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Microwave Technology - A Potential Tool in Pharmaceutical Science

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Abstract: Recently Microwave is exhibiting good potential tools in the field of Pharmaceutical science. In the present review an attempt was made to focus on what is microwave, how is it generated and what importance may it have. Microwave radiation, an electromagnetic radiation, is widely use as a source of heating in organic synthesis Microwaves have enough momentum to activate reaction mixture to cross energy barrier and complete the reaction. The basic mechanisms observed in microwave assisted synthesis are dipolar polarization and conduction. The benefits of microwave synthesis including increasing speed, yield and clear chemistry with decreasing time, have provided the momentum for many chemists to switch from traditional heating method to microwave assisted chemistry. The present review highlights the current scenario of microwave technology in pharmaceutical sector.
Keywords: Microwave, electromagnetic radiation, dipolar polarisation, conduction, Application in pharmaceutical science.

Introduction

A microwave 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 [1]. Wavelengths between 1 cm and 25 cm are extensively used for RADAR transmissions and remaining wavelength range is used for telecommunications. [2].
Two main effects of microwave irradiation on meter are distinguished [2]

1. Thermal effects results from dipolar polarization and ionic conduction.
2. Electrostatic polar effects which lead to dipole-dipole-type interactions between the dipolar molecules and the charges in electric field. In this way, more polar states appear to be more stable in the electric field. This phenomenon could be the origin of specific non-thermal microwave effects.

The electric component causes heating by two mechanisms [2, 3]

⇒ Dipolar polarisation
⇒ Ionic conduction

Microwave frequency bands

Microwave irradiation consists in electromagnetic wave in the range 300 MHz to 300 GHz that corresponds to wavelengths of 1 cm to 1 m. The microwave region of the electromagnetic spectrum lies between infrared and radio frequencies. [5, 6]

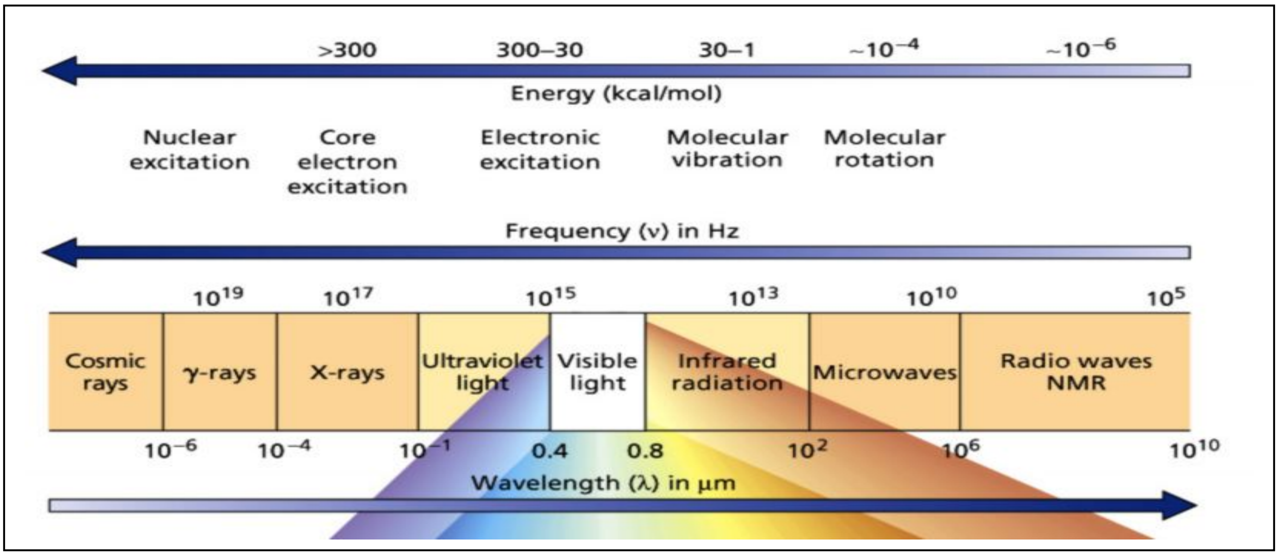

Fig.1. Range of frequencies of electromagnetic radiation [3]

Advantages [9, 10, 11]

Microwave include following advantages, over the conventional heating.

