Current applications of microwave chemistry have motivated researchers to test the viability of microwave technology in other categories of reactions, and explore its newer applications. In addition to these developments, leading market players have tried to address the issue of scalability by developing products that have scaled up chemical reaction from milligrams to kilograms.

Developments in microwave chemistry during the last two years have been in the following categories:

1. Scaling up reactors to higher-yield volumes
2. Application of microwave chemistry to new reactions

6.1 Scaling Up of Reactors to a Higher Volume of Yields

Two main approaches have evolved to address the issue of scaling up microwave reactors. The first approach scales up single-mode reactors through a flow-through reactor, and the second scales up multi-mode reactors to a batch reactor.

6.1.1 Flow-through Microwave Reactor

A flow-through microwave reactor is capable of scaling up single-mode yield from grams to kilograms. CEM Corporation has developed a patented technology for its *Voyager* flow-through single-mode reactor. An advantage of the flow-through reactor is its ability to perform dual-mode operations between liquid and solid phase reactions. Milestone s.r.l's flow SYNTH continuous flow reactor allows scale up from grams to kilograms with full temperature and pressure control. It provides precise monitoring and control of the process parameters.

Though the flow-through single-mode microwave reactor has been a breakthrough product in meeting chemists' requirements pertaining to liquid phase reactions, the product has limitations with regard to handling solids and admixture-based reactions.

6.1.2 Batch Reactor

Another breakthrough related to successful scaling up is multi-mode reactors. Batch reactors are capable of accommodating larger volumes of reactants in a multi-mode operation in one go, and therefore can conduct reactions to produce higher yields. Biotage AB and Milestone s.r.l have developed batch reactors to scale up the yields of reactions - Biotage AB with a batch reactor called Emrys™ Advancer, and Milestone s.r.l with its MRS batch reactor.

6.2 Microwave-assisted Rate Acceleration of Organic Reaction

6.2.1 The Akabori Reaction

The application of microwave heating to hydrazenolysis[56] reaction in the Akabori Reaction has enabled the reaction to take place in minutes, compared to hours when conventional heating methods are used. The classical Akabori Reaction, devised in 1952, helps in identifying C-terminus amino acids in a peptide chain. It involves the heating of a linear peptide in the presence of anhydrous hydrazine in a sealed tube for several hours[57].

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[56] Definition: A chemical method that uses hydrazine to cleave amide bonds, e.g., the glycosylamine linkage between a sugar residue and asparagines, or the acetamide bond in *N*-acetylhexosamines

[57] Bose AK, Ing YH, Lavlinskaia N, Sareen C, Pramanik BN, Bartner PL, Liu YH, Heimark L
J Am Soc Mass Spectrom 2002 Jul 13:839-50

Peptides, better known as proteins, play an important role in cell metabolism. They act as a biological catalyst and participate in the generation of cell structures[58]. Peptides exist in nature as a linear chain linked by peptide bonds.

An important concern for biochemists and biologists is the characterisation of proteins. It is important to know how many and which amino acid(s) a polypeptide chain contains, and their sequence.

6.2.2 The Wittig Reaction

The Wittig reaction is carried out between aromatic aldehydes and stabilised ylides to generate alkenes. Since the method of generating ylides is a rate-determining step, the conventional method is a slow process. However, microwave heating performs the reactions in minutes[59].

The Wittig reaction is based on the principle that phosphines (the P equivalent of amines) easily forms phosphonium salts with alkyl halides, and these salts readily lose HX with a strong base. The resulting product is called an ylide or a phosphorane.

$PH_3P + CH_3CH_2Br$ ---->$CH_3CH_2\text{-}^{+}PH_3 + Br^{--}$ -----> $CH_3CH{=}PH_3$ ----> $CH_3CH^{-}\text{--}\,^{+}PH_3$

The ylide is a polar molecule with a carbanionic carbon. These ylides, when they react with aromatic aldehydes, readily react to give alkenes.

$CH_3CH^{-}\text{--}\,^{+}PH_3 + PhCHO$ -----> $PhCH{=}CHCH_3 + Ph_3PO$[60]

The process of the conversion of aromatic aldehydes to alkenes has found industrial applicability for processes that requires alkene synthesis at the end, or as an intermediate product.

