

**APPLICATIONS OF SONOCHEMISTRY IN DRUG DELIVERY AND FORMULATIONS: A
REVIEW**Mittal Darji¹, Rahul Lalge^{1*}, Adwait Pradhan¹¹Department of Pharmaceutical Sciences and Technology, Institute of Chemical Technology, Mumbai,
Maharashtra, India

ABSTRACT: Sonochemistry is the branch of science which deals with passage of ultrasonic waves to enhance or alter chemical reactions. The use of ultrasound in chemical reactions in solution provides specific activation based on a physical phenomenon: acoustic cavitation. The range from 20 kHz to around 1 MHz is used in sonochemistry whereas frequencies far above 1 MHz are used as medical and diagnostic ultrasound. Ultrasonic waves induce chemical effects on the reaction system, such as generation of free radicals which augment the rate of reaction. Besides this, ultrasound may have other mechanical effects on the reaction system, such as increasing the surface area between the reactants, accelerating dissolution rate. This review elucidates several applications of sonochemistry in the pharmaceutical industry including sonophoresis, sonocrystallization, lowering extraction time, solution atomization and crystallization by sonication, melt sonocrystallization and particle rounding technology. This review also gives an idea about the applications of sonocrystallization in formation of aerosols, enhancing inhalation drug delivery and sonochemical preparation of biomaterials. Its significance in transdermal drug delivery, chemotherapy and cell therapy is also discussed herewith. It has been proved that ultrasound can be effectively used for treatment of sewage sludge and degradation of dangerous chemicals including chlorinated hydrocarbons, aromatic compounds, agrochemicals and pesticides from the agricultural industry, explosives, dyes from the textile industry and surfactants etc. The purpose of this review paper is to put forth the information available in the literature so as to promote further research in the field of sonochemistry.

Key Words: Sonochemistry, ultrasound, acoustic cavitation, sonophoresis, sonocrystallization, sonication, chemotherapy

INTRODUCTION

Although the use of ultrasound as the primary means of stimulating chemical reactions and processes has been known for many years, this safe form of irradiation has become increasingly popular during the last two decades along with the emergence of other stimulating techniques (e.g., microwaves, photochemistry, electrochemistry, or high pressure) in the search for more environmentally benign conditions. Large rate enhancements and selectivities are usually observed and represent the most important pluses. The interaction of sound waves with matter is far from being trivial, though a rather reductionist approach points to effects related to both piezo- and thermochemistries. Sonochemistry is a branch of science that deals with the chemical and mechanical effects of ultrasound. This irradiation appears to be more general than other activation techniques as the system requires essentially an ultrasound source and a liquid (either aqueous or organic), which contrasts with specific requirements in electrochemistry (conducting media), microwaves (polar media or species/ions), photochemistry (presence of chromophores), or supercritical conditions (elevated pressure or temperature in closed systems). Ultrasound-assisted chemistry is generally associated with a series of key characteristics such as safety, energy savings, use of ambient conditions, waste prevention, and improved mass transfer, among others.

The greenness of sonochemistry like other activation techniques, should however be assessed with care and from a critical point of view. If one uses either microwaves or ultrasound with toxic reagents and the subsequent separation and purification steps require the extensive use of volatile organic solvents, the whole protocol is not green at all. Clearly, the benefits associated with a safer technique disappear. Sound consists of pressure waves transmitted through a channel (solid, liquid or gas) as series of compression and expansion. Newton paid attention to sound propagation and was probably the first to describe the relationships between the speed of sound and measurable properties of the medium such as density and pressure. In his Principia, Newton postulated that the speed of sound is equal to the square root of the ratio between the elastic force and the density of the propagation medium. This assumption, however, gives rise to inaccurate estimates (lower than experimental values). Sound propagation is not an isothermal process, but rather adiabatic, a fact that could only be proved in the nineteenth century with the advent of thermodynamics. The reason is that propagation does not allow enough time for heat exchange to occur between the compression and rarefaction zones of the sound wave; approximately isothermal processes will only occur at the boundary layer to a surface. Humans can sense these pressure waves through their ears if frequencies lie in the range of 10 Hz to approximately 18 kHz. These frequencies are similar to those of low-frequency radio waves; however, sound is markedly different to electromagnetic radiation and lacks a quantum nature. Although sound transmission causes some excitation in the medium, in the format of intensified molecular movement, appreciable effects of interest in chemistry and other applied sciences require higher frequencies with threshold intensity. Ultrasound has therefore frequencies beyond human hearing, i.e., above 18 kHz. For comparative purposes, one can speak of the sound spectrum covering a range of frequencies in which audible sound occurs in a narrow region between infrasound (just below 10 Hz) and ultrasound irradiation, the latter being the subject of interest to sonochemists.

