www.sphinxsai.com

PharmTech

International Journal of PharmTech Research
CODEN (USA): IJPRIF ISSN : 0974-4304
Vol.1, No.4, pp 1039-1050, Oct-Dec 2009

Microwaves in drug discovery and development: A Review

A.R. Tapas[1*], D.D. Magar[2], P.S. Kawtikwar[1], D.M. Sakarkar[1], R.B. Kakde[3]

[1]Sudhakarrao Naik Institute of Pharmacy, Pusad, Dist.-Yavatmal
[2] Dr Bhanuben Nanavati College of Pharmacy, Mumbai.,India
[3]University Department of Pharmaceutical Sciences, R.T.M. Nagpur University, Nagpur.
***Corresponding Author: Amit R. Tapas, Department of Pharmaceutical Chemistry, Sudhakarrao Naik Institute of Pharmacy, Pusad- 445204, Dist.-Yavatmal (Maharashtra India).**

E-mail: amit.tapas@gmail.com
Phone/Fax: +91 7233 247308, Mobile: +91 9325377391

Abstract: The impact of genomics and proteomics is additionally creating an explosion in the number of drug targets. This leads to the increasing demands for new small molecules in a very short period of time. This ultimately demands new technologies in the field of medicinal chemistry. Microwave assisted organic synthesis (MAOS) is the medicinal chemists friend in this aspect. Now a day MAOS is rapidly becoming recognized as a valuable tool for slackening some of the bottlenecks in the drug discovery process. Also the advent of microwave technology has intensified the search for pharmaceuticals amenable to microwave processing. The use of microwaves opens a new approach to control the physicochemical properties and drug delivery profiles of pharmaceutical dosage form without the need of excessive heat, lengthy process and toxic reactant. The goal of the present review is to present carefully scrutinized, useful, and practical information for both beginners and practitioners of MAOS. In addition his paper reviews the basis of application of microwave to develop pharmaceutical dosage forms.
Keywords: Microwaves, Medicinal Chemistry ,Drug Delivery Systems .

Introduction

Research and development (R&D) productivity upgrading is one of the biggest tasks facing the pharmaceutical industry. Advances in genomics and proteomics in recent years have led to a flare-up in the number of possible drug targets, and so pharmaceutical companies have made major investments in high-throughput screening and combinatorial chemistry to identify more potential drug candidates for these novel targets. Medicinal chemistry has benefited tremendously from the technological advances in the field of combinatorial chemistry and high throughput synthesis. These new tools have had a significant impact on both lead identification and lead optimization in the pharmaceutical industry. Lead compound optimization and medicinal chemistry are known to be the bottlenecks in the drug discovery process, and so a need arises for technologies that allow rapid synthesis of chemical substances. Large compound libraries can now be designed and synthesized to provide valuable leads for new therapeutic targets. Once a chemist has developed a suitable high-speed synthesis of lead, it is now possible to synthesize and purify hundreds of molecules in parallel to discover new leads and/or to derive structure-activity relationships (SAR) in unprecedented timeframes. Developing chemical compounds with the desired biological properties is time-consuming and expensive. Heat can be a chemist's friend in this respect, but even here problems can appear. Some organic constituents can be highly unstable at high temperatures, and uneven heating can lead to undesired side products. Thus, chemist continues to search for a safer and better way of performing efficient reactions. Consequently, there is increased interest in technologies and concepts that facilitate more rapid synthesis and screening of chemical substances to identify compounds with appropriate qualities. One such high-speed technology is microwave-assisted organic synthesis (MAOS). Most people reading

this article have no doubt used a microwave oven to prepare food, so it is no great leap of logic to suppose that the same energy used to heat bowl of soup could be harnessed for microwave-assisted organic synthesis (MAOS) reactions.

Microwave-assisted heating under controlled conditions is an invaluable technology for medicinal chemistry and drug discovery applications because it often dramatically reduces reaction times, typically from days or hours to minutes or even seconds[1]. Specifically, microwave synthesis has the potential to impact upon medicinal chemistry efforts in at least three major phases of drug discovery process: lead generation, hit-to-lead efforts, and lead optimization. In the recent decade, the microwave has been utilized to process dosage form. The drug delivery systems are processed and modified via the heating and/or electromagnetic effects of microwave. The microwave can be introduced during the preparation process of dosage forms and/or directly onto the preformed products. The physicochemical properties of excipients can be specifically modified by microwave to provide the intended release properties of drugs in dosage form development.[2]

The goal of the present review is to present carefully scrutinized, useful, and practical information for both beginners and practitioners of MAOS. Also we hope to demonstrate in this review the utility of this technique, and the potential that this methodology can give to drug discovery process.

Microwave Mayhem

A microwave (figure 1) is a form of electromagnetic energy, which falls at the lower end of the electromagnetic spectrum and is defined in a measurement of frequency as 300 to 300,000 Megahertz, corresponding to wavelengths of 1 cm to 1 m. Wavelengths between 1 cm and 25 cm are extensively used for RADAR transmissions and remaining wavelength range is used for telecommunications. All domestic kitchen microwave ovens and all dedicated microwave reactors for chemical synthesis that are commercially available today operate at a frequency of 2.45 GHz (corresponding to the wavelength of 12.25 cm) in order to avoid interference with telecommunication and cellular phone frequencies[3].

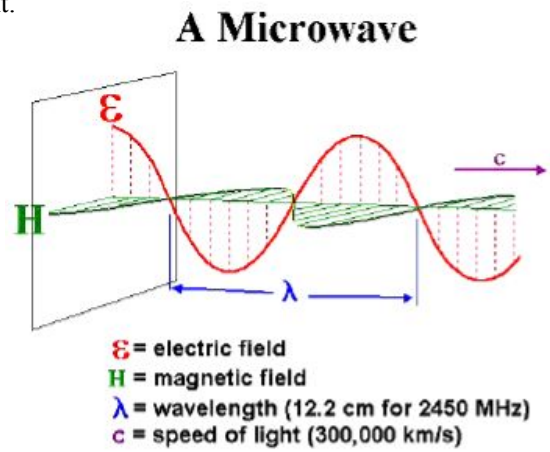


Figure 1 | Microwave: a form of electromagnetic energy

Microwave energy consists of an electric field and a magnetic field, though only the electric field transfers energy to heat a substance. The magnetic field is latent. The energy in microwave photons is very low relative to the energy required for molecular bonding. The typical oxygen, hydrogen-oxygen or carbon-carbon bond falls in the range of 80-120 kcal/mol: microwave energy is an order of less magnitude. Thus, microwaves will not affect molecular structure. In the excitation of molecules, the effect of microwave absorption is purely kinetic[4].