6.2.3 Other Organic Reactions

In addition to the organic reactions mentioned above, it has been proven that microwaves are of prime importance in the following reactions[61]:

1. The Heck Reaction, involving palladium-catalysed vinylic substitution, can be completed in 15-30 minutes, using microwaves. The formation of cinnamic acids involves a reaction between aryl bromide and acrylic acid, a standard Heck reaction. Using Methyl cyanide as a solvent, 1 mol % $Pd(OAc)_2/P(o\text{-}tolyl)_3$ as a catalyst, and triethyl amine as the base in the presence of microwave radiation leads to completion of the reaction in 15 minutes at 180 ^{0}C. Oxidative Heck coupling, involving Pd^{II}-catalysed carbon-carbon coupling of aryl boronic acids with alkenes, can be achieved in 5-30 minutes at 100-170 ^{0}C.

2. Microwave heating accelerates the rate of the Suzuki reaction, which typically involves the palladium-catalyzed cross-coupling of aryl halides with boronic acids. Various aryl bromides and iodides have been successfully coupled with aryl boronic acids, using microwave heating at 150 °C for 5 minutes with 0.4 mol % of Pd(OAc)2 as catalyst. For the Suzuki reaction, Aryl chlorides require high temperatures of 175 °C.

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[58] Reference: http://www.biologie.uni-hamburg.de/b-online/e17/17d.htm

[59] Reference: Kinetic study of microwave-assisted Wittig reaction of stabilised ylides with aromatic aldehydes, Frattini, S. / Quai, M. / Cereda, E., Tetrahedron Letters, Sep 2001

[60] Reference: http://www.sunderland.ac.uk/~hs0bcl/org8.htm

[61] Reference: http://www3.interscience.wiley.com/cgi-bin/fulltext/109799813/HTMLSTART

3. The formation of heterocyclic rings by cyclocondensation under conventional reaction conditions requires several hours or days for completion. Microwaves help in increasing the rate of reaction, for example, the formation of 4-hydroxy-1H-quinolin-2-ones from anilines and malonic esters. In conventional heating in an oil bath at 220-300 °C, the reaction takes several hours for completion. With the use of microwave heating, the reaction is completed in 10 minutes at 250 °C.

4. Glycoylation reactions are generally slow. Microwaves help in increasing the rate of this reaction up to 15%. Glycoylation reactions use oxazoline donors with low reactivity and are primarily responsible for the low reactivity. Microwaves increase the glycosylation rate. Dimers of N-acetyllactosamine are prepared, linked by the alkyl spacers of microwave-assisted glycosylations with oxazoline donors in the presence of pyridinium triflate as a promoter. Microwave irradiation at 80 °C for 20 minutes resulted in a moderate to high yield of dimers, with increased yields of 12-15 % over the conventional process.

5. The Mannich reaction is an important transformation, producing ß-amino ketones. The reaction requires drastic conditions, long reaction times and low yields. The use of microwave radiation can help in increasing the rate of the Mannich reaction. It has been reported that the reaction between formaldehyde, secondary amine in the form of hydrochloride salt, substituted acetophenone, with dioxane as a solvent, in the presence of microwave irradiation at 180 °C for 8-10 minutes, produces ß -amino ketones in moderate to good yields.

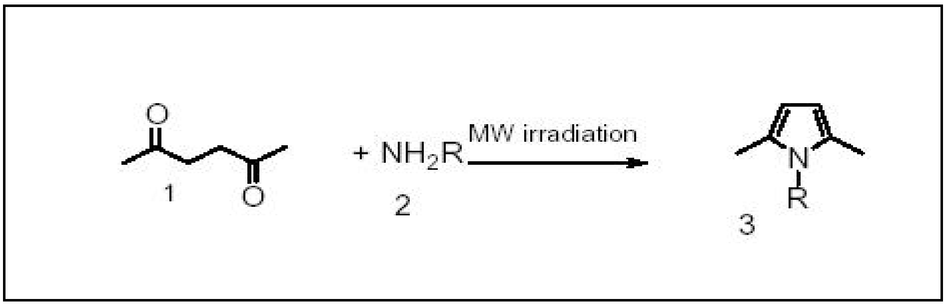
6.2.4 Microwave-assisted Solvent-free Reactions

The most challenging problem faced by the chemical industry has been the use of solvents. It is estimated that one molecule of solute requires around a hundred to a thousand molecules of solvent. Recently, efforts have been made to reduce the use of solvents by using microwaves and materials which can absorb or adsorb reactants and carry out chemical reactions in the presence of microwaves.

