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A CONCISE REVIEW: NANOEMULSION-BASED DRUG DELIVERY SYSTEMS FOR TUBERCULOSIS THERAPY

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ABSTRACT

The World Health Organization identifies tuberculosis (TB), caused by Mycobacterium tuberculosis, as a leading infectious killer. Although conventional treatments for TB exist, they come with challenges such as a heavy pill regimen, prolonged treatment duration, and a strict schedule, leading to multidrug-resistant (MDR) and extensively drug-resistant (XDR) strains. The rise of MDR strains endangers future TB control. Despite these concerns, the hunt for an efficient treatment continues. Nanocarriers, such as nanoemulsion, lipid nanoparticles, nanosuspensions, liposomes, and polymeric micelles, facilitate targeted delivery of anti-TB drugs. The benefits of nanocarriers include reduced drug doses, fewer side effects, improved drug solubility, better bioavailability, and improved patient compliance, speeding up recovery. Additionally, nanocarriers can be made even more targeted by linking them with ligands such as mannose or hyaluronic acid. Nanoemulsions are colloidal dispersions having smaller globule size that ranges from 20-600 nm. Nanoemulsions are nano carrier drug delivery system for the protection of drugs from severe environmental conditions like pH, oxidation and hydrolysis. Nanoemulsions are normally contains oil phase, aqueous phase, surfactants and co-surfactants. Different methods are employed for the preparations of nanoemulsions are high pressure homogenization, microfluidization, ultrasonication, spontaneous emulsifi-cation, membrane emulsification, phase inversion temperature and solvent displacement method. Nanoemulsions are nano carrier system with safe and effective delivery of lipophilic and hydrophilic drug and also used in targeting.

KEYWORDS: Tuberculosis, Mycobacterium tuberculosis, Nanoemulsion, Nanocarriers.

Introduction

Among the most important global health challenges are infectious diseases such as tuberculosis (TB), acquired immunodeficiency syndrome, and human immune deficiency virus infection.[1] *Mycobacterium tuberculosis*, an aerobic, Gram-positive, non-motile, acid-fast tubercular, rod-shaped bacillus, causes airborne TB, which mostly affects the lungs but may also impact extra-pulmonary regions. Due to their lipid-rich cell walls, mycobacteria may live within alveolar macrophages. The tubercle bacillus, *M. tuberculosis*, which is spread via airborne droplets and can remain, live, and divide every 16–20 h inside alveolar macrophages, is the principal method of transmission for this dangerous illness. Per the latest report by World Health Organization (WHO), about 10.6 million cases of TB were reported in 2021, comprising 6 million men, 1.2 million children, and 3.4 million women.[2] It was estimated that about 1.6 million people died from TB in 2021 throughout the world. About 80% people infected by TB reside in low- and middle-income countries. The main causes for TB include weakened immune system, chewing of tobacco, undernourishment, and other complications such as diabetes and HIV infection. In 2021, 2.2 million new TB cases were attributed to undernourishment, 740,000 to alcohol use disorders, and 690,000 to smoking throughout the globe. To reach the global goal set at a high-level UN meeting on TB in 2018, USD 13 billion is required annually for TB prevention, diagnosis, treatment, and care. It is expected that TB detection and treatment saved 74 million lives between 2020 and 2021.[3] TB is the second highest infectious cause of death after COVID-19 and the thirteenth major cause of mortality across the world. TB exists in all nations and among all age groups, but it can be treated and avoided. One of the Sustainable Development Goals (SDGs) of the United Nations is to end the TB epidemic by 2030.[4]

Chemotherapy is currently the only option for the clinical management of TB patients, with cure rates of up to 95% when given correctly to those with drug-susceptible TB. However, the majority of anti-TB medicines have subpar pharmacokinetic characteristics, which frequently prevent them from performing to their full potential in clinical situations. Poor bioavailability due to variable drug absorption and unwanted first-pass metabolism, lengthy regimens with high dosing frequencies, and individual and combined drug toxicity as well as severe adverse effects are some of the issues related to the therapeutic limitations of the current anti-TB regimens. These challenges contribute to low patient adherence, therapeutic

failure, and the alarming emergence of multidrug-resistant (MDR) strains, all of which explain TB's current lethal state and the pressing need to advance anti-TB treatment.[5]