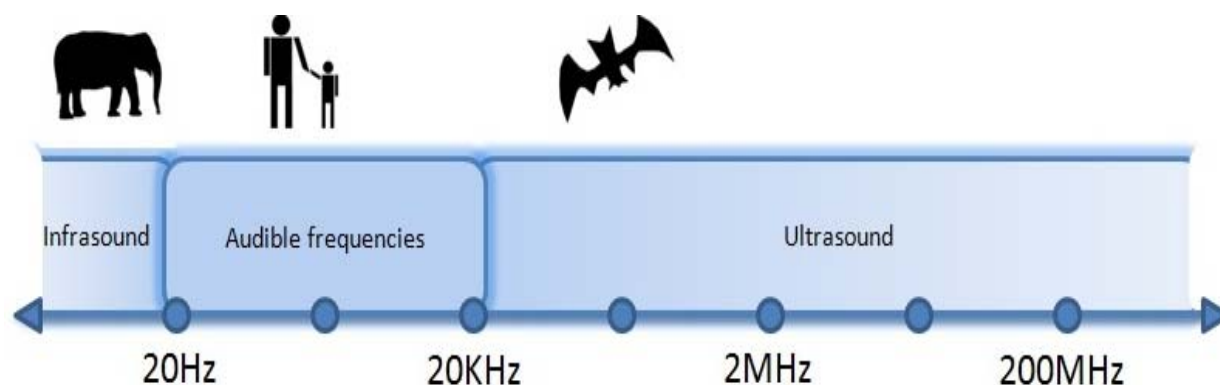


Figure 1: Sound frequencies (scale in Hz)

It is customary to divide ultrasound into two regions: conventional power ultrasound, up to 100 kHz, as most devices usually operate within such frequencies and diagnostic ultrasound, from about 1–10 MHz (Figure 2). The latter, which possess much shorter wavelengths and hence better resolution in detecting phase changes, is used in medicine (echography) for fetal and soft-tissue imaging. Provided that the ultrasonic intensity is sufficiently low, the irradiation causes no harmful effects and represents the ideal choice in the early stages of pregnancy. Fetal echoes are obtainable many weeks before the fetus skeleton is visible by x-rays.

Pharmaceutics is a discipline of pharmacy that deals with all facets of the process to turn new chemical entity into appropriate medication. Pharmaceutics is concerned with the development of a pure substance into dosage form such as tablet, capsule, suppository, nasal spray, injection, lozenges liniment cream, ointment, eye drop, inhaler, etc. Pharmaceuticals are vital to health systems; they can complement other types of health care services to reduce morbidity and mortality rates and ameliorate the standard of living. Pharmaceuticals cannot be considered mere ordinary commodities or even basic health stimuli as they have curative and therapeutic qualities. This article is intended mainly to review the application of ultrasound in the field of pharmaceutics, from drug dispensation, formulation, to its delivery. It also spots various related factors encompassing their diverse processes. Numerous domains have been explored for their great prospective for future development e.g., crystallization, enhanced drug delivery, drying, conducive in polymerization and de-polymerization, extraction, chemotherapy, filtration, cell therapy, homogenization and synthesis.