The classical Paal-Knorr pyrrole synthesis has been adopted to microwave conditions. Pyrrole, a hetrocyclic compound, is characterised by a ring structure comprising four carbon atoms and one nitrogen atom. Pyrrole (C_4H_5N) is the simplest representative of pyrrole class.

The condensation between 2,5-heptanedione (1) and a primary amine (2) yields 2,5 dimethylpyrroles (3) under solvent-free conditions in excellent yields and purities (Figure 13). Reaction times are reduced to seconds rather than days in conventional thermal synthesis. Energies around 100-200 watts are required for the completion of the reactions, which can be scaled up to 3 g of the product.

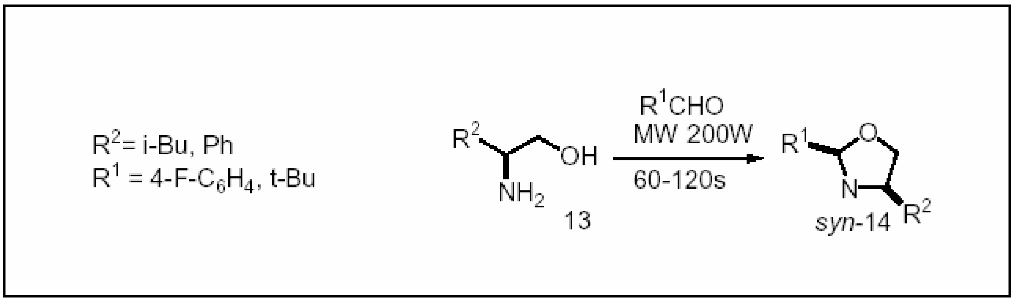
Figure 13: Paal-Knorr Pyrrole Synthesis



Source: Microwave Accelerated Solvent Free Reactions in Organic Synthesis An Environmentally Benign Technology

As in the case of condensations yielding pyrroles, oxazolidines (Figure 14) can be obtained in excellent yield after 40-60 seconds of radiation time at 200 watts. In these examples, it is worth noting that small amounts of dimethylformamide (DMF) had to be added to the reaction mixture to facilitate the conversion of microwave energy into thermal energy.

Figure 14: Preparation of Oxazolidines



Source: Microwave Accelerated Solvent Free Reactions in Organic Synthesis An Environmentally Benign Technology

6.2.5 Synthesis of Zeolites

The synthesis of NaA Zeolite on porous α-Al_2O_3 has been conducted by microwaves. Zeolites are microporous crystalline solids with well-defined structures. Generally, they contain silicon, aluminium and oxygen in their framework, and water and/or other molecules within their pores. The synthesis of NaA Zeolites on porous α-Al_2O_3, can be achieved in 15 minutes, compared to the classical reaction which requires three hours[62]. Zeolites have a number of applications, such as that of a solid-acid catalyst in organic chemical synthesis, water purification, filtration, air treatment and conditioning.

6.2.6 Synthesis of Nanocomposites

Researchers have shown that it is possible to generate nanoparticles in the laboratory. Microwaves[63] have been used to generate high-precision temperature conditions to enable the catalytic cracking of the passivation layer[64] generated during the synthesis of nanoparticles, which can be generated through an electrochemical reaction. One of the steps in this electrochemical process is the purification of the passivation (passive) layer that is formed over the electrode where the deposition of nanoparticles is taking place. This passive layer, on deposition, restricts the exposure of the inner material of the electrode over which the deposition of nanoparticles is taking place. The layer is cracked by catalytic action under high

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[62] Reference: Synthesis of NaA zeolite membrane by microwave heatingXu, X. / Yang, W. / Liu, J. / Lin, L., Separation and Purification Technology, Oct 2001

[63] Reference: http://www.ed.ac.uk/news/ebulletin/April03/article33198.html

[64] Definition: The passivation layer sheaths the electrode from further reacting electrolytically

temperature. In this system, pyridine was used as a reaction solvent. There was evidence pertaining to the simultaneous formation of the semiconductor and the polymerisation of the monomer[65]. Examples of the generation of nanoparticles via microwave radiation include the preparation of CdS-PVK (poly-vinylcarbazole) nanocomposites through an in-situ microwave radiation method.

