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Application of Ultrasound in Pharmaceutics

[1]Farrah Ishtiaq, [2]Robina Farooq, [2]Umar Farooq, [2]Ather Farooq, [1]Maria Siddique,
[2]Hasnain Shah, [3]Mukhatar-Ul-Hassan, [4]Muhammad Ashraf Shaheen

[1]Department of Environmental Sciences, [2]Department of Chemistry,
COMSATS Institute of Information and Technology, Abbottabad, Pakistan
[3]Institute of Chemistry, Punjab University, Lahore, Pakistan
[4]Department of Chemistry, University of Sargodha, Pakistan

Abstract: This paper is intended to mainly review the application of ultrasound in the field of pharmaceutics, as drug dispensation, formulation, its delivery and consumption etc. and will also identify various related factors encompassing their diverse processes or methods; various areas have been identified for their great potential for future development e.g., crystallization, evaporation, extraction, homogenization, oxidation, synthesis etc. Application of ultrasound affects many factors akin to increasing skin permeability to a variety of drug molecules (sonophoresis); ultrasounic microfeeding and solid free forming in pharmaceutical dosing; destroy the contaminants; production of nanoparticles of biodegradable polymers by the emulsion-solvent extraction/evaporation methods and uses of sonocrystallisation in pharmaceutics.

Key words: Ultrasound · Extraction · Evaporation · Crystallization · Pharmaceutics · Sonication · Sonolysis · Chemotherapy · Synthesis

INTRODUCTION

Pharmaceutics is a discipline of pharmacy that deals with all facets of the process to turn new chemical entity (NCE) into proper medication. Pharmaceutics deals with the formation of a pure substance into dosage form such as a capsule, injection, suppository, cream, ointment, eye drop, inhaler, nasal spray etc. Pharmaceuticals are indispensable to health systems; they can complement other types of health care services to reduce morbidity and mortality rates and enhance quality of life at the systems levels. Pharmaceuticals, if used appropriately, have the power to make our lives qualitatively better and longer. As pharmaceuticals have curative and therapeutic qualities, they cannot be considered simply ordinary commodities or even basic health stimuli for that matter.

This paper is intended mainly to review the applications of ultrasound in the field of pharmaceutics, as drug dispensation, formulation, its delivery etc. It also identifies various related factors encompassing their diverse processes or methods. Various areas have been identified for their great potential for future development e.g., removal, decomposition, irradiation, degradation, crystallization, drying, extraction, filtration, homogenization, synthesis, freezing etc. [1-9].

ROLE OF ULTRASOUND IN DIFFERENT PROCESSES OF EXTRACTION

Ultrasonic Chemical Extraction: A rapid, sensitive and accurate ultrasonic extraction and capillary (Gas Chromatography) GC method has been developed for the determination of nicotine in pharmaceutical formulations. The results obtained in this study indicate that ultrasound is a reliable tool for the fast extraction of nicotine in pharmaceutical formulations. Capillary GC can directly separate and quantifies the components in ultrasonic extracts. It would not need subsequent clean-up step, which usually requires in reversed-phase (High-Performance Liquid Gas Chromatography) HPLC methods. In addition, GC methods do not require environmentally harmful organic mobile phase as is needed in HPLC methods. This method has been

Corresponding Author: Dr. Robina Farooq, Department of Chemistry,
COMSATS Institute of Information and Technology, Abbottabad, Pakistan

successfully used to determine the nicotine content in both nicotine chewing gum and transdermal patches [10].

To extract nicotine from the pharmaceutical formulations, the ground chewing gum sample, or small pieces of transdermal patch was placed in 15mL glass vial containing 10mL heptane and sonicated for 20, 40 and 60 min at 37°C in the ultrasonic bath. The complete extraction of nicotine was obtained in less than 20 min from the transdermal patch and 60 min from the chewing gum. Ultrasonic extraction reduced the extraction time from 24 h to less than 20 min. in comparison with the use of conventional cold extraction technique.