Traditionally, chemical synthesis has been achieved through conductive heating with an external heat source, where the temperature is elevated because of ΔT and heat is driven into the substance, passing first through the wall of the vessel in order to reach the solvent and reactants (figure 2a). This is a slow method for transferring energy into the system, because it depends on the thermal conductivity of the various materials that must be penetrated. It also results in a higher external temperature than the final internal temperature, which is problematic as the required internal temperature can only be reached by sufficiently increasing the surface temperature of the material over the desired temperature. Microwave heating (figure 2b) is a very different process: the microwaves couple directly with the molecules that are heating, leading to a rapid rise in temperature. Because the process is not dependent upon the thermal conductivity of the materials, the result is an instantaneous heating of anything that will react to either, dipole rotation or ionic conduction, the two fundamental mechanisms for transferring energy from microwaves to the substance being heated[5]. Dipole rotation (figure 2c) is an interaction in which polar molecules or polar species try to align with the rapidly changing electric field of the microwave. The motion of the molecule as it tries to orient to the field results in a transfer of energy. It is the electric field

component of the microwave irradiation, rather than the magnetic field component, that is responsible for the effect. When a dipole tries to re-orientate itself with respect to an alternating electric field, it loses energy in the form of heat, by molecular friction. The heat generation is dependent on the nature of the dipole and the frequency of the applied radiation. If the frequency of the radiation is too high, the dipole does not have time to align itself with the field before the field changes direction again. In these circumstances, no motion and consequently no heating occurs. Similarly, no heating occurs if the dipole aligns itself perfectly with the alternating electric field and, therefore, follows the field fluctuations. However, if the applied field is in the intermediate frequency region (e.g. microwave radiation), a phenomenon occurs that lies between these two extremes. In this situation, the dipole has time to respond and align itself with the field, but the fluctuations of the field are so rapid that the dipole does not follow it perfectly. This results in the generation of heat. The second way to transfer energy is ionic conduction (figure 2d), which results if there are free ions or ionic species present in the substance being heated. The electric field generates ionic motion as the molecules try to orient to the field, causing rapid heating. The temperature of the substance also affects ionic conduction; as the temperature increases, the transfer of energy becomes more efficient. Also one of the most important thing is that as microwave heating is generated from within the sample, the reactants experience fewer hot spots than they would in an immersion bath, where the walls of that reaction vessels are warmer than their cores. This homogeneous heating allows the reaction temperature to rise quickly (up to 10 ^{0}C/s) and minimizes the generation of side product[6].

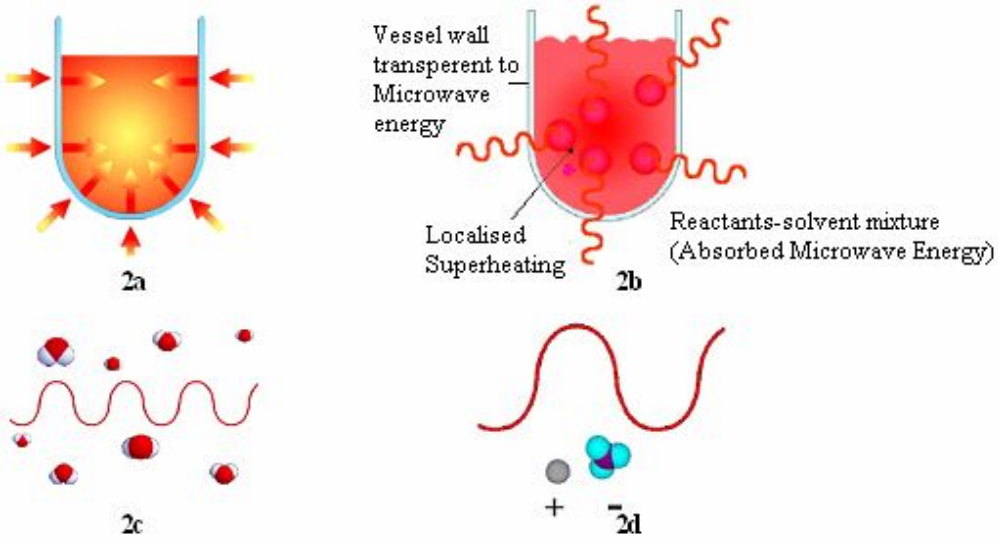


Figure 2 | Working mechanism of Microwave Chemistry: 2a | Schematic of sample heating by conduction: Temperature on outside surface is in excess of boiling point of liquid, 2b | Schematic of sample heating by microwaves, 2c | Dipole rotation: Microwave electric field interaction with Water molecule, 2d | Ionic conduction

One of the most important things in MAOS is the choice of solvent[7]. All conventionally used solvent can be used for microwave-mediated transformations. However one must aware that solvent interact differently with microwaves, according to their dielectric properties. When comparing the ability of different solvents to interact with microwave radiation, two important considerations are (1) the solvent's ability to absorb microwave energy and (2) its ability to convert the absorbed energy into heat. The interaction of a solvent with microwave irradiation is highly complex. As well as being dependent on the solvent's dielectric properties, which are in turn dependent on the temperature of the solvent and the frequency of the applied radiation, the interaction is also dependent upon the viscosity of the solvent (which is also temperature dependent). The best approximation for the comparison of different solvents is to compare their loss tangent values. The loss tangent (tanδ) is defined as the tangent of the loss angle (δ), which is the ratio between the dielectric constant, ε' (which describes the solvent's ability to absorb microwave energy) and the loss factor ε'' (which quantifies the efficiency with which the absorbed energy is converted to heat)[8] (Eqn 1).

$$\tan \delta = \varepsilon'' / \varepsilon' \qquad \text{[Eqn 1]}$$

Values of solvent loss tangents can be found in Table 1 below.