Advanced drug delivery systems require the development of a nanotechnological technique, which is a rapidly evolving cutting-edge scientific field that includes a wide range of disciplines such as chemistry, physics, and biology as well as special nanodimension structures with therapeutic applications in pharmacology and the biomedical field. Many researchers are interested in the development and standardization of nanocarriers for various reasons, such as reduction in drug doses, minimal adverse effects, solubility and bioavailability improvement of drugs, targeted drug delivery resulting in improved patient compliance, and acceleration in recovery of patients.[6] These nanocarriers include solid lipid nanoparticles, nanostructured lipid carriers, liposomes, nano-emulsion, nanosuspension, nanoparticles, polymeric micelles, and dendrimers. The nanocarriers appear to be a viable and intriguing approach to solve the limitations associated with conventional treatment associated with TB.[7]

Besides the above mentioned treatment, vaccination is also another option for prevention of TB. The WHO advises that, despite the Bacille Calmette–Guerin (BCG) vaccine's success in preventing TB and reducing mortality among infants and young children who have received vaccinations since birth, it is important to take into account the vaccine's capacity to produce "trained immunity" by causing non-specific immune sensitization to other pathogens.[8] Additionally, it might aid in lowering the prevalence of infectious diseases, such as malaria, that are resistant to antimicrobials. Several benefits, including the large surface area of the sub-micron-sized particles, increased interaction of the vaccine with the large surface area of the respiratory mucosa and enhanced penetration into bacilli-loaded granulomas attributed to nanotechnology-based approaches, may particularly benefit in targeting the most common respiratory forms of TB against which BCG appears to be ineffective.[9] Previous research has shown the ability of the antigens implanted on nano-particulate platforms to improve immune response to other pathogens causing other infectious diseases, indicating the possibility of TB vaccines having the same capability once created.

TB Pathophysiology

Tubercle bacilli nuclei in droplets that reach the lungs' alveoli during breathing cause infection, in a step called aerosolization (Figure 1).[10] These tubercle bacilli are ingested by alveolar macrophages, the majority of which are killed or inhibited. After preventing the

acquisition of the phagosome and lysosome, *M. tuberculosis* reproduces intracellularly inside the macrophages. Asymmetric cell division is a special kind of cell division seen in *M. tuberculosis*. Those bacteria may spread, if they are alive, through the lymphatic system or the circulation to the regional lymph nodes, the apex of the lung, kidneys, brain, and bony parts of the body, where TB sickness is most likely to develop. This process of dissemination sets the immune system for an expanded response.[11] To use an analogy, a bacterial jail called a granuloma aims to isolate a bacterium beneath an enclosure of immune cells. Both macrophages and lymphocytes that surround and enclose *M. tuberculosis* constitute the granuloma itself. TH1, natural killer (NK) cells, dendritic cells, macrophage, regulatory T cells (Treg), foam cells, giant cells, epithelioid macrophage, neutrophils, and B cells are some of the cells implicated in the granuloma. In clinical significance, primary and secondary TB are the two forms of TB. In immunocompromised individuals, primary infection is the one that develops when the immune system cannot handle it. At this point, the infected person releases infectious aerosols of *M. tuberculosis* and infects the next susceptible person. Suppose *M. tuberculosis* is present but not eradicated by the immune system or granuloma. In such instances, the illness is believed to be latent and could turn into secondary TB.[12]