Sonocrystallization

Crystallization is an omnipresent operation for manufacture of fine chemicals, pharmaceuticals or intermediates whether derived from chemical or biochemical processing. Nucleation and crystallization can be mediated by acoustic cavitation and streaming (Graham Rucroft, et al. 2005) Sonocrystallization is mediated by the bubbles caused by such acoustic effects. These bubbles are transient microreactors that facilitate faster chemical reaction and crystallization. In effect significant energy is transferred to molecules suspended or in solution over a very short time. Sonocrystallization is involved in one or all of the crucial steps in the nucleation and crystallization process. The sonocrystallization process involves:

- Improved mass transport which improves clustering and templating
- Rapid cooling after cavitation collapse
- Transient high supersaturation close to the collapsing bubble
- Pressure increases reducing the temperature for crystallization
- Shock waves to assist in nucleation
- Overcoming energy barriers for nucleation

Mechanism of Sonocrystallization

A widely used explanation is the so-called “hot spot” theory, which attributes nucleation to local hot spots, created by the concentration of kinetic energy in the collapsing cavity or due to rapid cooling afterwards. Local temperatures in excess of 5000 K in the gas phase and 2000 K in the liquid phase have been reported due to hotspots. Heat dissipation happens within 2 μm , so cooling rates are of the order of 10⁹ K/s. Another popular mechanism is based on the fact that the pressure shockwave caused by cavity collapse creates locally high pressures. There are substances for which the solubility reduces with pressure, this increases the local supersaturation and could induce nucleation. A hypothesis related to the shockwave effect states that nucleation is initiated due to segregation of the solute and solvent near the bubble wall. This is caused by high pressures occurring in the ultimate phase of bubble collapse. Yet another series of hypotheses suggest that nucleation occurs during bubble expansion. Solvent evaporating into the bubble or cooling of the liquid interface layer increases local supersaturation, which could lead to nucleation around the cavity. Also of interest is the electrical theory, which proposes the consequences of cavitation are caused by electrical charges on the cavity interface layer.

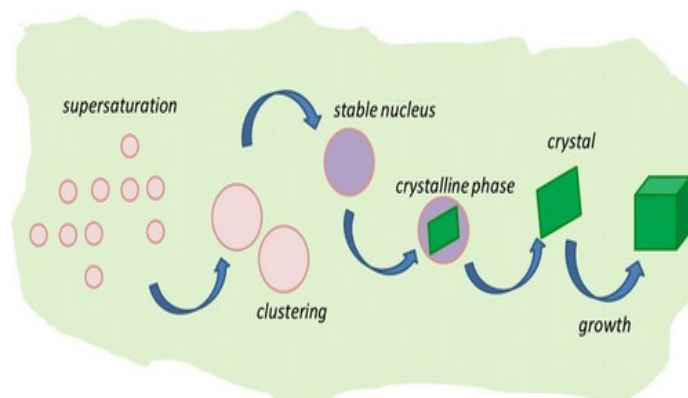


Figure 2: Crystal growth

Sonocrystallization can be used mundanely for polymorph control, improving crystal-size distribution and morphology, reducing impurities, and superior solid-liquid separation. Moreover it can help in augmenting secondary nucleation by disrupting crystals or agglomerates. Significantly, sonocrystallization is a viable manufacturing option whether for continuous flow mode, batch mode or for in-situ generation of seed crystals. Crystallization of drug actives and intermediates is a ubiquitous process for removal of impurities and procuring a suitable solid-state form in readiness for formulation and milling. Generally it is straightforward but quite often it can be a troubling process step. Crystallization processes include cooling, evaporative, anti-solvent and salt formation variants to name but a few. A key challenge in pharmaceutical active crystallization is manufacturing the desired solid form with the desired chemical and physical properties.

- Produce a metastable crystalline form
- Focus on stable crystalline form
- Opportunities for amorphous drug product
- Manufacture the right size particle in principal manufacture
- Optimize crystallization yield.