Table 1 | Physical properties of common solvents

Solvent	b.p. (^{0}C)	ε'	ε''	tan δ	Microwave absorbance
Ethylene Glycol	197	37.0	49.950	1.350	Very Good
DMSO	189	45.0	37.125	0.825	Good
Ethanol	78	24.3	22.866	0.941	Good
Methanol	63	32.6	21.483	0.659	Good
Water	100	80.4	9.889	0.123	Medium
DMF	154	37.7	6.070	0.161	Medium
Acetonitrile	81	37.5	2.325	0.062	Medium
MDC	40	9.1	0.382	0.042	Low
THF	66	7.4	0.348	0.047	Low
Toluene	110	2.4	0.096	0.040	Very Low

Low absorbing solvents may also be treated with microwaves, but are poorly heated if they are used in pure form. However, as reaction mixtures are often composed of different (polar) reagents, there should always be enough potential for efficient microwave coupling. Also if only small amounts of polar reagents are used, the low absorbing solvent may acts as a "heat sink", drawing away the thermal heat from the reagents, thereby protecting thermally labile compounds and keeping the reaction temperature low[9]. When the dielectric properties of the sample are too poor to allow efficient heating by microwave radiation, the addition of small amounts of additives (e.g ionic salts) that have large loss tangent values can significantly overcome these problems and enable adequate heating of the whole mixture. One phenomenon encountered when performing microwave heating is that the boiling points of solvents can be raised up to 26 ^{0}C above their conventional values; this is known as the superheating effect. This higher boiling point can be maintained in pure solvents for as long as the microwave radiation is applied[10].

Microwave Reactors

Two types of MAOS reactors are available: multimode units and monomode units[11]. The multimode unit is best described by the standard kitchen microwave oven. Although this unit is relatively inexpensive, the distribution of electric field is heterogeneous, leading to the formation of hot spots in the chamber. Also, because it is difficult to set the temperature in such a unit, reaction reproducibility is poor. For this purpose the microwaves that enter, are reflected by the walls of the cavity or built-in magnetic stirrers, and therefore interact with the sample in a chaotic manner[12]. In monomode unit, however the electromagnetic energy is focused by a waveguide, which leads to a more homogeneous distribution of the energy in the chamber. Thus, by using fiber-optic probes, infrared sensors, or even a digital thermometer and software it is possible to regulate the reaction temperature and pressure[13]. In perspective of drug discovery, there is a key difference between the two types of reactor systems: in multimode cavities several reaction vessels can be irradiated simultaneously in multi-vessel rotors or deep-well microtitre plates; but in monomode units only one vessel can be irradiated at any time. However, high throughput can be achieved in monomode systems by using integrated robotics.

Figure 3 | The CEM Explorer™ instrument

Microwave Impact on Drug Discovery Process

The increasing demand for new molecules led to the invention of new technologies in the field of medicinal chemistry. The impact of MAOS is not only limited to organic chemistry but it now also being used in the areas like lead discovery and optimization, drug development and even in the clinics.

Lead Discovery

Nowadays, MAOS is gaining a wide spread acceptance in drug discovery laboratories. The current trend in the pharmaceutical industry is to generate comparatively small, focused libraries containing ~30-300 compounds for a typical drug discovery project. With the competitive nature of the drug discovery industry, lead discovery groups are challenged to develop promising programmes rapidly and secure a strong intellectual position early. Productivity crisis which are arising because of rising cost of R & D and decreases in the number of FDA approvals can be minimized through microwave technology, by accelerating the chemical reaction from hours or days to minutes. Because of its speed MAOS or more correctly Microwave-assisted parallel synthesis is tool that is ideally suited to combinatorial chemistry[14]. The microwave-assisted combinatorial synthesis (MICROCOS) was first developed by Khmelnitsky et al.

in which reactions were performed in a 96-well microtitre plate[15]. The method was able to produce libraries of diverse pyridines high throughput, automated, single step, and parallel synthesis[16]. Today the main use of MAOS for combinatorial chemistry and high speed parallel synthesis is in the area of multi-component reactions such as Bibinelli reaction. Kappe has published a effective Biginelli synthesis assisted by microwaves (Figure 3a)[17]. Brain et al. have devised a rapid and efficient synthesis of 1,3,4-oxadiazole in high yield and purity (Figure 3b)[18].

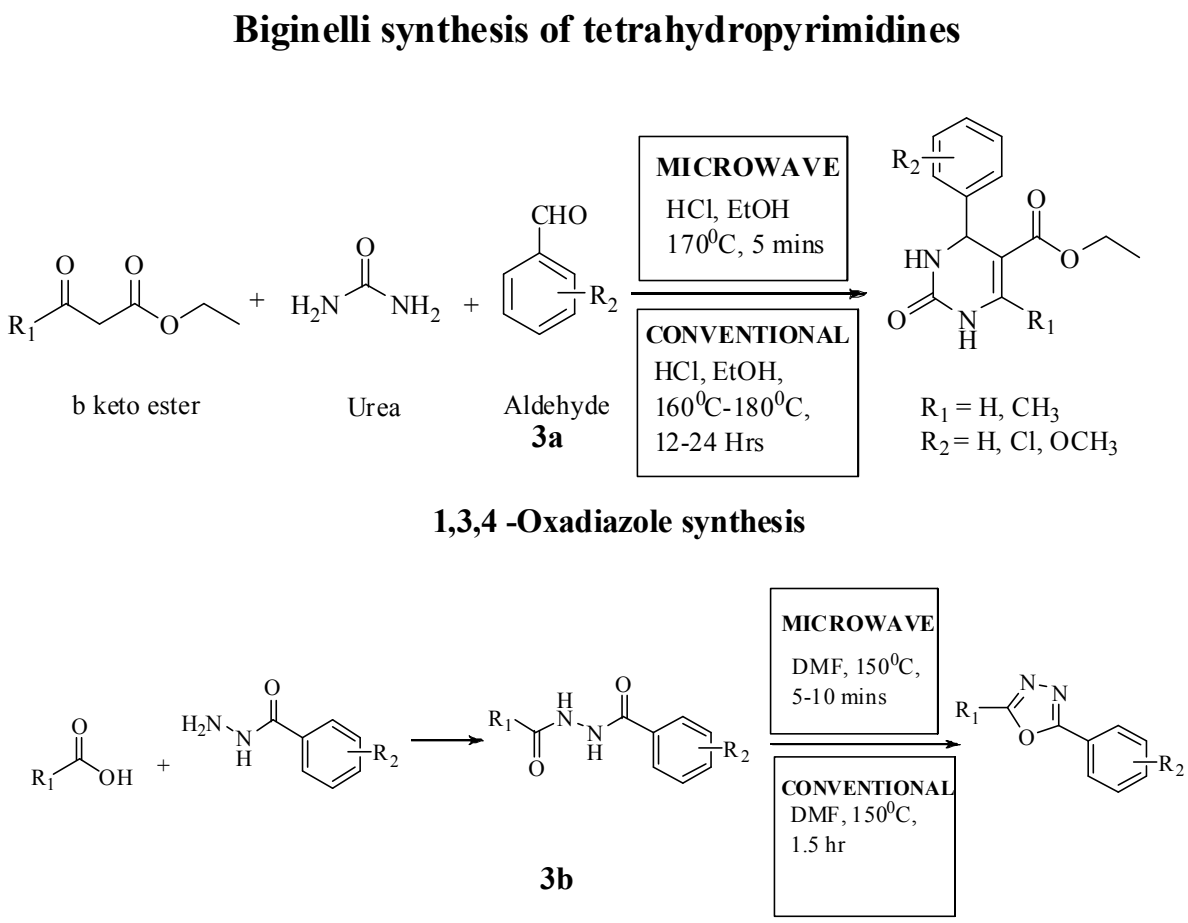


Figure 3 | Examples for the Lead Discovery, 3a | Biginelli synthesis of tetrahydropyrimidines, 3b | MW synthesis of 1,3,4- Oxadiazole synthesis