The benefit of using ultrasound in plant extraction has already been demonstrated for a number of compounds of interest to both the pharmacology and food industries [11]. Specific examples of the benefits include the extraction of tea from dried leaves with water using ultrasound and thus increasing the yield upto 20% at 60°C, approaching the efficiency of thermal extraction at 100°C [12]. A reduction in the maceration time from 8 h to 15 min has been reported in the extraction of the alkaloid reserpine from Rawolfia Serpentina [13]. The efficiency surged in extracting pharmacologically active compounds from Salvia Officinalis with some 60% of the target compounds extracted within 2 h at around ambient temperature [14].

Analyte Extraction Using Ultrasonic Technique: The application of ultrasound significantly accelerated the analyte extraction. In the conventional method each extraction step takes up to 24 h whereas with the ultrasonic extraction method, it took less than 20 min to achieve the same extraction efficiency. The ultrasonic extracts were directly chromatographed on capillary GC column and a base line separation was achieved within 10 min. The consumption of environmentally harmful organic solvent in this developed (ultrasonic extraction) UE-capillary GC method is much lower than in conventional extraction-HPLC methods. The UE-capillary GC method uses only 1/6 of organic solvent needed in conventional extraction. The subsequent GC analysis does not consume organic in case of HPLC. This green analytical method has been successfully applied to determine the nicotine content in both chewing and transdermal systems [10].

Continuous Ultrasound-assisted Extractions with High Intensity Ultrasonic Probe: Solid-phase extraction (SPE) has been regarded as a popular procedure for isolation of phytochemicals, purification of plant crude extracts and/or pre-concentration of target compounds of interest [15]. A dynamic continuous ultrasound-assisted extraction with high intensity ultrasonic probe (CUAE-HIUP) combined with solid-phase extraction (SPE) for pre-concentration and clean-up of the extract prior to high-performance liquid chromatography (HPLC) determination of the main biological active ingredients, sodium Danshensu and four tanshinones (dihydrotanshione I, tanshinone I, cryptotanshinone and tanshinone IIA) from root of Salvia miltiorrhiza bunge has been developed. The method was successfully applied to determine the five biological active ingredients in root of S. miltiorrhiza bunge and Danshen-containing pharmaceutical formulations. The combination of CUAE-HIUP with SPE shows the main advantage of shorter time, small amounts of plant material, efficient but minimum expenditure on solvents and reagents. The reduced sample preparation time and increased throughput will be very useful for the isolation and purification of compounds in terms of their pharmacological and other bioactive properties [16].

AN ULTRASONIC DRIVEN POWDER TRANSPORT SYSTEM

The transport and dosage of granular materials are important components of Process Engineering. Very accurate mixing process in chemical, pharmaceutical and food industries demand for an exact control of powder feeding. A novel powder-feeding device developed at the Heinz Nixdorf Institute and is based on piezoelectrically excited traveling waves suggested by many workers on this principle [17,18]. An acrylic pipe, which is stimulated to oscillations in the form of traveling waves through piezoelectric impulses, is used to convey the powder. A piezoelectric actuator is used for generating a progressive wave in an acrylic-pipe; Fig. 1(a). The acrylic pipe has specific damping properties which allow the excitation of a progressive flexural radial wave in a pipe, using only a single piezoelectric actuator; Fig. 1(b) [19].

An ultrasonic driven powder transport system was developed; Fig. 2, in which the wave stimulation and expansion in pipes, constructed from relatively strongly absorbing materials, are used. The movement of a progressive wave in the acrylic pipe and especially the desired movement of the surface points are essential for a powder transport. The developed ultrasonic driven powder system distinguishes itself from conventional dosage systems through the following points: simple