Crystallization is processing in pharmaceutical and pharmaceutical intermediate manufacturing and involves the cycles of crystal nucleation and crystal growth. Balancing these fundamental steps is critical if one is to control a crystallization method in order to deliver consistent product. There are various reliable processes to help reliably form seed crystals in classical batch crystallization, thus enabling control of crystal size distribution, morphological control, elimination of impurities in the crystal and enhanced solid-liquid separation behaviour. For example adding finely divided (micronized) seed crystals can be applied at any prevailing supersaturation in a batch crystallization process and continued as appropriate to deliver the desired particle distribution or polymorph. At high supersaturation indiscriminate nucleation can occur, often at the expense of crystal growth, leading to troublesome processing. Carefully controlling a crystallization process can add significant value-added benefits that are capitalized through new process patents that can be created for individual products, thus securing and extending marketing timescales. A number of controls can be applied in secondary manufacture of pharmaceutical ingredients and lend themselves to polymorphic systems. By controlling nucleation, we can take control of and improve crystal size distribution, morphology, impurities, polymorphism, bulk density and solid-liquid separation. Mechanical disruption techniques can also induce secondary nucleation by mechanically disrupting crystals or loosely bound agglomerates. A number of techniques can be applied at any stage in a pharmaceutical product pipeline from discovery through to process optimization / manufacture and formulation / drug delivery. The techniques can be used in early laboratory studies through to full industrialization.

Melt Sonocrystallization

Melt Sonocrystallization is a particle engineering technique involving the application of ultrasonic energy to the soft or viscous molten mass, dispersed in immiscible liquid (Vikram Deshmukh, et al. 2013). In other words, solidification/crystallization from emulsified melt is carried out under the influence of ultrasonic energy. This technique was initially developed for development of sintered crystals and porous glassy beads. The extent of ultrasound energy received by the melt in the emulsified state determines properties of the resultant particles, which is dependent on ultrasound energy input and solidification rate of the melt. The rate of solidification depends on glass transition temperature of the material and temperature of the medium. Application of ultrasound at temperatures above transition temperature has shown to favor crystallization, whereas processing below transition temperature results in amorphous state. The mechanical stress due to sonication results in sintered crystals or porous beads. The porous nature and potential for producing crystalline as well as amorphous particles offers flexibility to the technology and is looked upon for improvement of solubility of poorly soluble pharmaceuticals.

Particle Rounding Technology

Particle rounding technology includes suspending the starting material in a liquid, which is a partial solvent, and applying ultrasonic vibrations to the suspension, whereby the starting material is shaped and ground to produce a final suspension of ground and rounded particles. Particle rounding technology was invented by Armament Development Authority in Israel for shaping of explosives. In heterogeneous solid-liquid systems, the interface produces a perturbation in the sonic field, which induces an asymmetric collapse of the cavitation bubbles. At extended interfaces several times larger than the resonance cavitation size, the result is a microjet of liquid passing through the cavitation that impinges with the solid surface at velocities estimated around 100 m s⁻¹. This phenomenon is the origin of the erosion effect and used for ultrasonic shaping and surface modification. The technology is applied for shaping of drugs and excipients. The main benefits of particle rounding technology include:

Improved packing density of powders, enhanced flow of powders, reduced electrostatic charges, manufacturing by direct compression of material without granulation, and higher filler loading in composite pastes. Well-defined rounded particles with improved flow of oxcarbazepine (antiepileptic API with rod like crystals), diltiazem HCl (antihypertensive API), and metformin (an oral type 2 antidiabetic drug, which do not flow at all) are developed. This technology is applied to improve compressibility of fructose. Rounded particles of lactose are developed for improved inhalation delivery.