- ✓ Uniform heating occurs throughout the material as opposed to surface and conventional heating process.
- ✓ Process speed is increased.
- ✓ Desirable chemical and physical effects are produced.
- ✓ Floor space requirements are decreased.
- ✓ Better and more rapid process control is achieved
- ✓ In certain cases selective heating occurs which may significantly increase efficiency and decrease operating cost.
- ✓ High efficiency of heating,
- ✓ Reduction in unwanted side reaction (reaction Quenching),
- ✓ Purity in final product,
- ✓ Improve reproducibility
- ✓ Environmental heat loss is save
- ✓ Reduce wastage of heating reaction vessel
- ✓ Selective heating i.e. heating selectively one reaction component.
- ✓ Super heating: conventional heating is done from out side, therefore the core of solvent may be as much as 5ºC cooler than the edge, while in microwave, the core is 5ºC hotter than the outside, because of surface cooling, therefore in microwave, we can raise the boiling point of solvent by as much as 5ºC, an effect is known as super heating.

Tab.1. Difference between conventional and microwave assisted heating [10, 11]

Sr.No.	Conventional	Microwave
1	Reaction mixture heating proceeds from a surface usually inside surface of reaction vessels	Reaction mixture heating proceeds directly inside mixture
2	The vessel should be in physical contact with surface source that is at a higher temperature source (e.g. mental, oil bath, steam bath etc.)	No need of physical contact of reaction with the higher temperature source. While vessel is kept in microwave cavities.
3.	By thermal or electric source heating take place.	By electromagnetic wave heating take place.
4.	Heating mechanism involve- conduction	Heating mechanism involve- dielectric polarization and conduction
5.	Transfers of energy occur from the wall, surface of vessel, to the mixture and eventually to reacting species.	The core mixture is heated directly while surface (vessel wall) is source of loss of heat.
6.	In the conventional heating all the compound in mixture are heated equally	In microwave, specific component can be heated specifically
7.	Heating rate is less	Heating rate is several fold high
8.	In conventional heating, the highest temperature (for a open vessels) that can be achieved is limited by boiling point of particular mixture.	In microwave, the temperature of mixture can be raised more than its boiling point i.e. superheating take place.

Application of Microwave in Pharmaceutical Science

Microwave assists 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 [12]. The use of laboratory microwave ovens for organic extraction elevates sample preparation to the same level of sophistication as sample analysis. Shrishailappa Badami et al was also developed microwave assisted extraction technique to optimize the extraction of mucilages and pectins from several commonly used plant sources such as Fenugreek, Drum Stick, Asparagus, Mustard, Guava, Orange-peel and mango[13].Mattina et al. have applied Microwave assisted extraction to obtain taxanes from Taxus biomass [14]. It is now possible to speed up extraction, reduce costs, boost effectiveness, consistency and simplicity of reactions.

Advance Microwave extraction system

The ETHOS 1 is built to offer the highest performance and best safety features in the industry; it offers fast vessel heating together with homogeneous microwave distribution throughout the cavity. [15]

Microwave digestion

Microwave digestion is one of the standard sample preparation procedures for elemental determination in analytical chemistry. In closed microwave-transparent pressure vessels the samples are heated together with a suitable acid solution to temperatures that are typically between 200°C and 260°C so that the sample is completely degraded and dissolved. The great advantage of using a microwave field is the speed of heating the sample and the acid solution. However, the precise details of the heating process depend on the nature of the sample, its weight, etc. [15, 16]

Microwave in chemistry synthesis

Microwave synthesis has the potential to influence medicinal chemistry efforts in at least three major phases of the drug discovery process: generation of a discovery library; hit-to-lead efforts; and lead optimization. A common theme throughout all these processes is speed. Greater speed provides a competitive advantage, and allows for more efficient use of expensive and limited resources, faster exploration of structure–activity relationships (SARs), enhanced delineation of intellectual property and more timely delivery of crucially needed medicines [17]. In medicinal Chemistry – Biotage Emrys Creator EXP was developed a single mode microwave reactor for synthesis. The system is used for the efficient optimization of reaction conditions using microwave synthesis (sealed vessels, processing volume 0.5 - 20 mL, max pressure 20 bar, IR temperature sensor) [18] .