Lead Optimization

Microwave-assisted heating has been shown to be an invaluable optimization method since it reduces reaction times dramatically, typically from days or hours to minutes or seconds. Many reaction parameters can be evaluated in a few days to optimize the desired chemistry. Kidwai et al. have shown microwaves to be effective in the synthesis of the novel antibacterial β-lactams (figure 4; **1**), quinolines (figure 4; **2**) and ciphalosporins.(figure 4; **3**)[19-22]. Ley and his group have discovered the convenient and efficient microwave synthesis of the well known commercially available important pharmaceutical drug sildenafil (Viagra™).(figure 5)[23]. Also microwave technology has been applied for the synthesis of inhibitors of malerial proteases plasmepsin I and II (PlmI and PlmII, respectively). The recent publication of the genome of *Plasmodium falciparum*, the most lethal protozoan parasites causing malaria, has revealed a number of new targets for drug intervention. Among these are the haemoglobin-degrading aspartic proteases PlmI and PlmII[24,25].

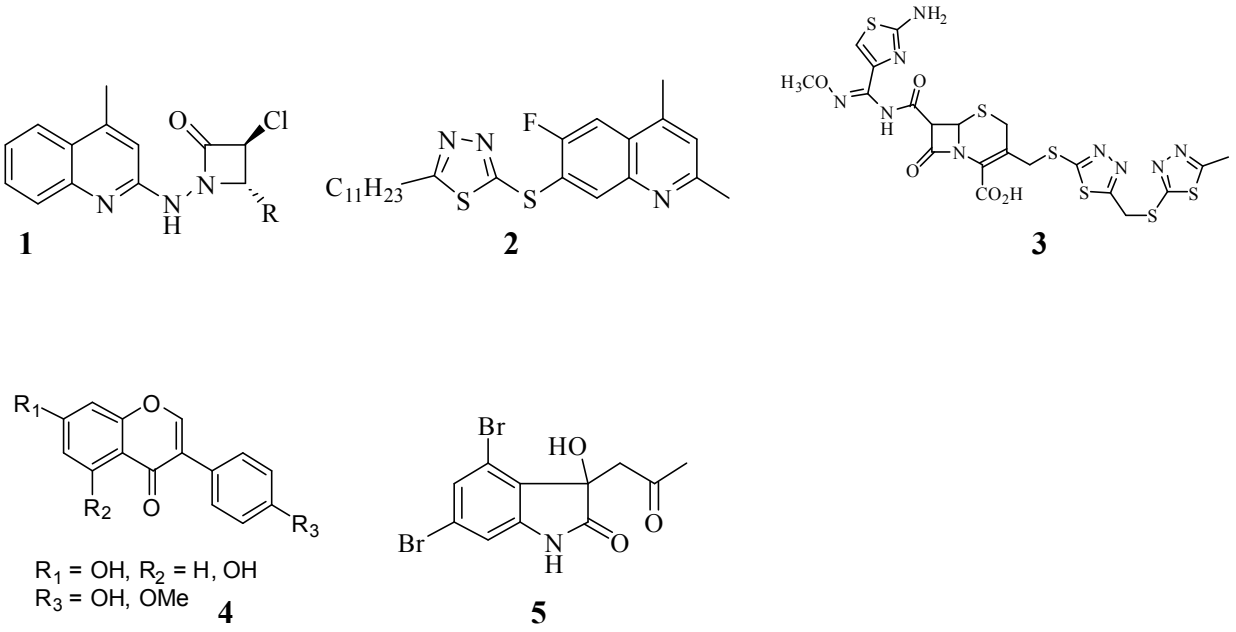


Figure 4 | Examples of the compounds synthesized with the use of microwave assisted medicinal chemistry

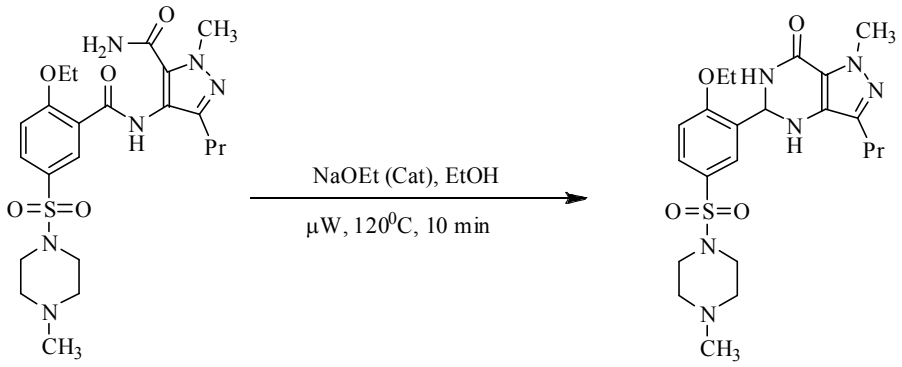


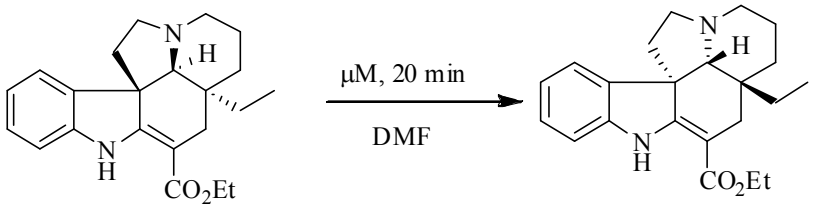
Figure 5 | Microwave-assisted Sildenafil (Viagra™) synthesis.