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[65] Reference: Rong He, Xue-feng Qian, Jie Yin, Li-juan Bian, Hong-an Xi and Zi-kang Zhu, In situ synthesis of CdS/PVK nanocomposites and their optical properties, Jan 2003

7 Intellectual Property in Microwave Chemistry

7.1 Evolution of Research

The evolution of intellectual property in the field of microwave chemistry has occurred in two phases. In the first phase, research and development focused on performing chemical analysis by using microwave equipments. In the second phase, conducting chemical synthesis with the use of microwave instruments emerged as the key area of research.

7.1.1 Development Phase of Chemical Analysis

In the early 1980s, research in the field of microwave chemistry began with the development of instruments used for drying products, such as agricultural and food grains, and manufactured products such as fats and oils. The 'precision heating' (refer to section 3.4.7) quality of microwaves later gained popularity and encouraged companies such as CEM Corporation to introduce instruments that enabled the industrial use of microwave radiation. The discovery of precision heating through microwaves led to their application in ash analysis in the mid-1980s. Industrial ash analysis was introduced for samples such as polymers, wastewater sludge, activated sludge, industrial wastes, river bottom sediments, etc.

Microwave radiation was used to dry chemicals in laboratories for chemical analysis. Initially, microwave laboratory-heating apparatus faced problems such as uneven heating and reflection of microwaves back to the source. These problems were even more critical for multiple-sample heating apparatus, in which the level of energy losses and uneven heating was even higher.

CEM Corporation, the pioneer in industrial microwave-heating equipments, attempted to solve the problem of uneven heating by introducing a new laboratory analyser. It filed a patent for this technology (US4835354), which incorporated a rotational table for uniform heating.

Milestone s.r.l. filed a patent (US5725835) for a microwave heating device having a novel arrangement for moving a container, so that materials can be heated between loading and heating positions.

Subsequently, research was primarily focused on developing instruments that use microwave heating in chemical processes such as ashing, digestion of organic compounds, chemical extraction and pyrolysis, etc. During this phase, Milestone s.r.l and CEM Corporation were the only organisations developing microwave instruments for chemical analysis in laboratories.

Till 1995, a total of around 37 patent publications [66] were granted in the field of chemical analysis, more than 90% of which were assigned to CEM.

7.1.2 Development Phase of Chemical Synthesis

The ability of microwaves to enhance the rate of chemical reaction was discovered in the late 90s. This opened up a completely new category of research applications, which included applications related to the use of microwave heating in chemical and biochemical reactions.

Since microwave radiation proved highly beneficial in conducting chemical synthesis in laboratory conditions, microwave synthesis was identified as the most promising

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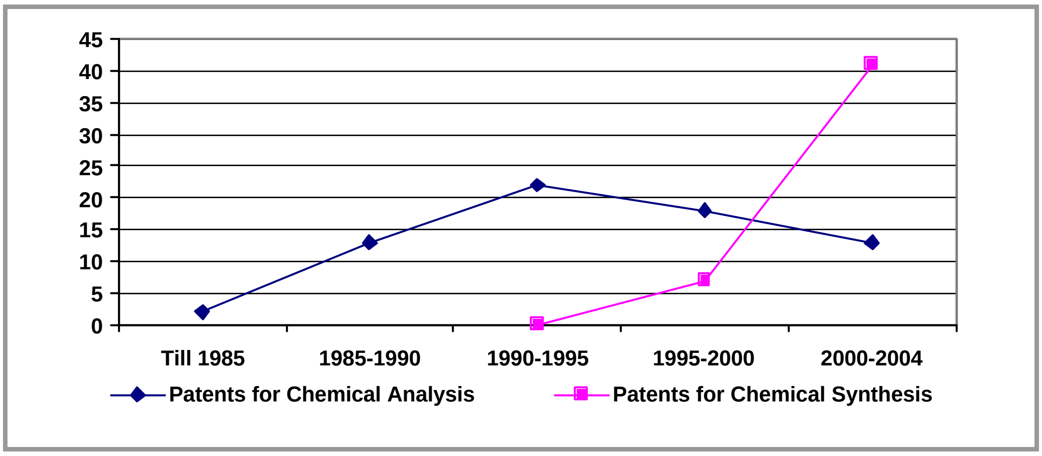
[66] Source: Evalueserve Analysis. This includes one patent per patent family