TB Diagnostic

There are several ways TB can be diagnosed. The different methods display different advantages and disadvantages. For example, the sputum smear microscopy (SSM) examination remains one of the most accessible and affordable diagnosis tools and is often the only available technique in developing countries. However, its poor sensitivity and high rate of false negatives can lead to misdiagnosis or under-diagnosis and delay the start of an effective therapeutic approach. Some recent upgrades to this technique, involving the use of fluorescent antibodies or digital pathology tools, might help to overcome some of its current limitations, but they also increase costs and might not constitute a desirable approach in countries with deficient healthcare system]. Another gold standard approach is the culture of M. tuberculosisin specific growth media, which often can simultaneously allow for the evaluation of antibiotic susceptibility.[13]

Molecular biology tools include Xpert RIF/MTB, which reduces the time required for a diagnosis while improving its sensitivity; loop-mediated isothermal amplification (LAMP) and droplet digital polymerase chain reaction (ddPCR), which enables accurate diagnosis even with very small amounts of contaminated samples.

Immunoassays are often valuable when the collection of infected secretions might be challenging, such as in pediatrics or in patients with mild symptomatology. The tuberculin skin test or interferon-γ release assay are often used. However, they do not distinguish between an active infection and a vaccination-induced immunological response, and they are often unreactive in immune-compromised individuals. Immuno-PCR is another alternative that enables the detection of circulating antibodies and/or mycobacterial antigens in blood samples or other fluids from patients.[14]

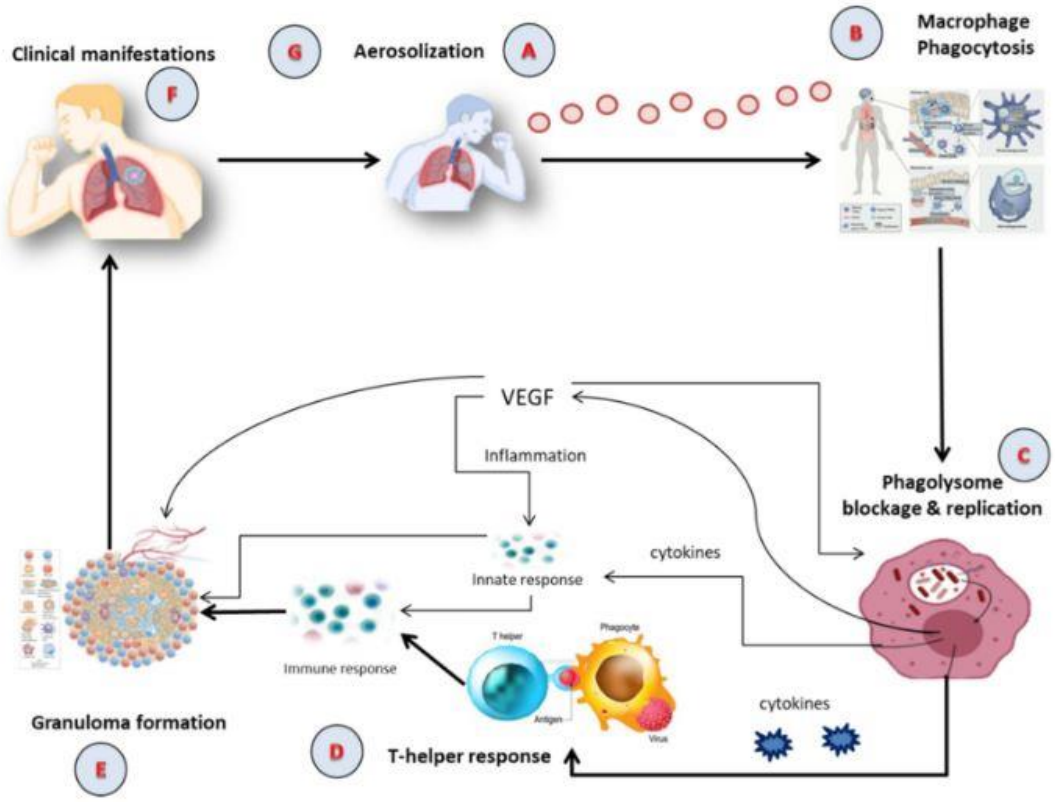

Figure 1: The Pathophysiology of active TB; (A) Aerosolization; (B) Macrophage phagocytosis; (C) Blockage and replication of phagolysosome; (D) T-helper response; (E)Granuloma formation; (F) Clinical manifestation; (G) Infection of susceptible person via aerosolization. VEGF: Vascular Endothelial Growth Factor.

