Psilocybin and MDMA for PTSD, Depression and Addiction Secession

Psilocybin

Psychedelic therapies for mental disorders are currently being intensively studied, with psilocybin perhaps having received the most attention. A systematic review and meta-analysis of clinical trials investigating psilocybin for depression and anxiety in the context of life-threatening diseases published in 2020 described the results as promising, indicating psilocybin's possible efficacy in conditions that are either resistant to conventional pharmacotherapy or for which pharmacologic treatment is not yet approved [1].

Psilocybin is a naturally occurring psychedelic prodrug compound produced by more than 200 species of fungi and naturally occurring substituted tryptamine that features an indole ring linked to an aminoethyl substituent. It is structurally related to serotonin, a monoamine neurotransmitter which is a derivative of the amino acid tryptophan. Psilocybin is itself biologically inactive but is quickly converted by the body to psilocin, which has mind-altering effects. Psilocybin is a white, crystalline solid that is soluble in water, methanol and ethanol but insoluble in nonpolar organic solvents such as chloroform and petroleum ether. It has a melting point between 220 - 228°C (428 - 442°F), and an ammonia-like taste. Its pKa values are estimated to be 1.3 and 6.5 for the two successive phosphate hydroxy groups and 10.4 for the dimethylamine nitrogen, so it typically exists as a zwitterionic structure.

Psilocybin is rapidly dephosphorylated in the body to psilocin, which is an agonist for several serotonin receptors, which are also known as 5-hydroxytryptamine (5-HT) receptors.

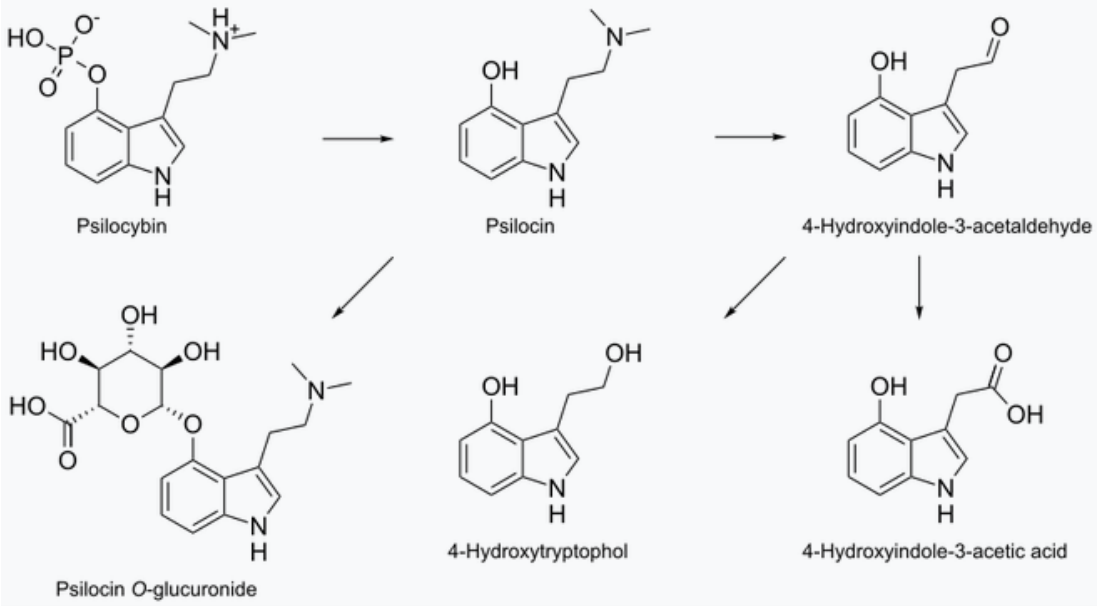


Fig.1 Pharmacokinetics of Psilocybin

Psilocybin is metabolized mostly in the liver. As it becomes converted to psilocin, it undergoes a first-pass effect, whereby its concentration is greatly reduced before it reaches the systemic circulation. Psilocin is broken down by the enzyme monoamine oxidase to produce several metabolites that can circulate in the blood plasma, including 4-hydroxyindole-3-acetaldehyde, 4-hydroxytryptophol, and 4-hydroxyindole-3-acetic acid. Within 24 hours, about 65% of the absorbed psilocybin is excreted into the urine, and a further 15 - 20% is excreted in the bile and feces.