Solution Atomization and Crystallization by Sonication

Solution atomization and crystallization by sonication (SAXS) technique was developed to produce active pharmaceutical ingredients with a narrow particle size distribution, centered around the optimum particle size for reproducible and maximized therapeutic efficacy. The SAXS process consists of three interdependent steps: (a) production of aerosol droplets of the solute from a carrier solvent using a suitable aerosol generator, (b) collection of the highly supersaturated droplets in a crystallization vessel containing a non-solvent of the drug, and (c) application of ultrasonic waves to a crystallization vessel to controllably induce homogeneous nucleation and crystal growth. By combining these steps and controlling relevant parameters, high-purity micron-sized sphere-like crystalline particles are produced. SAXS process involves rapid evaporation of solvent from micron-sized aerosol of a drug solution and production of highly supersaturated droplets of the solute molecules. These droplets are collected in a vessel. To enhance the kinetically limiting diffusion within the droplets, ultrasonic waves are concomitantly applied for nucleation and to minimize agglomeration, which improve the powder-handling properties of crystallized particles. Only on application of ultrasound does the droplets in the anti-solvent undergo nucleation and crystallization. Without ultrasound the particles solidify to semicrystalline and poorly defined particles. The major advantage of this technique relates to the use of any suitable aerosol generator, and that the whole process can be carried out under atmospheric pressure and ambient conditions. SAXS results in spherical crystalline particles within well-defined particle size range. It has the potential for batch and continuous processing at an industrial scale. The limitation of the method is the requirement of suitable organic solvent to dissolve the drug that undergoes evaporation at required rate.

Role of Ultrasound in Extraction

A rapid, sensitive and accurate method of ultrasonic extraction has been developed for nicotine in different pharmaceutical preparations (Yuegang Zuo, et al. 2004). The results indicate that ultrasound can be more precise tool for rapid extraction of nicotine in pharmaceutical preparations. The ultrasonic extraction can reduce the extraction time from 24 hours to less than 20 minutes as compared to the cold extraction technique. Solvent consumption is six times lower in ultrasonic extraction in contrast to similar conventional extraction methods.

Effect of Sonocrystallization in Formation of Aerosols

Sodium chloride aerosols have been widely used as part of bronchial provocation tests to identify people with active asthma and exercise-induced asthma and those who wish to enter particular occupations. Preparation of traditional nebulizers is energy intensive and time consuming. It can induce impurities into the desired product. It has disadvantages including inaccurate control of size of particles, undesired shape of the particle, surface and charge modifications and chemical degradation (Chan et al. 2003). Sonocrystallization offers several advantages including production of smaller sized crystal as compared to conventional crystallization as well as cost-effectiveness of apparatus. One more important advantage is that crystal growth occurs at lower supersaturation levels, where initial growth is controlled results in narrower size distribution of the product than uncontrolled crystallization process. Limitations of conventional crystallization techniques can be overcome by the technique of micronization.

Applications of Ultrasound in Transdermal Drug Delivery: Sonophoresis

Transdermal drug delivery offers several advantages over oral delivery and intravenous drug delivery. Main advantages of transdermal drug delivery are avoidance of first-pass metabolism, elimination of pain associated with injection and also improving therapeutic activity of the sustained released drugs (Donghee Park, et al. 2013). However, the efficiency of transdermal drug delivery is low because the stratum corneum of the human skin acts as effective and selective barrier to chemical permeation of the drug molecules. Indeed, the low permeability of the stratum corneum is the main reason that only a small number of low molecular weight drugs are capable of being transported through this route. Various mechanisms are developed for the transdermal delivery of drugs at low frequency ultrasound. Since the absorption coefficient of the skin varies directly with the ultrasound frequency, it is hypothesized that the high-frequency ultrasound energy would concentrate more in the epidermis of the skin, thus leading to higher enhancements. It was found that a 20 minutes application of ultrasound (0.2 W/cm^2) at 2 MHz frequency did not work significantly in delivery of salicylic acid across the skin. However, increase in intensity of ultrasound under the same conditions resulted in a 2 to 4 fold increase in transdermal salicylic acid transportation. (Bommanna, D. et al. 1992)

Effect of Ultrasound in Chemotherapy and Cell Therapy

Ultrasound has been used in many life science fields such as medical imaging and diagnostics, biological cell disruption etc. By combining focused ultrasound technology with the properties of MRI, a system has been developed that enables precise and accurate targeting within the cell tissues. In addition, temperature sensitive magnetic resonance sequences provide real-time feedback of small changes in temperature to ensure safe delivery of an effective thermal dose. Studies have been carried out in areas like breast, brain, and liver tumors.