Conventional Treatment Options and Its Limitations

The current vaccination used to prevent TB is called *Mycobacterium bovis* bacillus Calmette–Guérin (BCG), and it was first given out in 1921. The BCG vaccine protects against TB in children between 60 and 80 percent of the time, but it is ineffective against pulmonary TB in adults. Instead of the BCG vaccine, which is only effective in children, the WHO advises pharmacological therapies for TB in adults; their efficacy has also been reported to differ

geographically.[13] Furthermore, because BCG is a live vaccine, those with impaired immune systems may acquire a disseminated infection. There is a pressing need to create new vaccines due to these limitations.

In most countries, some drug-susceptible TB is treated with an oral medication regimen. This treatment plan consists of two months of daily or three-times-per-week administration followed by four months of isoniazid and rifampicin of ethambutol (E), isoniazid (H), pyrazinamide (Z), rifampicin (R), and HRZE.[14] Treatment regimens have become increasingly complex due to the rise in TB complications, namely MDR strains, extensively drug-resistant (XDR) strains, HIV co-infection, the presence of comorbidities such as diabetes, and TB retreatment after recurrence. Drug-resistant TB may be treated by prolonging the course of treatment with drugs that the organism is susceptible to for up to 20 months or by adding an injectable antibiotic such as kanamycin, amikacin, or streptomycin.[15]

The currently available drugs for treatment of TB are distributed throughout the body via systemic blood circulation after being ingested or administered intravenously, and many molecules aggregate in other body regions rather than reaching the intended site, leading to adverse effects such as nephrotoxicity, hepatotoxicity, ocular toxicity, and ototoxicity. The majority of anti-TB medications are taken orally, which causes pharmacokinetic problems such as reduced bioavailability and a low therapeutic index. Drug therapy used in the traditional manner requires a protracted therapy regimen that involves the continuous and frequent administration of several medications, which lowers patient adherence to current therapies.[16]

Nanoemulsion Drug Delivery in TB

Due to various benefits such as lower doses, improved dosage regimens, reduced adverse effects, decreased drug degradation, improved solubility and bioavailability, and improved patient compliance over conventional therapy, nanomedicines have been shown to be effective therapies and result in encouraging outcomes for the treatment of TB. A wide variety of drug delivery systems using different types of nanocarriers have proven to be successful.[17] Controlled and sustained drug release is one advantage of nanocarrier-based anti-TB medications over free medicines . They also decrease dosing frequency and address the issue of poor compliance. Physical encapsulation, adsorption, or chemical conjugation are all ways that therapeutic drugs can be introduced into nanocarriers. Significantly, it is

possible to target host cells utilizing nanocarriers via either passive accumulation or active targeting.[18]