A typical duration of the effect of psilocybin is 3-4 hours[2]. It has been proposed that psychedelics mediate their treatment effects through the relaxation of (pathological) [3]. It has also been noted that psilocybin-occasioned mystical experiences correlate with indicators of treatment efficacy[4]. These experiences may include, for example, experiences of sacredness of life, or experiences of oneness with nature and other people (temporary dissolution of 'ego structures', or self-

transcendence); these may be seen as relaxation of high-level beliefs.

First known mention of psilocybin use occurs in a 1598 document describing the religious rituals of Aztecs in Mexico, in Western countries, therapeutic use of psilocybin begun in the 1960s [5]. In Europe, psilocybin was used as an agent to help activate unconscious material, i.e. re-create subconscious conflicts and memories in order to make them accessible to psychotherapy. The therapeutic effect was considered to result from long-term processing of this material, not from the pharmacological effect of psilocybin.

Oral doses of psilocybin are classified as follows: Very low doses at 0.045 mg/kg; low doses between 0.115-0.125 mg/kg, medium doses between 0.115-0.260 mg/kg, and high doses at 0.315 mg/kg [6]. The psilocybin would typically be present in a formulated dose in an amount of from 0.01 mg/kg to 1 mg/kg. A typical human dose (for an adult weighing 60-80 kg) would equate to a dose of somewhere between 0.60 mg and 80 mg. Favoured adult oral doses are likely to be in the range 1 mg to 40 mg. Micro-dosing, typically at about a tenth of these doses, is also possible with micro dose formulations typically lying within the range 0.05 mg to 2.5 mg.

Stability

It is already known that aqueous standard solutions of psilocin and psilocybin are photosensitive and thermolabile and undergo the oxidation upon exposure to air and light. Degradation of psilocybin was observed at 75°C, 100°C, 125°C, and 150°C. The decay in the concentration of psilocybin is significantly noticeable from 100C. Up to this temperature, the concentration of psilocybin reduced gradually.

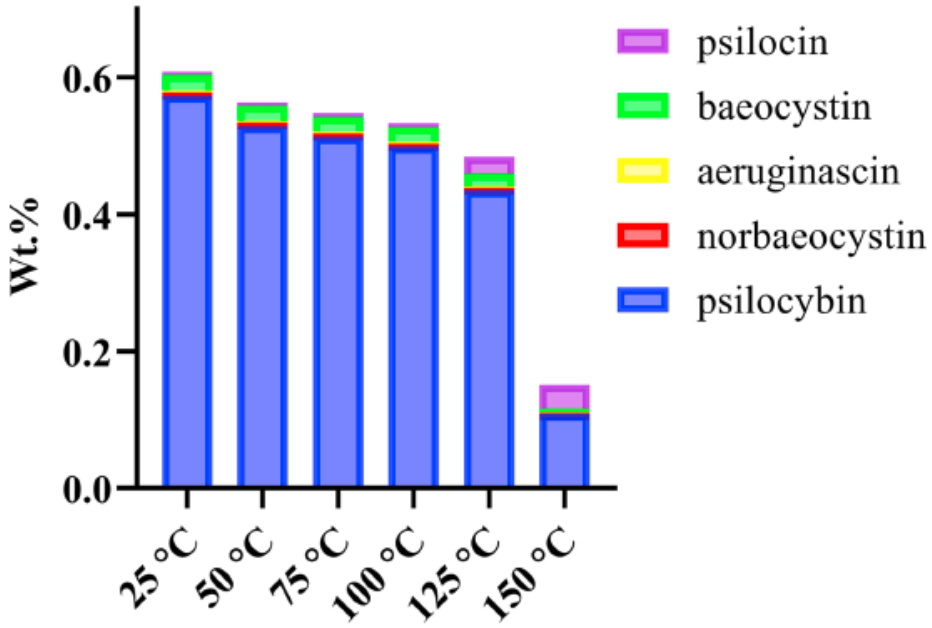


Fig. 2 Temperature stability of psychotropic tryptamines in eques solution that was heated in five replicates for 30 min

After one week of psilocybin solution storage the concentration of psilocybin reduced from 1.51 wt.% to 1.31 wt. %. The greatest loss of psilocybin was found in a sample stored in the light at 20°C, where the psilocybin value dropped to 0.96 wt.%.