Microwave Impact on Drug Development

Development of Active Drug Isomer

Microwave is beginning to play a greater role in process of drug development, especially in cases where classical methods require prolonged reaction times and forced conditions. A most interesting and important application of microwave activation is the epimerization of optically active compounds. A wide range of amino acids has been epimerized quantitatively within two minutes, thus avoiding the decomposition that is associated with the use of classical heating. Similarly, the complete epimerization of (-)-vincadifformine (figure 6) is achieved in <20 minutes to generate (+) isomer[26].

Figure 6 | Epimeization of (-)-vincadifformine.



Microwaves in Processing of drug delivery system

Microwaves in recent years can be used during the preparation process of dosage form and/or directly onto the preformed products. Alternatively, the microwave can be applied to process the excipients prior to their use in the formulation of drug delivery systems[27]. Also it is possible to modify the physicochemical properties of excipients to provide the intended release properties of drugs in dosage forms. Following subsection will describe the application of microwaves in drug delivery system.

Drying of Agglomerates

In recent years, microwave drying has gained greater interest. When moist material is subjected to microwave that selectively excite the polar molecules and ions causing them to align with rapidly alternating electric field. The frictional heat generated as a result of these rapid molecular rotations promotes evaporation of water. Microwave assisted drying of agglomerates can provide the faster drying at less energy expenditure. The rate of drying of agglomerates by means of microwave is largely governed the loss factor (loss tangent, tan δ)[28,29]. The loss factor of agglomerate is lower than that of solvents. The microwave energy is preferentially absorbed by solvent molecules. The solvent molecule has greater inclination to be heated under the inductive effects of microwave. This in turn results in quick drying of agglomerates at reduced energy expenditure. The use of high loss excipients as the granulation materials may delay the process of drying as such excipients could absorb microwave readily when compare to that of solvent. The efficiency of microwave drying is material dependent with a heavy reliance on the moisture content and physical properties of the moistened material. This distinguishes microwave drying from conventional drying methods such as vacuum, conductive or convective mode of drying where the exposed surface area of the wet material remains the overriding factor affecting the efficiency of heat transfer and drying performance[30]. When drying is carried out under microwave-assisted conditions, materials with higher moisture contents interact more readily with the waves as they possess higher dielectric constants and losses.[31,32] As a result, these materials may potentially experience greater heating and drying rates than those which are comparatively drier. Such moisture-targeting effects are beneficial when drying products of large volumes since moisture is seldom uniformly distributed within the product load undergoing drying. This selective nature of microwave energy enables moisture leveling and maintenance of overall product quality.[33] McLoughlin and other coworkers found that the moisture content variation within the material undergoing drying with microwave was lower than a conventionally dried product.[34] Thus microwave drying is especially useful for moisture sensitive materials. In addition, microwave drying technology is useful for production of very high potency dosage forms because it provides the possibility of drying in same production container. Thus, it reduces the likelihood of cross contamination and human contact with high potency drug.

Solvent	**Loss Factor**
Ethanol	8.60
Iso-propanol	2.90
Acetone	1.25
Pure Water	6.10
Pharmaceutical Material	**Loss Factor**
Lactose	0.02
Maize Starch	0.41
Microcrystalline Cellulose	0.15
Mannitol	0.06
Calcium phosphate	0.06
Calcium Carbonate	0.03

Table 2 │Loss Factor Values of Some Pharmaceutical Materials and Solvents

Effect on Drug Release Properties

Carbohydrate polymers such as pectin and alginate have been widely employed as the matrix carrier for small molecule drugs.[35-40] The wide application of biopolymers is attributed to their biodegradability and low oral toxicity. On the other hand the embedded drug molecules exhibit a fast rate of drug release via diffusion through the pores of matrix. Such rate of drug release is undesirable in the case of the need to target the drugs to lower part of gastrointestinal tract, particularly, the colon. Over the last 10 years, various approaches were made to reverse the rate of drug release from these matrices like

use of high concentration of multivalent metallic or non-metallic cation as crosslinking agents[41,42], effect of drug:polymer ratio, effect of molecular weight and chain conformation, also attempts have been made to coacervate pectin and alginate with chitosan to form the polyelectrolyte complex to get higher drug release retardation.[43] More recently Wong T.W. et al. describe that microwaves can also be utilized to modify the state of molecular interaction between chains of alginate and pectin, with aim to further delay the release of small molecule drugs such as diclofenac sodium and sulphathiazole from gel beads prepared from these polymers[44]. According to the studies under the influence of microwave, the aged gel beads give rise to different drug release profiles than those of freshly prepared samples. The aged alginate gel beads require intermittent cycles or longer duration of microwave irradiation to retard the release of drug from the matrix in contrast to freshly prepared matrix. Unlike the alginate gel beads, the drug release retardation property of aged alginate-chitosonium gel beads can be significantly enhanced through subjecting these beads to a single cycle or a shorter duration of microwave irradiation. There is no further change in drug release profile from these gel beads beyond one cycle of microwave irradiation.[45]

Gelatin has been largely investigated for the preparation of nano- and micro-particles because of its non-toxic, biodegradable, biocompatible, non-carcinogenic, non-immunogenic, and inexpensive nature. As gelatin is soluble in aqueous solutions gelatin-based delivery systems have to be crosslinked to control the drug release. The crosslinking over the years has been done with chemical and thermal methods. The safety of chemically crosslinked gelatin is still a concern as the presence of residuals of the crosslinking reaction (crosslinker) and the risk of formation of toxic products between the gelatin and the crosslinker, which could be released after ''in vivo'' biodegradation, may provide a restriction in using these crosslinker agents.[46] In thermal crosslinking the rate and extent of crosslinking are markedly governed by process temperature and time. Typically, more than one day is needed to generate an adequate level of crosslinkages needed for dosage form design.[47,48] As a result, the thermal crosslinking method is unattractive for the application in pharmaceutical and allied industries. The microwave has been investigated as the alternative mode to crosslink the gelatin matrix which is available as microspheres suspended in a polar liquid medium such as acetone. It is found that a period as short as 10 min is sufficient for effective crosslinking of gelatin microspheres.[49]

Microwaves in preparation of Solid Dispersion

The poor dissolution characteristic of relatively insoluble drugs is the rate limiting step in the absorption of a drug from a solid dosage form. In recent years there is a rising interest to design solid dispersion whereby one or more active ingredients are embedded in an inert solid matrix by the melting, solvent or melting-solvent method.[50-52] The dissolution of poor water soluble drugs can be greatly enhanced through reducing the particle size and/or crystallinity of drug during the preparation of solid dispersion. Preparation of solid dispersion by melting method involves heat, which may lead to decomposition or evaporation of the drug particles and/ or matrix former. Alternatively, solvent method demands a high operating cost for solvent, flame proof facilities, solvent removal and recovery system. The environmental problem of the use of organic solvent is also the problem of major concerned. Also physicochemical stability and dissolution properties of these prepared solid dispersion are affected appreciably by the storage conditions.[53]