Degradation of Toxic Chemicals from Effluent

In recent years, considerable interest has been shown on the application of ultrasound for destruction of hazardous chemical, i.e. degradation of chlorinated hydrocarbons, aromatic compounds, pesticides, explosives, dyes and surfactants. One of the major sources of these compounds is from municipal wastewater effluents. The occurrence of estrogen hormones in natural systems has become a subject of significant concern of scientific community. There are many sources of estrogenic pollution, like effluent from municipal and industrial wastewater treatment plants, animal wastes, bio-solids, septic tanks and landfills (Aquino, F. et al. 1998). Estrogenic hormones have also been associated to lower sperm counts in adult males and increase in chances of cancer. These compounds cannot be completely removed by biological processes at municipal wastewater treatment plants. The effect of ultrasonic waves on the degradation of various estrogen compounds that include 17 α -estradiol, 17 β -estradiol, estrone, estriol, equilin, 17 α -dihydroequilin, 17 α -ethinyl estradiol and norgestrel were conducted in single component batch and plug flow reactors. This sonolysis process produced 80% to 90% degradation of individual estrogens at initial concentration of 10 μ g per liter within 40 to 60 minutes (Adeoya-Osiguwa, S.A., et al. 2003). The estrogen degradation rates increase with increase in intensity of ultrasound. The sonolysis process could be used for the effective degradation of estrogen compounds present in aqueous solutions.

CONCLUSION

The major advantages that we get by using ultrasound in our process is shorter reaction; reduction of the sample preparation time; minimal amounts of material required; so minimum expenditure on solvents, reagents; efficient process overall. The increasing of the sample throughput is very useful for the isolation and purification of compounds of our interest from the point of view of their pharmacological and other bioactive properties and pharmaceutical formulation. Ultrasonic techniques when compared with the conventional methods like extraction, crystallization, evaporation, sonication, and sonolysis appears to be more effective. Sonolysis appeared to be more effective in the degradation of toxic materials in the pharmaceutical industrial effluents. In pharmaceuticals, the use of ultrasound gives improved environmental and health and safety considerations and also makes the process more economic. Low-frequency sonophoresis has helped to increase skin permeability to a variety of low- as well as high molecular weight drugs. Sonocrystallization is on its way to become a core technology in the pharmaceutical industry and it is expected to see more industrial application in the near future. On the other hand, a lower variability in the pharmaceutical availability is expected for the systems obtained using ultrasound-assisted compression. It is expected that this ultrasound control system could be developed and applied for the optimization of pharmaceutical freeze-drying cycles in industries. Photo-acoustic evaluation using ultrasound not only shows the elastic properties of the tablet materials but also helps in evaluating its internal structure. So basically we can infer that ultrasonic techniques are a thing for the future in the field of pharmaceuticals.

REFERENCES

- Adeoya-Osiguwa, S.A. (2003). 17 β -Estradiol and environmental estrogens significantly affect, mammalian sperm function. *Human reproduction*, 18:100–107.
- Adewuyi, Y.G. (2000). Sonochemistry: Environmental science and engineering applications. *Industrial Engineering and Chemistry Research*, 40:4681–4715.
- Alza Corporation, Mountain View, CA, <http://www.alza.com>
- Ando, T., Sumi, S., Kawata, T., Ichihara, J., and Hanafusa, T.J. (1984). *Journal of Chemical Society and Chemical Communications*, 3:436–439.
- Aquino, F., Bonrath, W., Couturier, L., Pauling, H., and Villaine, S. (1997). COST Workshop, Santorini, Greece.
- Aquino, F., Bonrath, W., and Pauling, H. (1998). Dehydration of 4-methyl-oxazole-5-carboxylic acid amide to 4-methyl-oxazole-5-carbonitrile.