After one month of psilocybin solution storage the degradation to approximately 50% of the initial concentration of all tryptamines occurred on storage under all conditions. The most significant decrease in concentration to 0.72 wt.% appeared in the sample that was stored in the light at 20°C. This effect is probably due to the photooxidation of alkaloids, The lowest concentration reduction to 0.85 wt.% was found in the dark at 20°C.

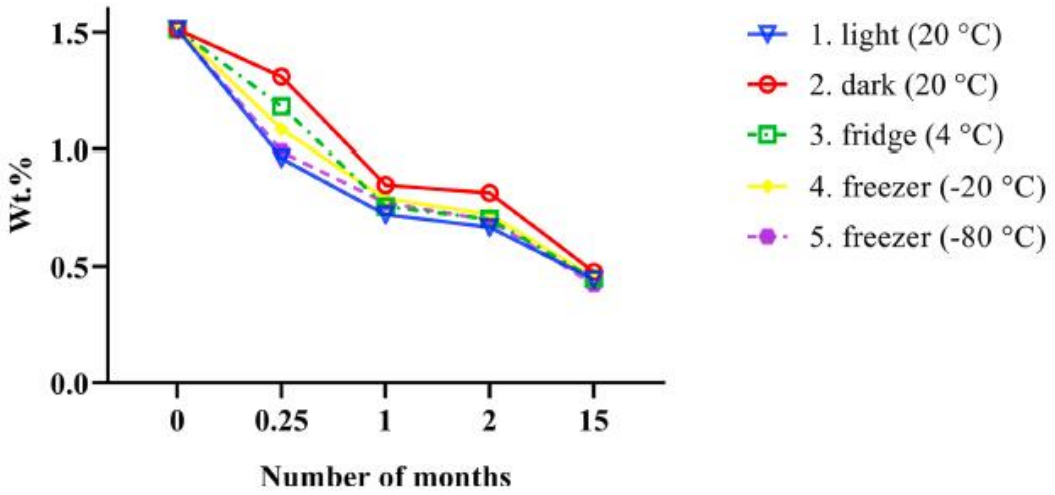


Fig.3 Stability of psilocybin as a major tryptamine after 15 months

Working Principle of Ultrasonic Extraction

Ultrasound is known as the simplest and most versatile method for cell disruption and the production of extracts. High-power ultrasound waves are successfully used in the food, pharma and nutraceutical industry to isolate targeted compounds from plant and animal tissues. Typical applications include the extraction of high molecular weight polysaccharides from medicinal mushrooms. One main advantage of ultrasound-assisted cell lysis and isolation the outstanding effectiveness of the extraction procedure, resulting in very high yields and fast extraction rates. Ultrasonic extraction is a purely mechanical procedure, whose working principle is based on the generation of acoustic cavitation.

When a liquid is sonicated with an ultrasound probe at 20kHz, 20,000 vibrations per second are transmitted into the medium. The ultrasonic waves travel through the liquid, where they create alternating high-pressure (compression) / low-pressure (rarefaction or expansion) cycles. During the low-pressure vacuum cycle, minute vacuum bubbles or cavities occur in the

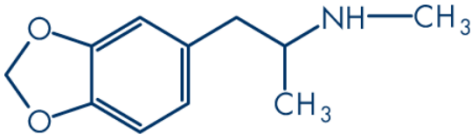
liquid, which grow over several pressure cycles. During the compression phase of the liquid and bubbles, the pressure is positive, while the rarefaction phase produces a vacuum (negative pressure.) During the compression-expansion cycles, the cavities in the liquid grow until they reach a size, at which they cannot absorb more energy. At this point, they implode violently. The implosion of those cavities results in various highly energetic sonomechanical effects, which are known as the phenomenon of acoustic / ultrasonic cavitation. During the implosion of ultrasonic cavitation bubbles, extreme energy dense forces such as high shear, liquid streaming and turbulences are created in the sonicated liquid. These cavitational forces disrupt cell walls of plants and release the intracellular compounds, including bioactive substances such as the hallucinogens psilocybin, psilocin, baeocystin and norbaeocystin from mushroom species. The alternating high-pressure/low-pressure cycles also promote intense mass transfer rates, which results in the superior extraction yield obtained by sonication. Via ultrasonic extraction, almost the complete number of active substances present in botanicals and mushrooms can be isolated.