Microwave enhanced chemistry represents a fundamental step forward in the capabilities of synthetic chemists. Since its introduction, it has allowed to run reactions faster than ever before, with higher yields and reliably from milligrams to much larger quantities, without the need of reaction re-optimization. Milestone provides appropriate solutions also for many undergraduate laboratories, providing students with an in-depth view on the new advancements of the modern synthesis [19].

Advantage of microwave synthesis [19]

- Higher reaction temperatures can be obtained by combining rapid microwave heating with sealed-vessel (autoclave) technology
- In many instances significantly reduced reaction times, higher yields and cleaner reaction profiles will be experienced, allowing for more rapid reaction optimization and library synthesis.
- Solvents with lower boiling points can be used under pressure (closed vessel conditions) and be heated at temperatures considerably higher than their boiling point.
- Microwave heating allows direct 'in core' heating of the reaction mixture, which results in a faster and more even heating of the reaction mixture.
- Specific microwave effects that cannot be reproduced by conventional heating can be exploited — for example, the selective heating of strongly microwave-absorbing catalysts.
- Easy on-line control of temperature and pressure profiles is possible, which leads to more reproducible reaction conditions.
- Microwave heating is more energy efficient than classical oil-bath heating because of direct molecular heating and inverted temperature gradients.
- Can easily be adapted to automated sequential or parallel synthesis

Kidwai et al. have shown microwaves to be effective in the synthesis of the novel antibacterial β- lactams, quinolines and cephalosporin [20, 21, 22].

Ley and his group have discovered the convenient and efficient microwave synthesis of the well known commercially available important pharmaceutical drug sildenafil (ViagraTM) [23].

Also microwave technology has been applied for the synthesis of inhibitors of malerial proteases plasmepsin I and II (PlmI and PlmII, respectively). [24, 25]

Ashraf et al and his group have discovered that microwave irradiation can be used as a facile and general method for the construction of a variety of triazoloquinazolinones and benzimidazoquinazolinones [26].

Microwave in drying and sterilization

Microwave drying is new drying technology that shortens drying times, reduce drying defects, increase the potential for product innovation and provide a seamless integration into automated manufacturing systems. Therefore 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 [27].

Pharma-Micro - is a rotary vacuum microwave dryer and sterilizer [28]. Due to combination of vacuum and microwave heating Pharma-Micro provides high quality drying and sterilization of any substances and materials. Pharma-Micro provides high level of drying and sterilization at relatively low temperatures avoiding conventional drying problems:

- change of composition and structure of materials
- Undesired sintering, agglomeration and induratio.
- contamination of the products with combustion products of gas or oil .

Benefit of microwave drying [28]

- ✓ Can be used to dry very fine structures and large dimensions
- ✓ Provides reduced drying times
- ✓ Can easily be integrated into automated systems
- ✓ Lends itself to the development of new products
- ✓ Provides increased productivity and flexibility
- ✓ Reduces handling errors and production costs.

Microwave equipment is also used nowadays to measure the moisture content in the pharmaceuticals [29]. Online moisture can be detected for microwave vacuum dryer using Near Infrared Spectroscopy (NIS), though only if the moisture content of product is 6% or less. Thus, drying can be made continuous process with precise control of moisture [30]. The effect of drying on granular products, treated in microwave and conventional tray dryer was evaluated. It showed that loose and tapped bulk densities, percentage compressibility, hardness and dissolution time of granules prepared through microwave & conventional tray dryer were not significantly different ($p > 0.05$). Reduction in drying time was the only difference. This lack of shift of granule characteristics was noted as an added advantage [31]. Introduction of application of microwave for drying of pharmaceuticals led to its utility in single pot processes i.e. incorporating mixer granulator & dryer. In this method the process is continuous and faster, thus, reducing loss of product during change of processes. Therefore it helps in cost reduction & increase in annual yield, which was demonstrated by Glaxo (Evreux, France) [32, 33]. Solute migration is a usual problem faced when granulations are dried but certain data also suggests that microwave drying minimizes such migration [34]. When migrations were compared between fluidized, vacuum, infrared & microwave dryer, maximum migration was seen in infrared dryer, where as microwave and vacuum dryer showed good uniformity in comparison throughout the bed of material [35].