Recently, Kerc et al.[54], Bergese et al.[55], and Moneghini et al.[56] have explored the usefulness of microwave as the alternative mode of preparation for solid dispersion. Kerc et al. describe the method in which physical mixture of both felodipine drug and porous amorphous silicon dioxide carrier is subjected to microwave treatment at 500 W for different periods of time, between 5 and 15 min. The drug release propensity is higher in samples subjected to microwave irradiation for a longer period of time. The drug release propensity of microwave-treated physical mixture is greatly higher than those of pure drug, physical mixtures which are untreated by microwave or treated by vacuum at 100°C, or obtained using solvent deposition method. These observations are ascribed to a reduction in the level of crystallinity of drug following its treatment by microwave in the form of a physical mixture. Similarly Moneghini et al. prepared microwave activated solid dispersion systems in different ratios of Ibuprofen to PVP/VA 64 or HP-β-CD by irradiating these physical mixtures to microwave at 600 W for 6 and 15 min. These activated systems were able to remarkably increase the dissolution profile of poorly soluble Ibuprofen.

In another study by Bergese et al. the microwave has also been utilized to produce solid dispersion using the concept of hybrid heating. Low loss pharmaceutical materials have a poor electrothermal coupling capacity with microwave. They are difficult to be heated by microwave at room temperature. Nevertheless, they could absorb the microwave energy upon preheating to a suitable temperature and beyond which they will couple with the microwave. Using a high loss reactor, the reactor could absorb the microwave energy readily at a low temperature, convert the energy to heat, and transfer the heat to the low loss pharmaceutical materials by diffusion which in turn promotes the coupling capacity of processing mass with microwave. The solid dispersion prepared thusfar via hybrid heating includes nanomatrix with nanocrystals and molecular clusters of drug embedded in the core, and microcrystals of drug adhered onto the surfaces of matrix. This in turn is envisaged to enhance the dissolution propensity of water-insoluble drugs.

Effect on Tablet and Film Coating

The use of microwave has a strong implication in design of sustained-release drug delivery system such as matrix

and coated tablet. Ispaghula husk, the dried seed coats of Plantago ovata, has been employed in the manufacture of matrix tablet. But the poor gel forming tendency and formation of soft tablet limits its use. Also modification of Ispaghula husk by hot air oven treatment does not appear to be able to induce rigid gel formation. Also prolong heating may degrade polymer and thus the network of polysaccharide needed to sustain the release of drug is lost. Treatment of Ispaghula husk by microwave has shown to introduce superior swelling and rigid gel formation properties to the husk, in both distilled water and simulated gastric fluid (pH 1.2). The matrix tablets prepared from microwave-treated Ispaghula husk swell considerably and do not erode during the in vitro dissolution testing.[57]

The drug release property of a tablet is modified by the addition of a polymeric coat onto the matrix. The polymer coat is commonly introduced to the tablet from aqueous solution or suspension of polymer. The drying of polymer coat can be effected by microwave and/or hot air. The film coat dried using microwave is more elastic, has more tensile strength than oven or air dried films and faster rate of drying, but possesses slightly lower level of tensile strength than that dried using hot air current.[58]

Other Application of Microwaves

Microwaves in Plant Drug Extraction

Conventional techniques i.e. Soxhlet extraction, for the extraction of active constituents are time and solvent consuming, thermally unsafe and the analysis of numerous constituents in plant material is limited by extraction step. High and fast extraction ability with less solvent consumption and protection offered to thermolabile constituents are the attractive features of this new promising microwave assisted extraction (MAE) technique[59]. This technology is particularly useful in the extraction of particulate-associated and semi-volatile compounds collected on filters and adsorbents such as polyurethane foam.

Microwaves in Analytical Chemistry

Microwave assisted differential thermal analysis (MW-DTA) is a new technique that combines the advantage of MW heating with the benefits of differential temperature measurement to give a sensitive means of probing the thermal properties of materials as a function of temperature is developed by Parkes et al.[60] The coupling of microwave based devices to the steps of analytical procedure, such as pre-concentration, chromatographic separation or detection, which allow total or partial automation of the whole analytical process is reported by J. L. Luque-Garcia et al.[61] Various methods are now a days possible with this coupling such as a microwave-ultrasound combined reactor, a focused microwave-assisted Soxhlet extractor, a microwave-assisted dryer and a microwave-assisted distiller which provide a good prospects for the use of microwave radiation in analytical chemistry. Above specific features of analytical operations with microwave treatment provide the trends for development of analytical methods using microwaves[62].

Microwave heating in Immunohistochemistry

Temperature controlled microwave technology has been used to accelerate immunohistochemistry. The time required for the immunostaining procedures can be cut by atleast 20 times with help of microwave irradiation[63].

Concluding Remarks

In the recent years, the use of microwaves has become very attractive in organic chemistry. Infact with respect to conventional heating i.e. conduction, convention or radiation with infrared light, microwave irradiation offers several advantage such as rapid volumetric heating, no overheating at the surface, addressable heating, energy saving and low operating cost. However, its acceptance and evolution are progressing at furious rate. The main advantages of MAOS are faster and cleaner reactions, higher yields, development of new pathways and green chemistry. In past microwaves, were often used only when all other options to perform a particular reaction had failed, or when exceedingly long reactions times or high temperature were required to complete a reaction. This practice is now slowly changing and because of the growing availability of microwave reactors in many academic and industrial laboratories, routine synthetic transformations are now being carried out by microwave irradiation. Recently it is discovered that *in situ* monitoring of microwave-assisted reactions is possible by Raman spectroscopy which will facilitate a further increase in efficiency and speed[64]. In the today's competitive era MAOS is one of the major tool for the rapid lead generation and optimization through which medicinal chemists will able to deliver critically needed new chemical entities (NCEs) and candidate drug. In recent years, the microwave is utilized to process drug delivery system such as agglomerates, gel beads, microspheres, nanomatrix, solid dispersion, tablet and film coat. Practically, the microwave could induce drying, can change drug release properties by polymeric cross linkages and drug-polymer interaction, and also improve drug dissolution via modifying the structure of drug crystallites. The use of microwave opens a new route to control the physicochemical properties and drug delivery profiles of pharmaceutical dosage forms. It provides the intended release characteristics of drugs in dosage forms without the need for excessive heat, lengthy process and/or toxic reactants.