The advantages of ultrasonic extraction are the high extraction yield of psychedelic compounds (i.e. psilocybin, psilocin, baeocystin, norbaeocystin), the free choice of solvent (e.g. water, ethanol, water-alcohol mixture etc.), as well as the simple and safe operation. Due to the intensive mechanical forces of sonication, ecological and mild solvents such as water, ethanol etc. are usually sufficient to achieve an extraordinary extraction rate and yield. As a result, ultrasonic extraction shortens the extraction time and enables a reduced use of solvents or the use of milder, gentler solvents. This means that ultrasonic extraction allows for both, higher

extraction rates and extracts of superior quality (e.g. cold water extracts). Since the process temperature can be precisely controlled during the sonication, thermal decomposition of the extracts due to excessively high temperatures as well as evaporation of the substances are avoided.

MDMA

MDMA is a synthetic substance originally developed in 1912 by the Merck chemical company. MDMA is an abbreviation for methylenedioxy-methylamphetamine.



Molecular formula: $C_{11}H_{15}NO_2$
Molecular weight: 193.2

Like the amphetamines, MDMA and its related compounds are amines that can exist either as free bases or as salts of various acids. MDMA base is a colourless oil insoluble in water. Investigational indications include as an adjunct to psychotherapy in the treatment of post-traumatic stress disorder (PTSD) and social anxiety in autism spectrum disorder [7,8,9]. In 2017 the United States Food and Drug Administration (FDA) approved limited research on MDMA-assisted psychotherapy for post-traumatic stress disorder (PTSD),[10,11] with some preliminary evidence that MDMA may facilitate psychotherapy efficacy for PTSD [12,13,14].

Pharmacokinetics

The MDMA concentration in the blood stream starts to rise after about 30 minutes, and reaches its maximal concentration in the blood stream between 1.5 and 3 hours after ingestion. It is then slowly metabolized and excreted, with levels of MDMA and its

metabolites decreasing to half their peak concentration over the next several hours [15]. It is clear that the increase in the net release of serotonin (and possibly dopamine) is the major mechanism of action underlying the distinctive mental effects of MDMA, whereas the increased release of noradrenaline is mainly responsible for the physical effects that it shares with amphetamine.

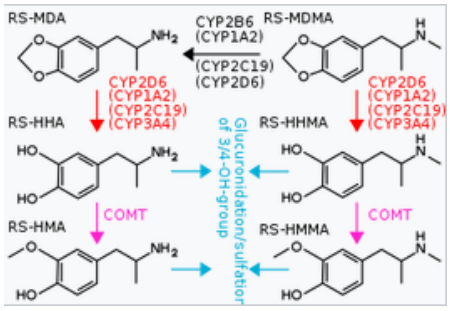


Fig. 4 Main metabolic pathways of MDMA in humans.

Dosing

A typical human dose (for an adult weighing 60-80 kg) would equate to a dose of somewhere between 75 mg and 100 mg. Doses of 50 mg, 75 mg and 125 mg to healthy human volunteers produced peak blood concentrations of 106 ng/mL, 131 ng/mL and 236 ng/mL respectively. The drug is broken down metabolically, mainly in the liver, where an enzyme designated CYP2D6 is chiefly responsible[16]. Elimination of the drug from the body is moderately slow, the half-life for MDMA disappearance from the blood being of the order of 8 hours. Because it takes about 5 half-lives (i.e., about 40 hours for MDMA) for over 95% of the drug to be cleared from the body, this may explain the persistence of troublesome after-effects for one or 2 days after use. Some of the metabolites of MDMA are still pharmacologically active, especially its first metabolite, MDA, so that the duration of action may be somewhat longer than the duration of MDMA itself in the body.