Advent of a new method i.e., microwave sterilization carries significance [36, 37]. The sterilization is brought about by microwave dielectric heating effect. The efficiency of microwave sterilizer was put to test via sterilization of two heat labile drugs, ascorbic acid & pyridoamine phosphate, both in solution form. The result showed that though reduction of bio-burden was equal to that of autoclaving, autoclaved drugs showed certain deteriorations in quality, which was not observed in microwave sterilized drugs. Therefore microwave was reported to be holding an upper hand over autoclave [38]. The validation requirement of microbicidal suitability of microwave created a need to find out biological indicator for microwave sterilization. Sasaki and the co-workers showed that sterilization effect of microwave is due to production of heat and there is no other non-thermal mechanism. This suggested that spores of Bacillus stearothermophilus are an appropriate biological indicator in validation of microwave sterilization [39]. Sterilization of vials was not affected regardless of its position in the sterilizer thus indicating uniform heating ability of the microwave [40]. A continuous microwave sterilizer (CMWS) has been developed [41]. The high temperature and short time sterilization by microwave heating in a CMWS were evaluated. Bacillus stearothermophilus spores were used as biological indicator [42]. The lethal effect of microwave sterilizer was equal to that of autoclave [43].

Remon et al investigated that a high-shear granulation system was used in combination with microwave drying in granulation process [44]. Colmbo et al have studied Effect of Residual Water Content on the Physico-Chemical Properties of Sucralfate Dried Gel Obtained by Microwave Drying [45] .Common pharmaceutical excipients and active ingredients, wetted with specific solvents, were dried in a combined microwave–convective system [46]

Microwave thawing

Thawing is process where freeze stored drugs brought to normal physiological temperature before administration especially if an injection. One of the methods for thawing is the use of microwave. Stability of majority of drug preparation was unaffected except for some preparations, thus providing criticism for microwave thawing. The stability of many drugs both physical and chemical was not affected after microwave thawing [47]. Microwave thawing reduced process cost as well as preparation time. G. J. Sewell, A. J. Palmer & P. J. Tidy showed the effect of infusion volume, infusion load size and microwave power on rate of thawing. Frozen infusions of 100-500 ml volume were thawed evenly and reproducibly without overheating. Linear relationships were demonstrated for microwave power output and thawing rate and for infusion load size and thawing time. It was noted that these relationships enable predetermination of microwave thawing times. On the basis of the results guidelines for this system were developed [48]. Microwave thawing also caused about 10% reduction in microbial count. Cloxacillin sodium, Flucloxacillin sodium and Ticarcillin disodium were reconstituted in 0.9% sodium chloride and in 5% dextrose solutions, stored frozen for up to 9 months, and stability of the antibiotics were assayed following microwave thawing [49,50] . All of them retained at least 90% of their original potency throughout the study period. However, Cloxacillin and Flucloxacillin in 5% dextrose showed a yellow discoloration after 6 months' storage. It was suggested that these 2 formulations not be stored for more than 3 months before use. The stability of intravenous Augmentin (Amoxycillin sodium and Clavulanate potassium) in a range of vehicles was investigated. Aqueous solutions frozen at –20 C and thawed by microwave radiation lost more activity than those stored at 25 C [51]. Intravenous Adriamycin (Doxorubicin hydrochloride) could not be thawed with microwave as it got overheated leading to decomposition of the drug. Thawing frozen solutions in a microwave oven adversely affected the stability of Cefuroxime sodium (Zinacef) in aqueous solutions, with or without phosphate buffer, and in 5% dextrose and 0.9% sodium chloride injections. Local sequestration of the antibiotic during freezing and that of heating rapidly to boiling may be the possible reason for degradation during microwave radiation [52]. It was observed that oligo-elements are unstable when stored at -20 C for 60 days and then thawing in a microwave oven. They must be added after defrosting the solution. The stability of 6 antibiotics in IV fluids in polyvinyl chloride (PVC) containers after freezing and microwave thawing were established [53].