field for research by researchers and manufacturers alike. This resulted in a large number of patents being filed in the field of microwave synthesis after 1997.

In effect, a major shift occurred in relation to the research activity of various manufacturers of microwave instruments. Major players in the market shifted the focus of their research from development of chemical analysis to development of instruments for chemical synthesis, and designing microwave apparatus for conducting chemical reactions (Figure 15).

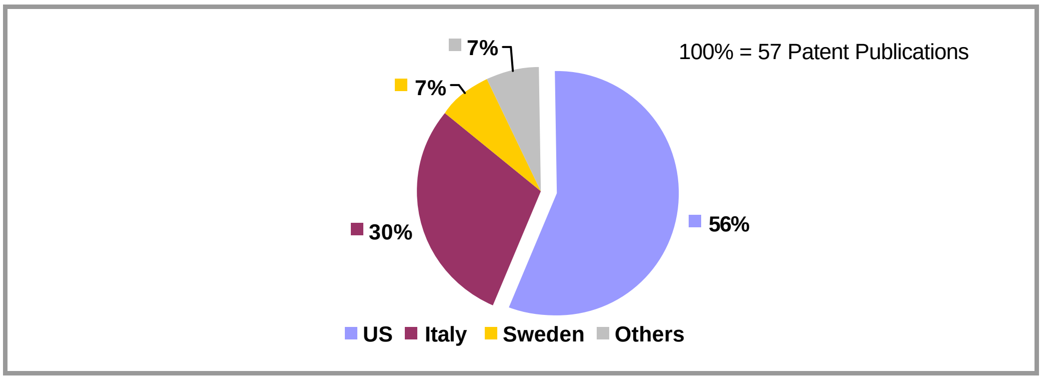
Figure 15: Number of Patent Publications Granted in Microwave Chemistry



Source: Evalueserve Analysis

The geographic distribution of patents granted in the field of microwave chemistry also went through great change during this phase. The patents filed by organisations from the US reduced to 56% of the total number of patents filed during this period (Figure 16). European countries such as Italy emerged as the new hub for research on microwave chemistry, with 30% of the patents granted to the respective organisations in Italy. In Sweden, 'Biotage AB[67]' emerged as a leading developer of microwave chemical synthesis instruments, and in Italy, Milestone s.r.l led the way with its chemical analysis equipment.

Figure 16: Country-wise Distribution of Patent Publications from 1996-2004



Source: Evalueserve Analysis

7.2 Important Areas of Research

As mentioned earlier, development of intellectual property in the field of chemical analysis has slowed down. Research by manufacturers and researchers is aimed at improving existing instruments and converging them into a single product.

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[67] Previously Personal Chemistry

On the other hand, development of intellectual property in chemical synthesis is growing, as key manufacturers of microwave instruments are directing their research towards developing specialised equipment for chemical synthesis, to achieve higher yields on a large scale.

7.2.1 Reactions at High-pressure Conditions

Manufacturers of microwave-assisted chemistry instruments have developed patents to attain high-pressure conditions inside the microwave instrument. Research in this area has been focused on attaining high pressure and high temperature conditions in a reactor, and developing sensors that can measure these high-pressure conditions, without the risk of their getting damaged[68].

7.2.2 Convergence of Instruments for Chemical Analysis

Patent number US6242723, filed by Milestone s.r.l, focuses on converging important chemical analysis processes such as digestion, hydrolysis, separation, agitation and precipitation in a single equipment.