The usual “recreational” dose of MDMA or MDEA produces blood levels in the range of 100–250 ng/mL, or 100–250 µg (0.1–0.25 mg) per litre. Most of the cases of serious toxicity or fatality have involved blood levels ranging from 0.5 mg/L to 10 mg/L.

Drug Delivery

In recent years, a host of potent new drugs have become available for clinical. Current expectations are that additional potent drugs will continue to become available in the future. Almost all pharmacological agents continue to be administered via two routes, by oral administration for absorption through the stomach or intestines or by intramuscular or intravenous injection, despite the fact that both of these routes suffer from significant disadvantages under typical situations. The simplest and most prevalent administration route is oral administration. Oral administration of a drug suffers from the disadvantage. The absorption of the drug is dependent upon the movement from the stomach to the small and large intestines and the effects of secretions from these organs. There is often a substantial delay between the time of oral administration of a drug until it begins to have the desired therapeutic effect on the patient's system. Generally, a drug must pass from the stomach into the small and large intestines before it will be absorbed into the patient's bloodstream; unfortunately, this typically takes forty-five minutes or longer. For some applications, such a delay is unacceptable. Many drugs taken orally are metabolized almost immediately. They are removed from or rendered ineffective by the patient's system before they can have any therapeutic effect. This occurs because the veins from the stomach and the small and large intestines drain into the liver. Thus, drugs entering the patient's bloodstream through the stomach and the intestines immediately pass through the

patient's liver before distribution throughout the remainder of the patient's body. In addition to the other adverse effects resulting from large amounts of the drug being removed by the liver, oral administration is also disadvantageous because of the cost in providing such a large dose of the drug.

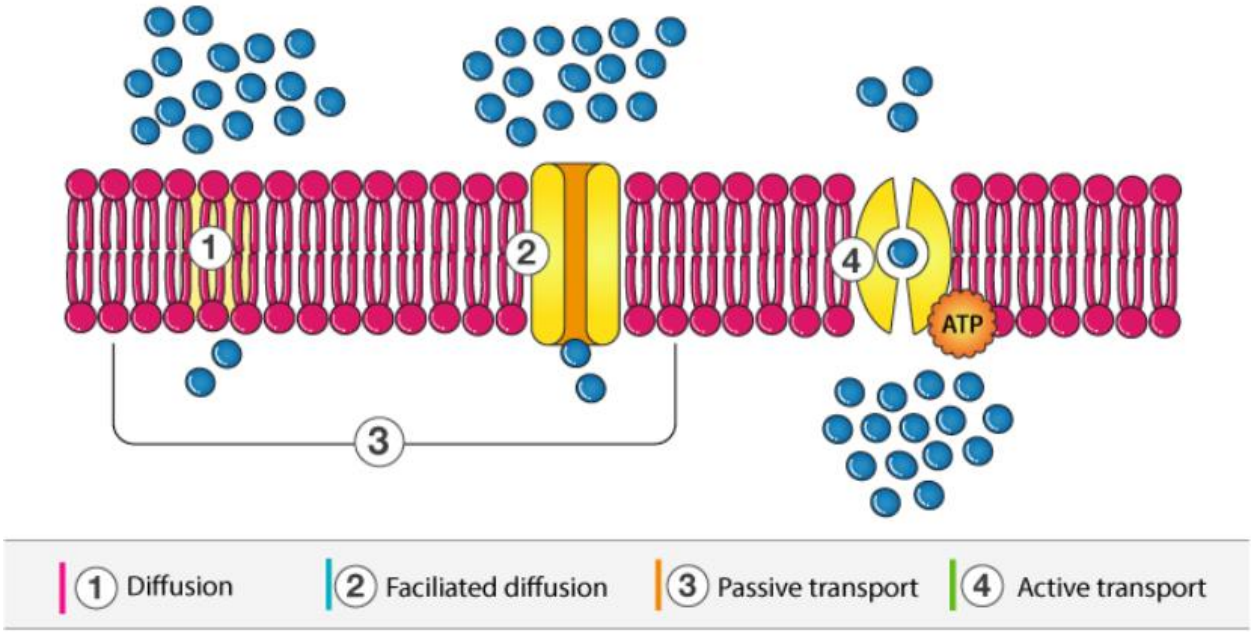
In order to avoid these serious disadvantages inherent in the oral administration modality, physicians frequently resort to the injection modality for administering many drugs. Injecting a drug (generally intravenously or intramuscularly) results in rapid entry of the drug into the patient's bloodstream; in addition, this type of delivery avoids the removal of large quantities of the drug by the patient's liver that accompanies oral administration. Rather, the drug becomes rapidly distributed to various portions of the patient's body before exposure to the liver; thus, the drug is removed by the liver at a substantially slower rate. Difficulties to select an appropriate dose for oral administration, is even more profound when utilizing the injection modality of administration. This is because smaller doses have an increased effect due to the rapidity with which the drug enters the bloodstream and because large doses of the drug, when injected, are not immediately metabolized by the liver.