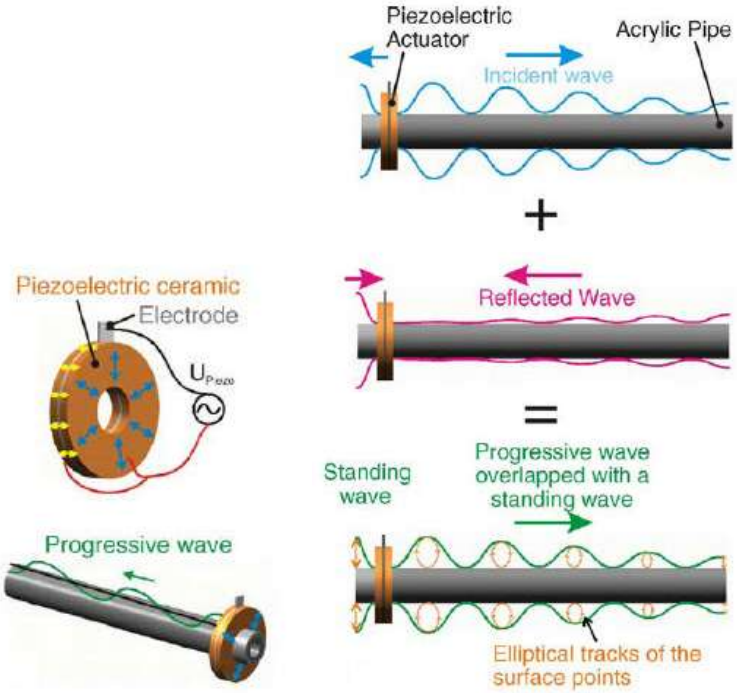

Fig. 1: Progressive wave in acrylic pipe

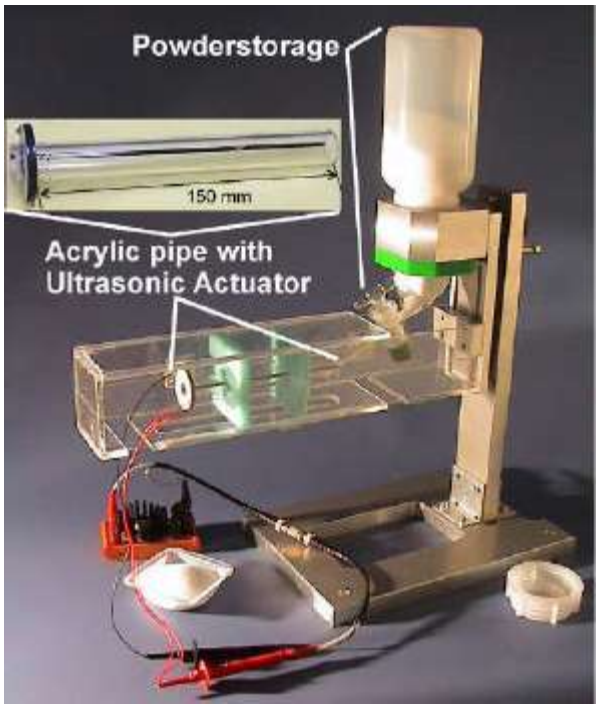

Fig. 2: Ultrasonic feeding device without viscosity increase (dashed lines)

structure, nearly no wear and tear in operation, cost effective and easy to integrate into existing production plants. The technology also allows miniaturization, operation in the low voltage area and a very careful, exact dosage. The experimental investigations of this prototype for ultrasonic powder feeding showed that it is possible to feed small amounts of powder with extremely high quantitative accuracy. But it also was confirmed experimentally that the performance of this system, like most piezoelectric systems, showed a significant sensitivity concerning environmental conditions. (e.g. temperature, ageing, load influence of the outside, production inaccuracies, etc.) [19]

APPLICATION OF ULTRASOUND IN TRANSDERMAL DRUG DELIVERY

Transdermal drug delivery offers several advantages over traditional drug delivery systems such as oral delivery and injections: the attractive attributes of transdermal drug delivery includes avoidance of first-pass metabolism, elimination of pain that is associated with injection and the opportunity for the sustained release of drugs. However, the efficiency of transdermal transport of molecules is low because the stratum corneum of the human skin is an effective and selective barrier to chemical permeation [20]. S. Mitragotri *et al.*, reported in vitro permeation enhancement of several low-molecular weight drugs under the same ultrasound conditions [21]. D Bommannan and co workers [22, 23] hypothesized that since the absorption coefficient of the skin varies directly with the ultrasound frequency, high frequency ultrasound energy would concentrate more in the epidermis, thus leading to higher enhancements. They found that a 20 min application of ultrasound (0.2 W/cm^2) at a frequency of 2 MHz did not significantly enhance the amount of salicylic acid penetrating the skin. However, 10 MHz ultrasound under the same conditions resulted in a 4-fold increase and 16 MHz ultrasound resulted in about a 2.5-fold increase in transdermal salicylic acid transport [22, 23].