Nanoemulsions are colloidal dispersion of oil-in water/water-in-oil or mini-emulsion that forms nano size globules having a size range from 20-600 nm and it is stabilized by the film layer of surfactants and co-surfactants. The large amount of surface active agents is required in microemulsion, while fewer amounts are required in nanoemulsion. Nanoemulsions are kinetically stable, thermodyna-mically unstable and clear transparent emulsions. These systems are an excellent vehicle for drug delivery, which allows uniform distribution and penetration of drug on the skin due their small globule size and, large surface area. The bioavailability and solubility of both water soluble and water insoluble drugs can be enhanced using nanoemulsions.[19] Intravenous nanoemulsions are good drug delivery and drug targeting systems except for lung and mononuclear phagocytic system. Nanoemulsion increases the lipophilicity of lipophilic drugs by esterification with long chain fatty acid, so that, they are better for lipophilic drugs and also provide stabilization, prevent enzymatic degradation or oxidation of labile drugs. When nanoemulsions are employed as edible coating, hey increase the efficacy and shelf life of food products in comparison to normal emulsion and also enhance the nutritional value, quality, and physical stability of the product. Nanoemulsions can be prepared methodically as creams, shampoo, gels, sprays, aerosols and can be administered via topical, intravenous, intranasal, oral, pulmonary and ocular routes. This type of delivery system could be used in the protection of various drugs from severe environmental factors like pH, oxidation and hydrolysis to target some organ by utilizing their increased permeability and by escaping reticulo-endothelial system in parenteral. Nanoemulsions have a tendency to break down over time due to a variety of destabilization mechanisms, such as gravitational separation, coalescence, flocculation, and Ostwald ripening. Physical properties and stability of nanoemulsions have been improved by the addition of stabilizers and co-adjuvants; since molecular interactions strongly influence structure and rheological behavior. In emulsions due to Ostwald ripening globules sizes increase and cause instability of emulsion, therefore in nanoemulsions wax (oil blend of mono, di, triglycerides) nd ampiphilic block copolymer (polyethylene oxide, polycaprolactone) are used at high temperature that are soluble in oil phase for prevention of Ostwald ripening. Nanoemulsion can be stabilized by adding sufficient quantity of surfactants and/or co-surfactants. Nano-emulsion also prevents coalescence in system by formation of

thicker hydration at interface and elasticity increase by addition of more water soluble surfactant.[20]

Nanoemulsions are classified on the basis of their compositions, oil in water nanoemulsions in which oil droplets are dispersed in continuous aqueous phase while in water in oil nanoemulsions, water droplets are dispersed in oil phase and in bi-continuous nano-emulsions, wherein microdroplets of oil and water are interspersed within the system. Some of the advantages of nanoemulsions include that both lipophilic and hydrophilic drugs can be delivered, their kinetic stability is high, they provides large surface area for absorption due to their smaller size, skin permeability of drug can be increased, non-toxic and non-irritant, mask the taste and has good aesthetic property, improves patient compliance and acceptance, increases the bioavailability and biocompatibility, eliminates variability in absorption. Drugs can be protected from hydrolysis and oxidation. There are some drawbacks like high melting substances have low solubilizing capability, for stabilizing the nanodroplets, high amount of surfactant and co-surfactant are required, stability of nanoemulsions is affected by the environmental factors like temperature and pH.[21]

Components of Nanoemulsions

Active pharmaceuticals ingredients (APIs), oils, surfactants, co-surfactants, aqueous phase, and additives are required for the formulation of nanoemulsion.[22,23]

(a) Oil: Oils are used for the solubilization of lipophilic drugs and increasing the drug transport through biological membrane and skin surface.

(b) Surfactants: Polarand nonpolar region arepresent in surfactant molecules. According to the nature of polar group within the molecules, the surfactants are categorized into anionic, cationic, non-ionic and zwitter ionic groups. They can contribute by decreasing the interfacial tension between two immiscible liquids and make them miscible. For the preparation of w/o nanoemulsions, the surfactants having low hydrophilic lipophilic balance (HLB) value may be used, while for preparation of o/w nanoemulsions, the surfactants with high HLB value are used.

(c) Co-surfactants: For the preparation of nano-emulsion, single chain surfactants are not able to decrease the oil/water interfacial tension. Therefore, co-surfactants are used along with surfactant which decreases the interfacial tension by increasing the fluidity and entropy of the system.

Table 1: Compositions of Nanoemulsion.