Transmucosal dose-to-effect delivery of a drug is somewhat slower to provide active concentrations of a drug in a patient's system than is the use of an intravenous injection. Nevertheless, it has been discovered that the transmucosal route can be adapted so that any loss in the speed of drug uptake is more than offset by the ability to administer the drug noninvasively (much to the appreciation of the patient) and by the ability to control the dose received by the patient vis-a-vis the effect of the drug. A drug must be lipophilic in order to be absorbed across mucosal tissue. However, this requirement

is not a serious limitation since a large number of drugs are naturally lipophilic or can be provided in a lipophilic form.

Transport of large molecules thorough the biological membranes

A targeted drug delivery system is most often a drug associated with a macromolecule, designed to be localized at a specific anatomic region in the target site. Recently, there has been a greater focus on utilizing receptor-mediated carriers, such as monoclonal antibodies, that interact with cell surface receptors at the drug's intended site of action. An alternative approach is to utilize carriers that have receptors on the capillary endothelial cells. While ever more sophisticated means of delivering medicine to specific locations in the body are being developed to overcome this problem of non-specificity, we observed that Nature has already evolved elegant ways of sending biological molecules to where they are needed. The hormone binding mechanism is the example of naturally occurring site-specific carriers. Hormone carriers release their ligands at sites of inflammation.



Biological membranes dictate the existence of life. This universal component of the cell is the key operator for maintaining cellular homoeostasis. Amphiphilic lipid molecules, the building blocks of membrane bilayer arrange themselves in a wise manner to generate a highly hydrophobic environment at its core, which in turn arrest passage of all molecules irrespective of their chemical moieties. This nature of the bilayer fabricates the need of protein transporters that selectively admit the entry of different molecules. The fine balance between cellular survival and apoptosis relies on a magnificently knitted signal transduction system, the mode of cellular communication. These functional aspects feature the interweaving between lipids and residing proteins of the membrane bilayers. Though amphipathic lipid molecules are the main building blocks for membrane bilayer formation, presence of proteins have made the bilayer, being able to perform many biological functions, essential for cell survival. The hydrophilic heads of different glycerophospholipids, glycolipids and sterols advantageously arrange themselves in a bilayer while their hydrophobic tails form aggregates to provide a disordered structure with high entropy. This elevated entropy level of membrane allows the phospholipids to diffuse along bilayer leaflets. Phospholipid translocation between leaflets i.e., vertical movements is seldom observed since the hydrophilic heads have to pass through a highly hydrophobic inner environment which requires overcoming a high activation energy barrier, however this translocation seems necessary for cell endocytotic process. The all-pervasive phospholipid asymmetry across the bilayer, the resultant of lipid translocation is responsible for conserving cellular mechanical properties. Disruption of this asymmetric distribution leads to disturbed interaction between proteins and lipids in the inner leaflet of the membrane which triggers the