PHOTO ACOUSTIC EVALUATION OF PHARMACEUTICAL TABLETS

In photo acoustics, the ultrasound is generated by means of pulsed laser illumination. Titrimetric and spectrophotometric determinations has been done by L.O. Okunrobo [24] while normally photo acoustical methods are used in applications where a touching ultrasonic transducer would damage the sample or it itself would be damaged. This can be the case with porous and hygroscopic systems, e.g., pharmaceutical tablets, where the use of a coupling liquid would be detrimental to the structure of the tablets. Despite its low efficiency in producing ultrasound, the so-called thermo-elastic regime is attractive in many applications, because the phenomenon is nondestructive to the samples and the theory of such nondestructive testing is well established [25,26].

Variations in porosity, density and sodium chloride content of microcrystalline cellulose tablets were found to be related to parameters extracted from the through-transmitted ultrasonic wave forms. By using the amplitudes and ultrasonic velocities of these wave forms, it was possible to obtain values of a transverse to longitudinal amplitude ratio and also elastic parameters. The transverse to longitudinal amplitude ratio and the amplitudinal Poisson's ratio (Poisson's ratio is a measure of the simultaneous change in elongation and in cross-sectional area within the elastic range during a tensile or compressive test) were indicative of structural variations, e.g., changes in the porosity and the sodium chloride content of tablets. Changes in mechanical structure can affect the physical and biopharmaceutical properties and in some cases even the chemical stability, of pharmaceutical tablets [27].

EFFECT OF SONOCRYSTALLISATION IN THE FORMATION OF AEROSOLS

Sodium chloride aerosols have been widely used as part of bronchial provocation tests to identify people with active asthma, exercised-induced asthma and those who wish to enter particular occupations (e.g. police, army) or sports (e.g. diving). It has become practical to prepare dry NaCl powder that can be delivered using dry powder inhalers (DPIs) instead of traditional nebulisers this procedure is energy intensive, time consuming and can induce impurities into the product. It also has several other disadvantages including inadequate control of particle size, undesired particle shape, surface charge modifications, decreased crystallinity and possible chemical degradation [28, 29, 30]. These disadvantages of the micronisation process ultimately jeopardize the NaCl powder performance. Sonocrystallisation offers several advantages including production of smaller sized crystal as compared to conventional crystallisation, cost effectiveness of apparatus. The process can be run at

ambient conditions and the reaction vessel involved is of simple geometry making the cleaning process simple for the pharmaceutical requirements [31].

EFFECT OF ULTRASOUND IN CHEMOTHERAPY

Ultrasound has been used in many life sciences such as medical imaging and diagnostics, biological cell disruption and fermentation processes. The application of power ultrasound (20-100 kHz, or even up to 2 MHz) to chemical processing has seen steady progressive over the past 15 years or so and a widely reported aspect of this is the use of sonochemistry to promote or modify chemical reactions [32]. Traditional preparations used for delivery of drugs include ointments, gels, creams and medicinal plasters containing natural herbs and compounds. The development of the first pharmaceutical transdermal patch for motion sickness [33] in the early 1980s heralded acceptance of the benefits and applicability of this method of administration for modern commercial drug products. The success of this approach is evidenced by the fact that there are currently more than 35 (Transdermal Drug Delivery) TDD products approved in the USA for the treatment of a wide variety of conditions including: hypertension, angina, motion sickness, female menopause, male hypogonadism, severe pain, local pain control, nicotine dependence and recently, contraception and urinary incontinence. There are also several products in late-stage development that will further expand TDD usage into new therapeutic areas, including Parkinson's disease, attention deficit and hyperactivity disorder and female sexual dysfunction [34].

ULTRASONIC IRRADIATION OF TOXIC EFFLUENT

In recent years, considerable interest has been shown on the application of ultrasound for hazardous chemical destruction, including amongst others the degradation of chlorinated hydrocarbons, aromatic compounds, pesticides, explosives, dyes and surfactants [33]. The degradation of triphenylphosphine oxide (TPPO) in water, a toxic compound typically found in effluents from the pharmaceutical industry by means of ultrasonic irradiation at 20 kHz. Measurements of dissolved total carbon showed that liquid phase degradation by-products were more stable to ultrasonic irradiation than TPPO [34].