- In Luche, J.L. (1998). Chemical Processes and Reactions under Extreme or Non-Classic Conditions. European Commission: Luxembourg, Belgium, p. 123.
- Bommannan, D., Menon, G.K., Okuyama, H. (1992a). Sonophoresis: II. Examination of the mechanism(s) of ultrasound-enhanced transdermal drug delivery. *Pharmaceutical Research*, 9:47.
- Chan, H.K. and Chew, Y.N. 2003. Novel alternative methods for the delivery of drugs for the treatment of asthma. *Advanced Drug Delivery Reviews*, 55:793–805.
- Emery, R.J., Papadebi, M., Treitas Dos Santos, L.M. (2005). Extent of sonochemical degradation and change of toxicity of a pharmaceutical precursor (triphenylphosphine oxide) in water as a function of treatment conditions. *Environment International*, 31:207–211.
- Mitragotri, S., Edwards, D., Blankschtein, D., and Langer, R. (1995). A mechanistic study of ultrasonically enhanced transdermal drug delivery. *Journal of Pharmaceutical Sciences*, 84:697–706.
- Suri, R.P.S., Nayak, M., Devaiah, U., and Helmig, E. (2007). Ultrasound assisted destruction of estrogen hormones in aqueous solution: Effect of power density, power intensity and reactor configuration. *Journal of Hazardous Materials*, 146:472–478.
- Guo, Z., Zhang, M., Li, H., Wang, J., and Kougoulos, E. (2005). Effect of ultrasound on anti-solvent crystallization process. *Journal of Crystalline Growth*, 273: 555.
- Graham Ruecroft, Tylan Lu., David Hipkiss (2005). Sonocrystallization: The Use of Ultrasound for Improved Industrial Crystallization, *Organic Process Res. Dev.* pp 923-931.
- Farrar Ishtiaq, Robina Farooq, Umar Farooq, Ather Farooq, Maria Siddique. (2009). Application of Ultrasound in Pharmaceuticals, *World Applied Sciences Journal* 6, 886-893.
- Dong Chen, Sanjay.K.Sharma. (2011). Handbook on Applications of Ultrasound: Sonochemistry and Sustainability; ISBN: 978-1-4398-4207-2, pg-62 63
- Ashish Pahade, V.M.Jadhav. (2010). Sonophoresis: an Overview, *International journal of Pharmaceutical Sciences Review and Research*, Volume 03, Issue 02, Article 005.
- .Mitragotri S, Blankschtein D, Langer R. (1996). Transdermal drug delivery using low-frequency sonophoresis, *Pharm Res.* 13:411-420.
- Donghee Park, Hyunjin Park. (2013). Sonophoresis in transdermal drug delivery systems, *Ultrasonics*, Volume 54, Issue 01, 56-65.
- Yuegang Zuo, Liliang Zhang, Jingping Wu, Johnathan W. Fritz, Suzanne Medeiros, Christopher Rego. (2004). Ultrasonic extraction and capillary gas chromatography determination of nicotine in pharmaceutical formulations, *Analytica Chimica Acta*, 35-39
- Vikram Deshmukh, Tejaswini Deshmukh, (2013). Design and Development of Melt Sonocrystallization Technique for Carbamazepine, *Indian Journal of Pharmaceutical Education and Research*, 47(2), 199-205.

ISSN : 0976-4550

INTERNATIONAL JOURNAL OF APPLIED BIOLOGY AND PHARMACEUTICAL TECHNOLOGY



Email : ijabpt@gmail.com

Website: www.ijabpt.com