activation of macrophages and, thus promotes apoptosis. Along with the presence of these flexible lipid molecules, membrane proteins also contribute in maintaining the dynamic nature of biological membranes though they possess much slower rates in cis-trans diffusion. Apart from maintaining structural integrity of membranes, proteins are indispensable machineries in allowing or hindering movement of substances within cells, in transducing essential signals for maintaining physiological homoeostasis. The specific position of a particular protein in membrane dictates the assigned function of that protein and hence, the dense network of integral membrane proteins, membrane spanning proteins and peripheral proteins are crucial for maintaining functional status of biological membrane. The elixir of a properly functional membrane lies within the interaction between those membrane lipids and proteins. The lipid molecules, immediately adjacent to a protein form a shell or annulus where the fatty acyl chains of lipids are intermingled to the grooves and protrusions of protein molecules in order to give a rigid structural appearance. Since the interaction energy depends on several weak van der Waals and electrostatic forces, the lipid molecules loosen connection with specific proteins and give an unfavourable membrane conformation. Therefore, the dynamic nature of the bilayer depends on this annular site binding of lipids though the non-annular binding i.e., binding of phospholipids with transmembrane alpha helices of proteins provides a glance of discrete binding, where the head groups of lipid molecules are attached with protein moiety through strong hydrophobic interaction. This more specific non- annular binding, unlikely to annular binding, is almost devoid of steric hindrance and hence allows entry of lipid molecules by simple diffusion only. Not only lipid molecules, but also the proteins can be revamped either by tilting their helices or by rotating their side chains for being adapted within lipidic environment.

Another principal bio-molecule that declines the permeability of membrane is cholesterol, which is accountable for making the membrane less fluidic by interacting with polar head group and hydrocarbon chain of phospholipid through their own hydroxyl group and steroid ring structure respectively. In abstract, an ardent steric and operative synchrony between lipids and proteins furnish the unique ubiquitous structure of biological membrane. Since physiological as well as biophysical aspects of biological membrane like polarity and permeability are dependent on in-house lipid molecules, the ionic permeability modification in artificial membrane is an obvious consequence of lipid peroxidation. Lipid peroxide induced dismantled lipid assembly, composition alterations and dynamic changes within membrane lead to loosening of the integrity of biological membrane. An escalation in phospholipid bilayer rigidity owing to lipid peroxidation has been reported due to the formation of cross-linking between lipid molecules and loss of freedom of motion in bilayer. Additionally, this peroxidation process also affects membrane bound enzyme activity. The key cause behind such adverse actions of peroxides on biological membrane has been presumed to be the re-orientation of lipid molecules toward water-lipid head interface leading to reduction in the thickness of membrane along with impeded biological action.

Nebulizers as the delivery method

Creation of nebulizers in 1950 revolutionized drug delivery. In a mist producing apparatus used for medical purposes in which a liquid is atomized in a gas means the stopping operation of the atomizer was provided whenever the patient is not inhaling.

Initially, nebulizers have been used to deliver aerosolized medications in the treatment of patients with pulmonary diseases. Nebulizers are the aerosol device of choice when patients cannot

coordinate inhalation and actuation needed for the use of the pressurized metered-dose inhalers (pMDIs) or are not able to provide the necessary inspiratory flow required by the dry powder inhaler (DPI) for effective aerosol drug delivery. Nebulizers are divided into three categories: jet nebulizers, ultrasonic nebulizers, and mesh nebulizers.

While jet nebulizers are commonly used for the treatment of patients with pulmonary diseases, they are bulky and require a power source. Due to aerosolized droplets and solvent vapor that saturates the outgoing air, jet nebulizers cool the drug solution in the nebulizer and increase solute concentration in the residual volume. Jet nebulizers are effective in delivering formulations that cannot be delivered with pressurized metered-dose inhalers (pMDIs) and dry powder inhalers (DPIs). On the other hand, jet nebulizers can be difficult to use because of their need for compressed gas and additional tubing.

Ultrasonic nebulizers are more efficient and compact than jet nebulizers, they cannot be used to deliver proteins or suspensions. With the development of mesh nebulizers that use lower-frequency waves, heating issues that denature proteins during aerosol therapy are eliminated. Ultrasonic nebulizers incorporate a piezoelectric crystal vibrating at high frequencies (1-3 MHz) in order to produce aerosol. They are divided into two categories:

1. Large-volume ultrasonic nebulizers and
2. Small-volume ultrasonic nebulizers.

Whereas large-volume ultrasonic nebulizers are most commonly used to deliver hypertonic saline for sputum induction, small-volume ultrasonic nebulizers are used for delivery of inhaled medications. Ultrasonic nebulizers have many limitations compared to jet nebulizers. For instance, they have large residual volumes,

an inability to aerosolize viscous solutions, and degradation of heat-sensitive materials.