EFFECT OF ULTRASOUND ON THE SYNTHESIS OF DRUGS

The advantages of ultrasound in chemical reactions, shorter reaction time and higher yields, could be used in industrial application in pharmaceutical or fine chemical industry. Sonochemistry can be used for fast reactions or in the synthesis of expensive products. Scale-up problems must be solved with the aim to develop a technically feasible process. Development of process technology (reactor design, process simulation) is necessary. Important is the establishment of a commercialized process [33, 35,36].

Many studies have been carried out and it is well documented, that the advantages of ultrasound procedures are good yields, short reaction times and mild conditions [33, 35, 36]. No direct interaction is possible between ultrasound energy and the vibrational and electronic levels of molecules, an indirect phenomenon must be relay to induce a reaction. In 1984 ando and co-worker published a paper about reaction of benzyl bromide and alumina supported potassium cyanide in toluene [37]. This is the example that ultrasound irradiation induces a particular reactivity, leading to products differing in nature from those obtained conventionally and is called sonochemical switching shown below:

Sonochemical Switching: W. Bonrath 2002, [38] have found that under the influence of ultrasound this scheme can synthesize with 77% yield in a shorter reaction time. The application of ultrasound in chemical reactions for the reasons that using such type of non-classical methods give an alternative method for the influence of selectivity and yield of reactions. This application of ultrasound in the dehydration was tested with other amides. It was found that in these reactions amides could be dehydrated to the corresponding nitriles in good yields and in a shorter reaction time.

APPLICATION OF ULTRASOUND IN CELL THERAPY

By combining focused ultrasound technology with the properties of magnetic resonance imaging, a system has been developed (ExAblate 2000) which enables precise targeting within tissues. In addition, temperature sensitive (magnetic resonance) MR sequences provide real time feedback of focal rises in temperature to ensure safe delivery of an effective thermal dose [39]. Although

studies have been carried out in many different areas including breast, brain and liver tumors and uterine fibroids [40,41].

SONOLYSIS OF TOXIC COMPOUND IN PHARMACEUTICAL EFFLUENTS

The occurrence of estrogen hormones in natural systems like surface water, soil and sediment has become a subject of significant concern. There are many sources of estrogenic pollution which include effluent from municipal and industrial wastewater treatment plants, livestock wastes, biosolids, septic tanks and landfills. Estrogenic hormones have also been linked to lower sperm counts in adult males and an increase of cancer [42, 43].

The biological processes at municipal wastewater treatment plants cannot completely remove these compounds. The effect of ultrasound power density and power intensity on the destruction of various estrogen compounds which include: 17á-estradiol, 17 á-estradiol, estrone, estriol, equilin, 17 á-dihydroequilin, 17 á-ethinyl estradiol and norgestrel were conducted in single component batch and flow through reactors using 0.6, 2 and 4 kW ultrasound sources. The sonolysis process produced 80-90% destruction of individual estrogens at initial concentration of 10 μg/L within 40-60 min of contact time. The estrogen degradation rates increase with increase in power intensity of ultrasound [44].

CONCLUSION

Ultrasound shows the main advantage shorter reaction/ preparation time; reduction of the sample preparation time; usage of small amounts of material, efficient and minimum expenditure on solvents, reagents and the increasing of the sample throughput, it is very useful for the isolation and purification of compounds interested from the point of view of their pharmacological and other bioactive properties and pharmaceutical formulation. Ultrasounic techniques when compared with the conventional methods like extraction, crystallization, evaporation, sonication and sonolysis transdermal drug delivery methods appears to be more effective. Sonolysis appeared to be more effective in the destruction of toxic materials in the pharmaceutical industrial effluents. In pharmaceutics use of ultrasound give more economic process and improved environmental and health and safety considerations. Low-frequency sonophoresis has been shown to increase skin permeability to a variety of low as well as high-molecular weight drugs. Sonocrystallisation can become a core technology in the pharmaceutical industry and we can expect to see more industrial application in the near future. A lower influence of the particle size on the release properties is obtained for the US-tablets in comparison with traditional tablets. 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, after further studies, could be developed and applied for the optimization of pharmaceuticals freeze-drying cycles in industrial condition. Photo acoustic evaluation using ultrasound not only shows the elastic properties of the tablet materials, but also for evaluating the internal structure.

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