7.2.3 Improvements in Content Determination in NMR Analysis

Manufacturers of microwave devices have made improvements in the content determination of existing apparatus. The existing technique for the content determination of fats, oils, etc., depends greatly on Nuclear Magnetic Resonance (NMR) analysis, which may cause aberrations due to the presence of moisture in the sample. The new method of content determination first heats the sample under microwave radiation, and then performs the NMR analysis, after drying the sample. By attaining precision in the moisture content of the sample tested, the sample behaves in a near ideal condition and makes content determination more accurate.

7.2.4 Safe Conditions in the Reaction Vessel

Manufacturers are also directing their research towards maintaining a safe condition in the reaction vessel. Systems that use materials with low melting points in sensors have been used to investigate abnormal reaction conditions[69]. In the case of an abnormal reaction condition, the material melts and stops the supply of microwave radiation.

7.2.5 Scaling-up Reactions

Recently, most research in the field of chemical synthesis has been focused on scaling up of chemical reactions using microwave radiation. Manufacturers of microwave instruments have devised means of scaling up the yield of both single-mode and multi-mode microwave reactors. Based on the patents publications granted to date in this field, it is evident that research is still in a nascent stage.

Patent publications filed to date have tried to address the issue of scaling up by developing multiple microwave sources for multiple samples[70]. Another attempt takes multiple samples and irradiates them simultaneously by rotating the table carrying them[71]. Although these attempts have scaled up the yield of the reaction, they have certain limitations, including reflection of radiation on the microwave source and interference of radiation in the case of multiple radiations.

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[68] Patent number: US6534140, US6124582, US6287526

[69] Patent Publication Number: US20020096340A1

[70] Patent Publication Number: US20020084264A1

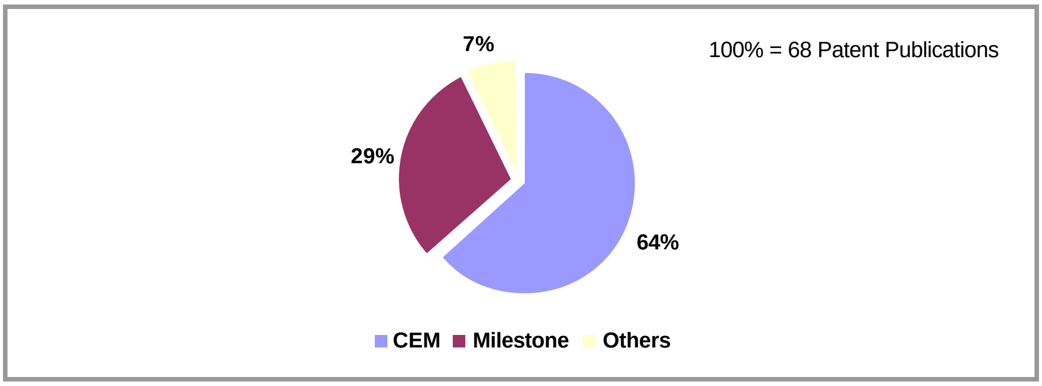
[71] Patent Publication Number: US20020175163A1

7.3 Key Players

The number of patents granted to key players in the field of microwave chemistry serves as a good indicator, to analyse the extent to which they have directed their research activities.

CEM Corporation and Milestone s.r.l are the two major players in the intellectual property of the chemical analysis market (Figure 17). CEM Corporation leads the market with the largest number of patent publications granted in chemical analysis.