Recent improvements in nebulizer technologies have led to the development of mesh nebulizers using micropump technology for aerosol production. They force liquid medications through multiple apertures in a mesh or aperture plate in order to generate aerosol. As small and portable nebulizers that are powered by either battery or electricity, they have silent operation, short treatment times, increased output efficiency, and minimal residual volume. Advantages of mesh nebulizers include consistent and improved aerosol generation efficiency, a predominantly fine-particle fraction reaching into the peripheral lung, low residual volume, and the ability to nebulize in low drug volumes.

Aerosol therapy via nebulizers is a well-established method. New types of nebulizers have yielded a number of improvements, such as compact design, portability, shorter treatment duration, and quiet operation, that are expected to improve patient adherence to therapy.

Conventional inhaler devices have a low efficacy in targeting small airways. Smart nebulizers can be used to increase deposition to small airways by adjusting the flow and depth of each inhalation based on patients “individual inspiratory capacity”.

Smart nebulizers employ adaptive aerosol delivery (AAD®) technology, which analyses the patient’s breathing pattern in order to determine the timing of aerosol drug delivery during inhalation. They analyse pressure changes of the airflow during the first 3 breaths to determine the correct starting point for drug delivery. Then, the device continues to monitor the preceding 3 breaths throughout the treatment and adapts to the patient’s breathing pattern. This adaptation reduces not only losses of aerosol during expiration but also the variation in drug delivery

during inhalation therapy while improving patient adherence to treatment. The smart nebulizer system may have a user interface that can communicate information to the patient/user, including without limitation treatment progression, inhalation flow rate and breathing rate, preferably with low latency. The interface may be incorporated into the nebulizer, such as the housing, or information from the nebulizer may be communicated to a standalone device, such as a peripheral device, including for example a smartphone or tablet, for viewing. Communication of the information is not limited to visual information, such as graphics or text, but may also include audible and haptic information, communication methodologies and components.

Active Pharmaceutical Ingredients (API) in nanoform

A proven approach to improving the dissolution properties of poorly water-soluble active component(s) molecules is to reduce particle size of the solid drug, as increased surface area of the dissolving drug particles correlates with increased dissolution rates. Reduction of particle size to nanoparticle range produces dramatic increases in surface area and thus the greatest opportunity for dissolution rate enhancement via this mechanism. Therefore, nanoparticle active component(s) delivery can provide faster dissolution, improved bioavailability and ultimately enhanced clinical efficacy.

Nanoparticles are solid, colloidal particles consisting of macromolecular substances that vary in size from 5 - 1000 nanometers. The drug of interest is dissolved, entrapped, adsorbed, attached or encapsulated into the nanoparticle matrix. The nanoparticle matrix can be comprised of biodegradable materials such as polymers or proteins. Depending on the method of

preparation, nanoparticles can be obtained with different properties and release characteristics for the encapsulated therapeutic agents. Typically, nanosuspensions of active pharmaceutical compounds are prepared by application of extremely high shear conditions to a mixture of the compound, an aqueous dispersion medium, and milling media (herein, high-shear milling). In most high-shear milling applications the milling media is a small polyester prill driven by the shear forces to which it is subjected, and acts like a microscopic ball mill, impacting the pharmaceutical compound present in the mixture (generally, the active pharmaceutical compound (APC) is present in the slurry initially as a powder, in the form of a macroscopic particulate. Typical equipment employed in preparing such nanosuspensions is a high-shear mixer in which a stainless-steel impeller rotates at multiple thousand RPM in a chamber holding a mixture of the active pharmaceutical compound, aqueous dispersion medium, and milling media. An example of commercially available equipment utilized in this process is the Elan Nanomill®.

The advantages of using nanoparticles for oral drug delivery, especially for dosing poorly soluble drug molecules, are well known and have been documented for over 40 years. Nanosuspensions is the potent approach to improve the solubility and bioavailability of poorly aqueous soluble drug entities. Nanosuspensions may be administer through a variety of routes involving oral, transdermal, ocular, parenteral, pulmonary, etc. with solving the different issues.

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