The most disadvantageous thing regarding microwaves, especially for drug discovery industry, is scalability. Scaling up syntheses from gram quantities to kilograms is essential for drug development, as this is a discouraging bottleneck for present-day process chemists. Many milligram- and gram-scale syntheses cannot be replicated, or even attempted for safety reasons, on larger scales. Microwave technology provides the possibility that the same chemistries used in the initial route can be safely scaled up, enabling chemists to spend their valuable time creating novel synthetic methods, not recreating them. Currently there are no documented published examples of the use of microwave technology for organic synthesis on a production scale level. So, the

scalability of microwave reactions still requires more development, especially in the technology and engineering field. Till now, there are a limited number of studies which focus on the effects of microwave on the physicochemical properties of excipients and drugs, as well as, the drug release properties of the formed products. The data of microwave influence on effect of loss factor, thermal conductivity, electrical conductivity, specific heat, moisture content, porosity, size, shape, temperature and other physicochemical attributes of pharmaceutical formulations on drug release are lacking. So it is therefore imperative to conduct research for the need to scale up syntheses from gram quantities to kilogram and to further understand the mechanism of action of microwave in modifying the drug release properties of dosage forms, as well as, to justify the advantages of microwave for use in processing of drug delivery systems.

References

1. Kappe CO, Stadler A. Microwaves in organic and medicinal chemistry. Weinheim: Wiley-VCH; 2005.
2. Wong TW, Chan LW, Kho SB, Heng PWS. Aging and microwave effects on alginate/chitosan matrices. J Control Release 2005; 104:461-475.
3. Adam D. Microwave chemistry: out of kitchen. Nature 2003; 421:571.
4. Baghurst DR, Mingos DMP. Application of microwave dielectric heating effects to synthetic problems in chemistry. Chem Soc Rev 1991; 20:1-47.
5. Bose AK, Manhas MS, Ghosh M et al. Microwave-induced organic reaction enhancement chemistry, two simplified techniques. J Org Chem 1991; 56:6968-6970.
6. Leadbeater NE, Torenius HM. A study of the ionic liquid mediated microwave heating of organic solvents. J Org Chem 2002; 67:3145-3148.
7. Lidstrom P, Tierney J, Wathey B, Westman J. Microwave assisted organic synthesis – a review. Tetrahedron 2001; 57:9225-9283.
8. Gabriel C, Gabriel S, Grant EH, Halstead BS, Mingos DMP. Dielectric parameters relevant to microwave dielectric heating. Chem Soc Rev 1998; 27:213-223.
9. Gedye R, Smith F, Westaway K et al. The use of microwave ovens for rapid organic synthesis. Tetrahedron Lett 1986; 27:279-282.
10. Lew A, Krutzik PO, Hart ME, Chamberlin AR. Increasing rates of reaction: Microwave assisted organic synthesis for combinatorial chemistry. J Comb Chem 20024; 95-105.
11. De La Hoz A, Diaz-Ortiz A, Moreno A. Microwaves in organic synthesis. Thermal and non-thermal microwave effects. Chem Soc Rev 2005; 34:164-178.
12. Strauss CR, Trainor RW. Developments in microwave assisted organic chemistry. Aust J Chem 1995; 48:1665-1692.
13. Giguere RJ, Bray TL, Duncan SM, Majetich G. Application of commercial microwave ovens to organic synthesis. Tetrahedron Lett 1986; 27:4945-4958.
14. Kappe CO. Controlled microwave heating in modern organic synthesis. Angew Chem Int Ed Engl 2004; 43:6250-6284.
15. Coterill IC, Usyatinsky AY, Arnold JM et al. Microwave assisted combinatorial chemistry: synthesis of substituted pyridines. Tetrahedron Lett 1998; 39:1117-1120.
16. Nuchter M, Ondruschka B. Tools for microwave assisted parallel synthesis and combinatorial chemistry. Mol Diversity 2003; 7:253-264.
17. Kappe CO, Kumar D, Varma RS. Microwave assisted high speed parallel synthesis of 4-aryl-3,4-dihydropyrimidine-2(1*H*)-ones using solventless Biginelli condensation protocol. Synthesis 1999; 10:1799-1803.
18. Brain CT, Paul JM, Loong Y, Oakley PJ. Novel procedure for the synthesis of 1,3,4-oxadiazoles from 1,2-acylhydrazines using polymer supported Burgess reagent under microwave conditions. Tetrahedron Lett 1999; 40:3275-3278.
19. Kidwai M, Kumar K, Kumar P. Microwave induced stereoselective synthesis and antibacterial activity of β-lactams. J Indian Chem Soc 1998; 75:102-103.
20. Kidwai M, Bhushan KR, Sapra P, Saxena RK, Gupta R. Alumina supported synthesis of antibacterial of antibacterial quinolines using microwaves. Bioorg Med Chem 2000; 8:69-72.
21. Kidwai M, Misra P, Bhusan KR, Saxsena RK, Singh M. Microwave assisted solid-phase synthesis of cephalosporin derivatives with antibacterial activity. Monatsh Chem 2000; 131:937-943.
22. Jnaneshwara GK, Bedekar AV, Deshpande VH. Microwave assisted preparation of isatins and synthesis of (+)-convolutamydine-A. Synth Commun 1999; 29:3627-3633.
23. Baxendale IR, Ley SV. Polymer supported reagents for multistep organic synthesis: application to the synthesis of sildenafil. Bioorg Med Chem Lett 2000; 10:1883-1986.
24. Gardner MJ et al. Genome sequence of the human malaria parasite *Plasmodium falciparum*. Nature 2002; 419:498-511.
25. Banerjee R et al. Four plasmepsins are active in the *Plasmodium falciparum* food vacuole, including a protease with an active site histidine. Proc Natl Acad Sci USA 2002; 99:990-995.
26. Takano S et al. Racemization of (-)-vincadifformine using a microwave oven. Chem Lett 1989; 1:87-88.
27. Vromans H. Microwave drying of pharmaceutical excipients: comparison with conventional conductive drying. Eur J Pharm Biopharm 1994; 40(5):333-336.
28. Doelling MK, Nash RA. The development of a microwave Fluid Bed Processor. II. Drying