Figure 17: Number of Patent Publications Granted in Chemical Analysis till 2004



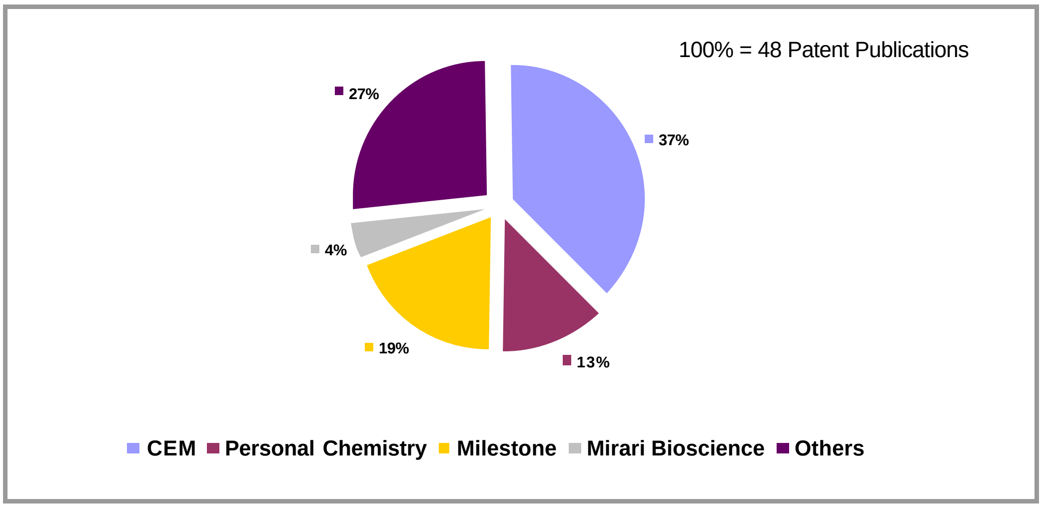
Source: Evalueserve Analysis

However, with the emergence of chemical synthesis as a major application in microwave chemistry, there has been a change in CEM Corporation's research focus, from chemical analysis to chemical synthesis (Figure 18). Since the late 90s, the company has actively focused on developing instruments that meet the requirements of synthetic chemists.

However, unlike chemical analysis research, research activities are well distributed in microwave chemical synthesis. Companies such as Biotage AB have conducted prolific R&D, grown rapidly in the last two-three years, and have evolved as major players in the field of chemical synthesis research.

In addition, companies such as Mirari Bioscience,.Questron Canada, Nucon Systems have also started filing patents for microwave chemical synthesis equipment. In the near future, these organisations may become major suppliers of equipment related to chemical synthesis.

Figure 18: Number of Patent Publications Granted in Chemical Synthesis till 2004



Source: Evalueserve Analysis

7.4 Emerging Research Areas

This section discusses the areas that will guide future research in the field of microwave chemistry. These areas can also be considered the growth drivers for instrument manufacturers, since breakthroughs in this field may cause the market scenario to change.

The following areas will guide future research:

- One of the critical problems faced by researchers, chemists and scientists while performing chemical synthesis is the scaling up of reactions to obtain higher yields. To tackle this problem, companies such as CEM Corporation, Biotage AB and Milestone s.r.l have developed flow-through reactors and batch reactors to scale up the yield of reactions carried out by using microwaves. Although this apparatus has proven to be a breakthrough, it has limitations relating to its efficiency in scaling up solid-state reactions and safety issues related to bulk absorption by the instrument walls. These limitations, in addition to possible innovative methods of scaling up, leave the field open for research in the near future.

- Microwave instrument manufacturers are focusing their research and product development on providing complete labstation solutions. They propose converging chemical analysis and chemical synthesis inside a single instrument. Two major concerns regarding the design of such products is their size and the mechanism adopted for conducting simultaneous chemical synthesis and analytic processes[72].

- Microwave chemistry, in histological research, has developed as a new area of research and shows favourable potential for growth in the near future[73].

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[72] Evalueserve Primary Research

[73] Evalueserve Primary Research

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9 Appendix

9.1 Market Size Estimation

9.1.1 Output Data

Table 7: Microwave Chemistry Market Size Estimation (2003) in $ m

COMPANY	CHEMICAL SYNTHESIS	ANALYTICAL	TOTAL
CEM	5.7	38.1	43.8
Biotage AB	19.2	0	19.2
Milestone s.r.l	2.1	14.4	16.5
Others	0	9.5	9.5
Total	**27.0**	**62**	**89**