Microwave used in pharmaceutical dosage form development

Application of microwave to prepare pharmaceutical dosage forms such as agglomerates, gel beads, microspheres [54], nanomatrix [55], solid dispersion [56], controlled release tablets formulation [60] and tablet film coating [57]. The microwave could induce drying, polymeric crosslinkages as well as drug-polymer interaction, and modify the structure of drug crystallites via its effects of heating and/or electromagnetic field on the dosage forms [57]. The use of microwave opens a new approach to control the physicochemical properties and drug delivery profiles of pharmaceutical dosage forms without the need for excessive heat, lengthy process or toxic reactants. Alternatively, the microwave can be utilized to process excipients prior to their use in the formulation of drug delivery systems [58]. The intended release characteristics of drugs in dosage forms can be met through modifying the physicochemical properties of excipients using the microwave. A new microwave-assisted method was used to prepare magnetic Fe_3O_4 particles and magnetic bovine albumin microsphere [59]. Wong et. al used microwave-treated water to increased the dissolution propensity of both hydrophilic and hydrophobic free drugs and drugs encapsulated in calcium cross linked alginate beads[60] . The first report to use microwave heating in the cross-linking of pharmaceutical carriers was made by Teng and Groves, who produced thermally denatured protein matrices useful as controlled-release systems. [60, 61]

Microwave in cancer therapy

The microwaves in the new technique heat--and kill--cells containing high amounts of water and ions, or electrically charged atoms. Cancer cells typically have a high content of both, while healthy tissue contains much less. The outpatient procedure uses a single tiny needle probe to sense and measure parameters during treatment. Side effects appear to be minimal. Microwave thermotherapy, also called microwave therapy, is a type of treatment in which body tissue is exposed to high temperatures to damage and kill cancer cells [64] or to make cancer cells more sensitive to the effects of radiation and certain anticancer drugs [62]. Microwave cancer therapy [63] in combination with radiotherapy was inferior compared to standard conventional radiotherapy with respect to disease control and survival for patients with breast cancer, lung cancer [65], lymphoma or prostate cancer.

Conclusion

In recent years, the use of microwave has becomes very attractive in the field of pharmaceutical science. Microwave technology offers several advantages over conventional heating method such as rapid volumetric heating, no over heating at surface, better and rapid process control, high heating efficiency, environmental heat loss can be avoided, energy saving, low operating cost and many more advantages. In today's competitive era microwave is one of the major tools for the rapid lead generation and optimization through which medicinal chemist will able to deliver critically need new chemical entities and candidate drug. Microwave also used in pharmaceutical drying that can change the drug release properties by polymeric cross linkages and drug interaction improves drug dissolution via modifying the structure of drug crystallites. Now a days microwave is also utilise in to the process drug delivery system such as gel beads, microsphere, agglomerate, nanomatrix, solid dispersion, tablet and film coating. The use of microwave open new route to control the physiochemical properties and drug delivery profiles of pharmaceutical dosage forms.

References

[1] Adam D.Microwave chemistry: out of kitchen. Nature 2003; 421:571.

[2] www.microwavetech.com/thero_ba

[3] www.microwave101.com/encyclopedia.

[4] Gabriel C.,Gabriel S., Grant, EH., Halstead, BS. & Mingos, DM. Dielectric parameters relevant to microwave dielectric heating, Chem. Soc. Rev. *1990;* 27:213–223.

[5] Lauf RJ, Bible DW, Johnson AC, Everliegh CA., 2–18 GHz broadband microwave heating systems. Microwave Journal 1993; 36(11):24–27.

[6] www.tpub.com

[7] Lucisano LJ, Poska RP. Microwave technology-fad or future, Pharm. Technol. 1998; 38:40 -42.

[8] Lucisano LJ, Poska RP. Microwave reflections - The status of technology, Pharm. Technol. 1997; 110:114-115.

[9] Honda K, Ebara T, Iijima K, Shimizu K, Miyake Y. Development of practical application of high frequency wave (microwave) continuous Sterilizer, *Eur. J. Parenter. Sci*. 1998; 3 (2): 39 - 47.

[10] Gedye RN, Smith F, Westaway K, Ali H, Baldisiera L. *Tetrahedron Lett*. 1986;27:279-282.