Performance and microwave physical characteristics of Typical Pharmaceutical granulations. Pharm Res 1992; 9(11):1493-1501.
29. Duschler G, Carius W, Bauer KH. Single-Step Granulation Method with Microwaves: Preliminary Studies and Pilot Scale Results. Drug Dev Ind Pharm 1995; 21(14):1599-1610.
30. Stahl H, Van Vaerenbergh G. Single-pot processing. In: Parikh DM (Ed.), Handbook of Pharmaceutical Granulation Technology. London: Taylor and Francis Group; 2005, 311-331.
31. Jones PL, Rowley AT. Dielectric drying. Dry Technol. 1996; 14:1063-1098.
32. Sanga E, Mujumdar AS, Raghavan GSV. Microwave drying: principles and application. In: Mujumdar AS, Suvachittanont S (Eds.), Developments in Drying. Bangkok:Kasetsart University Press; 2000, 112-141.
33. Jansen W, Van der Wekken B. Modelling of dielectrically assisted drying. J Microwave Power EE. 1991; 26:227-236.
34. McLoughlin CM, McMinn WA, Magee TRA. Microwave drying of pharmaceutical powders. Food Bioprod Process 2000; 78:90-96.
35. Acarturk F, Takka S. Calcium alginate microparticles for oral administration: II effect of form ulation factors on drug release and drug entrapment efficiency. J Microencapsulation 1999; 16(3):291-301.
36. Chan LW, Heng PWS. Effects of aldehydes and methods of cross-linking on properties of calcium alginate microspheres prepared by emulsification. Biomaterials 2002; 23:1319-1326.
37. El-Gibaly I. Oral delayed-release system based on Zn-pectinate gel (ZPG) microparticles as an alternative carrier to calcium pectinate beads for colonic drug delivery. Int J Pharm 2002; 232:199-211.
38. Murata Y, Miyashita M, Kofuji K, Miyamoto E, Kawashima S. Drug release properties of a gel bead prepared with pectin and hydrolysate. J Control Release 2004; 95:61-66.
39. Wong TW, Lee HY, Chan LW, Heng PWS. Release characteristics of pectin microspheres prepared by an emulsification technique. J Microencapsulation 2002; 19(4):511-522.
40. Wong TW, Lee HY, Chan LW, Heng PWS. Drug release properties of pectinate microspheres prepared by emulsification method. Int J Pharm 2002; 242:233-237.
41. Fundueanu G, Esposito E, Mihai D et al. Preparation and characterization of Ca-alginate microspheres by a new emulsification method. Int J Pharm 1998; 170:11-21.
42. Liu P, Krishnan TR. Alginate–Pectin–Poly-L-lysine Particulate as a Potential Controlled Release Formulation. J Pharm Pharmacol 1999; 51:141-149.
43. Takka S, Acarturk F. Calcium alginate microparticles for oral administration: I: effect of sodium alginate type on drug release and drug entrapment efficiency. J Microencapsulation 1999; 16:275-290.
44. Wong TW, Nurjaya S. Effect of microwave on drug release properties of matrices of pectin. Carbohydr Polym 2005; 62:245-257.
45. Wong TW, Chan LW, Kho SB, Heng PWS. Design of controlled-release solid dosage forms of alginate and chitosan using microwave. J Control Release 2002; 84:99-114.
46. Digenis GA, Gold T, Shah VP. Cross-linking of gelatin capsules and its relevance to their in vitro – in vivo performance. J Pharm Sci 1994; 83:915– 921.
47. Yannas IV, Tobolsky AV. Cross-linking of Gelatine by Dehydration. Nature 1967; 215:509.
48. Welz MM, Ofiner III CM. Examination of self-crosslinked gelatin as a hydrogel for controlled release. J Pharm Sci 1992; 81:85-90.
49. Vandelli MA, Romagnoli M, Monti A et al. Microwave-treated gelatin microspheres as drug delivery system. J Control Release 2004; 96:67-84.
50. Huang J, Wigent RJ, Bentzley CM. Nifedipine solid dispersion in microparticles of ammonio methacrylate copolymer and ethylcellulose binary blend for controlled drug delivery: Effect of drug loading on release kinetics. Int J Pharm 2006; 319:44-54.
51. Kim EJ, Chun MK, Jang JS et al. Preparation of a solid dispersion of felodipine using a solvent wetting method. Eur J Pharm Biopharm 2006; 64:200-205.
52. Gupta MK, Boner RH, Goldman D et al. Mechanism for Further Enhancement in Drug Dissolution from Solid-Dispersion Granules upon Storage. Pharm Dev Technol 2002; 7(1):103-112.
53. Craig DQM. The mechanisms of drug release from solid dispersions in water-soluble polymers. Int J Pharm 2002; 231:131-144.
54. Kerc J, Srcic S, Kofler B. Alternative solvent-free preparation method for Felodipine surface solid dispersion. Drug Dev Ind Pharm 1998; 24(4): 359-363.
55. Bergese P, Colombo I, Gervasoni D, Depero LE. Microwave generated nanocomposites for making insoluble drugs soluble. Mater Sci Eng C 2003; 23:791-795.
56. Moneghini M, Bellich B, Baxa P, Princivalle F. Microwave generated solid dispersions containing Ibuprofen. Int J Pharm 2008; 361:125-130.
57. Gohel, MC, Patel KV. Formulation Optimization of Diltiazem Hydrochloride Matrix Tablets Containing Modified Ispaghula Husk Using Factorial Design. Drug Dev Ind Pharm 1997; 23(11):1055-1061.
58. Joshi HN, Kral MA, Topp EM. Microwave drying of aqueous tablet film coatings: a study on free films. Int J Pharm 1989; 51:19-25.
59. Mandal V, Mohan Y, Hemalatha S. Microwave assisted extraction: an innovative and promising extraction tool for medicinal plant research. Phcog rev 2007; 1:7-18.

60. Parkes GMB, Barnes PA, Charsley EL, Bond G. Microwave differential thermal analysis in the investigation of thermal transitions in materials. Anal Chem 1999; 71:5026 -5032.
61. Luque-Garcia JL, Luque de Castro MD. Where is microwave-based analytical equipment for solid sample pre-treatment going? TrAC Trends in Analytical Chemistry 2003; 22:90-98.
62. Kubrakova IV. Microwave radiation in analytical chemistry: the scope and prospects for application. Russ Chem Rev 2002; 71:283-294.
63. Boon ME et al. A practical approach to routine immunostaining of paraffin sections in the microwave oven. Histochem J 1990; 22:347-352.
64. Pivonka DE, Empfield JR. Real time *in situ* Raman analysis of microwave assisted organic reactions. Appl Spect 2004; 58:41-46.

*****