Source: Evalueserve Analysis

9.1.2 Input Data

1. CEM sales in 2003 = $ 43.8 m[74]
2. CEM chemical synthesis sales in 2003 = $ 5.7 m[75]
3. CEM share in analytical market = 60-70%[76]
4. Total pro forma turnover of Biotage AB = MSEK 360[77]
5. Sales of Drug Discovery division of Biotage AB in 2003= SEK 265mn ($ 38.4m)[78]
6. Sales from Microwave chemistry equipment in 2003 = USD 19.2 m
7. Milestone s.r.l sales in 2003 = $ 16.5m[79]
8. Milestone s.r.l sales in analytical market = $14.5m[80]
9. Milestone s.r.l sales in chemical synthesis market = $2.1m[81]
10. Expected growth rate of chemical synthesis market = 15%-20%[82]
11. Expected growth rate of analytical market = 5%[83]
12. Share of Biotage AB in chemical synthesis market = 71
13. Biotage AB is not present in the analytical market[84]

9.1.3 Assumptions

1. Sales of small players is assumed to be negligible in the chemical synthesis market
2. The chemical analytics market is mature therefore the market structure remains the same
3. The pro forma turnover of the Discovery unit of Biotage AB has been taken as the net sales

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[74] Reference: http://www.cemsynthesis.com/html/releases.htm#News17

[75] Reference: http://www.cemsynthesis.com/html/releases.htm#News17

[76] Michael Collins, CEO, CEM, http://www.cemsynthesis.com/graphics/CEM.pdf

[77] Biotage AB, Annual Report 2003

[78] Biotage AB, Annual Report 2003

[79] Primary Search: Milestone s.r.l

[80] Primary Search: Milestone s.r.l

[81] Primary Search: Milestone s.r.l

[82] Michael Collins, CEO, CEM, http://www.cemsynthesis.com/graphics/CEM.pdf; Robert England, Director, Personal Chemistry

[83] Michael Collins, CEO, CEM, http://www.cemsynthesis.com/graphics/CEM.pdf

[84] Robert England, Director, Personal Chemistry

4. The turnover from the microwave chemistry apparatus unit of Biotage AB is assumed to be half of that of its discovery unit, as the discovery unit also includes purification equipments

9.1.4 Calculations

- CEM sales in analytical segment = Input Data (1) - Input Data (2) = $ 38.1 m
- Total sales in the analytical segment = CEM sales in analytical segment + Input Data (8) = $ 62m
- Sales of Others in analytical segment = Total sales in the analytical segment - share of CEM in analytical market – share of Milestone s.r.l in analytical market
- Total sales in chemical synthesis segment = sales of CEM in chemical synthesis segment + sales of Milestone s.r.l in chemical synthesis segment + sales of Biotage AB in chemical synthesis segment

9.2 Market Size Forecast

9.2.1 Output Data

Table 8: Microwave Chemistry Market Size Forecast Estimation (2004-2008) in $ m

SEGMENT	2004	2005	2006	2007	2008
Analytics	65.1	68.4	71.8	75.4	78.6
Chemical synthesis	32.4	38.8	46.7	56.0	67.2
Total	**97.5**	**107.2**	**118.5**	**131.4**	**145.8**

Source: Evalueserve Analysis

9.2.2 Input Data

- Analytics sale in 2003 = $ 62 m
- Chemical synthesis sale in 2003 = $ 27m
- Total sales in 2003 = $ 89m

9.2.3 Assumption

- Expected yearly growth rate of analytical market = 5%[85]
- Expected yearly growth rate of chemical synthesis market = 20%[86]

9.2.4 Calculations

Table 9: Microwave Chemistry Market Size Forecast Calculation (2004-2008) in $ m

SEGMENT	2003	2004	2005	2006	2007	2008
Analytics	62	62*(1.05)	$62*(1.05)^2$	$62*(1.05)^3$	$62*(1.05)^4$	$62*(1.05)^5$
Chemical synthesis	27	27*(1.20)	$27*(1.20)^2$	$27*(1.20)^3$	$27*(1.20)^4$	$27*(1.20)^5$

Source: Evalueserve Analysis

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[85] Michael Collins, CEO, CEM, http://www.cemsynthesis.com/graphics/CEM.pdf

[86] Michael Collins, CEO, CEM, http://www.cemsynthesis.com/graphics/CEM.pdf; Robert England, Director, Personal Chemistry

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