[11] Dwivedi S, Dubey R, Dwivedi A, Kaul S, Gupta P. Microwave Synthesis: A recent advancements in the field of synthetic chemistry, *Pharma Chem*. 2009; 10-14.

[12] 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.

[13] Shrishailappa B, Geethaa.B, Shivalinge G, Kulkarnia G. Microwave Assisted Fast Extraction of Mucilages and Pectins.Indian J.Pharm. Educ. Res. 2009; 43(3):260-265.

[14] Mattina NJ, Berges WA, Denson CL Microwave assisted extraction of taxanes from Taxus biomass. J Agric Food Chem. 1997; 45: 4691-4696.

[15] www.milestonesci.com

[16] www.berghof-instrument.de
[17] Brittany LH. Recent Advances in Microwave-Assisted Synthesis, Aldrichimica Acta. 2004; 37(2):66-76.
[18] www.biotage.com
[19] Mats L, Anders H.,Microwave-assisted high-speed chemistry: a new technique in drug discovery, Drug Delivery Technology. 2001; 6:406-416.
[20] Kidwai M, Kumar K, Kumar P. Microwave induced stereoselective synthesis and antibacterial activity of β-lactams. J Indian Chem Soc. 1998; 75:102-103.
[21] Kidwai M, Bhushan K, Sapra P, Saxena R, Gupta R. Alumina supported synthesis of antibacterial of antibacterial quinolines using microwaves. Bioorg Med Chem. 2000; 8:69-72.
[22] 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.
[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] Ashraf A. Aboul F, Mourad E, Hassan H, Eman A. Microwave assisted synthesis of triazoloquinazolinones and benzimidazoquinazolinones, Beilstein Journal of Organic Chemistry. 2007; 3: 11.
[27] McLoughlin CM, McMinn WA, Magee TR. Microwave drying of pharmaceutical powders. Food Bioprod Process 2000; 78:90-96.
[28] www.microwavetech.com/pharmamicro.php
[29] Bremecker K.Moisture Content Measurement in Pharmaceutical Products by Microwaves Pharm. Ind. 1983; 45 (1), 78 – 81.
[30] White J. On Line Moisture Detection for a Microwave Vacuum Dryer Pharm. Res. 1994; 11 (5):728 -732.
[31] Mandal TK. Evaluation of microwave drying for Pharmaceutical granulations, Drug Dev. Ind. Pharm. 1994; 21, 1683 – 1688.
[32] Pearlswing DM, Robin P, Lucisano L., Simulation modeling applied to the development of a single pot process using microwave/vacuum drying, Pharm. Technol. 1994; 44-60.
[33] Pearlswing DM, Robin P, Lucisano L. Rationale for selection of single-Pot manufacturing process using microwave/vacuum drying , Pharm. Technol. 1994; 28-36.
[34] Birderman A. Grolier Academic Encyclopedia, Grolier International, USA, 1987; 18: 299.
[35] Duschler G, Carius W, Bauer K. Single step granulation method with microwaves: - Preliminary studies & pilot scale Results Drug Dev. Ind. Pharm. 1995; 21 (14): 1599 –1610.
[36] Honda K, Ebara T, Iijima K, Shimizu K, Miyake Y. Development of practical application of high frequency wave (microwave) continuous Sterilizer, Eur. J. Parenter. Sci. 1998; 3 (2): 39 - 47.
[37] Sasaki K, Fukumura M, Miyake Y. Application of high frequency wave (microwave) Sterilization to Pharmaceutical Preparations, Eur. J. Parenter. Sci. 1998; 3(3): 73 – 84.
[38] Sasaki K, Honda W, Ohsawa S, Miyake Y, Kawashima Y. Study of microwave sterilizer for injection ampoules. Part 4 Application to sterilization of thermally liable drug solutions, Arch. Pract. Pharm. Yakuzaigaku. 1998; 58 (3): 125 –135.
[39] Sasaki K, Mori Y, Honda W, Miyake Y. Selection of biological indicator for validating microwave heating sterilization, PDA J Pharm Sci Technol. 1998; 52:60 – 65.
[40] Lohmann S, Manique F. Microwave sterilization of vials, Bull. Parenter. Drug. Assoc. 1986; 40:25 - 30.
[41] Sasaki K, Honda W, Iijima K, Ehara T, Okuzawa K, Miyake Y., Microwave continuous sterilization of injection ampoules, J. Pharm. Sci. 1996; 50:172
[42] Sasaki K, Honda W, Miyake Y.,Evaluation of high temperature and short-time sterilization of injection ampoules by microwave heating, PDA. J. Pharm. Sci. 1998; 52:5-12.
[43] Wong TW, Skhandar A, Kamal M, Jumi N, Kamarudin N, Mohamad Z., Effects of Microwave on Water and Its Influence on Drug Dissolution; Progress in Electromagnetics Research C. 2009; 11:121-136
[44] Kiekens F, Remon J., Influence of Chopper and Mixer Speeds and Microwave Power Level during the High-Shear Granulation Process on the Final Granule Characteristics Drug Development and Industrial Pharmacy, 1999; 25(12):1289–1293.
[45] Gainotti A, Losi E, Bettini R, Colombo P, Sonvico F, Baroni D, Santi, Colombo G.,Effect of Residual Water Content on the Physico-Chemical Properties of Sucralfate Dried Gel Obtained by Microwave Drying Drug Development and Industrial Pharmacy. 2005; 31:645–652.
[46] McMinnT W, McLoughlin CM, Magee TM., Microwave–convective drying characteristics of pharmaceutical, powders, Powder Technology. 2005; 153:23– 33
[47] Thomas PH, Tredree RL, Barnett MI., Preliminary studies on the freezing and thawing of

intravenous solutions, Br. J. Intravenous. Ther. 1983; 14, 15, 18, 20, 21.
[48] Tidy PJ, Sewell GJ, Jefferies TM. , Microwave freeze-thaw studies on Azlocillin infusion Pharm. J. 1988; 241: R22-R23.
[49] Vigneron J, Laurelli F, Phaypradith S, Hoffman M., Freezing of solutions for parenteral use: advantages and drawbacks-nine months experiment in the hospital pharmacy of Nancy, J. Pharm. Belg. 1992; 47: 504 –522.
[50] Ashwin J, Lynn B, Taskis C., Stability and administration of intravenous Augmentin, Pharm. J. 1987; 238:116 -118.
[51] Williamson M, Luce J., Microwave thawing of doxorubicin hydrochloride admixtures not recommended, Am. J. Hosp. Pharm. 1987; 44: 505 - 510.
[52] Gupta VD, Stewart KR., Stability of Cefuroxime sodium in some aqueous buffered solutions and intravenous admixtures , J. Clin. Hosp. Pharm. 1986; 11: 47-54.
[53] Tabor E, Norton R., Freezing and rapid thawing of antibiotic admixtures, Am. J. Hosp. Pharm. 1985; 42: 1507-1508.
[54] Vandalize MA, Romagnoli M, Monti A., Microwave-treated gelatin microspheres as drug delivery system., J Control Release. 2004; 96:67-84.
[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 buprofen., Int J Pharm. 2008; 361:125-130.
[57] 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.
[58] Wong TW. Use of Microwave in Processing of Drug Delivery Systems, Current Drug Delivery. 2008; 5:77-84
[59] Pawan C, Patidar H. Magnetic microsphere: as targeted drug delivery, Journal of Pharmacy Research. 2009; 2(5):964-966.
[60] Teng CD, Groves MJ. Microwave thermal denaturation of protein matrices as controlled release devices. J Control Release. 1990; 13:43-49.
[61] Rani J. The Effect of Microwave Thermal Denaturation on Release Properties of Bovine Serum Albumin and Gluten Matrices, AAPS PharmSciTech.2006; 7 (1):15
[62] www.righthealth.com/cysts
[63] Dr. John holt., Review of hot microwave cancer therapy, Commonwealth government of Australia, Sep 2005 (www.cancertreatmentwatch.org)
[64] Surgeons use microwave technology to destroy tumors, Science daily.feb-2009. (www.sciencedaily.com)
[65] New microwave technology can be safely applied to cancerous lung tumors, Science daily.nov-2007. (www.sciencedaily.com)

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