Components	Chemical Name	References
Oil	Myristic acid isopropyl ester	[22]
Surfactants	Span 60, Span 80, Span 85, Tween 80, Tween 60, Tween 20.	[23]
Co-surfactants	Ethylene glycol, Transcutol P, Tarnscutol HP, Isopropyl alcohol, Ethanol, Glycerine, Propylene Glycol, Propanol, n-butanol, PEG 400	[23,24]
Additives	Preservatives (methyl paraben, propyl paraben and benzalkonium chloride); Tonicity modifiers (xylitol, sorbitol, glycerol); Antioxidants (tocopherol, defoxamine mesylate, ascorbic acid); pH adjusting agents (NaOH and HCl solution); Stabilizers (Cholic acid, oleic acid, deoxycholic acid and their salts).	[24]

Methods of Preparation of Nanoemulsions

High Energy Methods

High pressure homogenization: In this method, for the formulation of nanoemulsion, high pressure homogenizer or piston homogenizer is used. By using this technique, nanoemulsion having droplet size 1nm can be prepared. At high pressure (about 500-5000psi) both oil and liquid phase are mixed together because of the impact of applied force in a small inlet orifice. Because of the applied force on the mixture of liquid, these produces hydraulic shear and intense turbulence and due to these fine particles of nanoemulsions are formed. This highly exothermic method has considerable efficiency and requires high energy for nanoemulsion preparation.[24] By using a high-pressure homogenizer at a pressure range of 200–500 bars at 60°C nanoemulsions are formed. Formulated nanoemulsion from the mixture of palm oil, distilled water, vitamin E, and nonionic surfactant tween 40 in three stages. Increase in pressure, number of homogenization stage and temperature, and the droplet size of nanoemulsion increases. Microfluidization: Oil phase and aqueous phases is mixed using microfluidizer device. Both phases are allowed to move in a homogenizer which results in the formation of emulsion. Stable nanoemulsion is formed by allowing the emulsion into the microfluidizer.[25] Interaction chamber contains micronized channel through which oil and water phase are passed at a pressure of about 500-20000 psi using high pressure positive displacement pump. Fine particles having submicron size range are formed when the mixture is flowing through the microchannels on to impingement area. In this technique, with the increasing homogenization pressure and emulsifier concentration, the droplet size decreases. Developed liquid and solid nanoemulsions using 10% (w/w) octadecane, 1-5% (w/w) sodium dodecyl sulfates by using high-pressure microfluidization (5000-28,500psi) at 45°C. Liquid

and solid octadecane nanoemulsions stabilize with sodium dodecyl sulfate using microfluidization. The study shows that the droplet sizes at nanoscale affects the crystallization and melting behavior to a greater extent.[26]

Ultrasonication: In this method, the formation of na-noemulsions requires high-intensity ultrasonic power 400W; waves having frequency more than 20 kHz are employed that produces very fine tiny droplets after ultrasonication i.e. 0.13, 1.0, 5.0 μm and volumetric mean size of 0.4 ± 0.5 μm. At system the excess pressure of the ambient value has been exerted by the use of constant amplitude sonotrode. Small numbers of bubbles are formed by increasing external pressure so that the droplet formation increases within an ultrasonic field. Therefore, the disintegration force of formed droplets increases with an increase in external pressure. The formed droplets become durable and more intense during the disintegration of bubbles at atmospheric pressure. In low ultrasonic system, droplet formation (cavitation) is the important mechanism of power immoderation. Nanoemulsions were prepared by mixing of cinnamon essential oil as an oil phase and deionized water and tween 80 as aqueous phase. The oil phase was added slowly to the aqueous phase at 25 °C with stirring during a magnetic stirrer at 500 rpm for 15 min to organize a coarse emulsion. The oil concentration was fixed at 1% w/w in each of coarse emulsions. The Tween 80 concentration was established at three different levels of 1%, 2%, and 3% w/w of the solution. The nanoemulsions were then prepared using an ultrasonic bath and an ultrasonic probe.[27,28]

Characterization of Nanoemulsion

Phase Behavior Study Ingredients (surfactant, oil part and liquid part) are usually optimized or characterized in phase behavior study. The dispersibility and phase of nanoemulsion will be determined with the assistance of phase inversion temperature methodology and self-emulsification methodology. Study will be proceed by placing different ingredients of nanoemulsion at different concentration in glass ampoules and totally homogenized at a certain temperature for a time till equilibrium. Anisotropic part will be known by polarized. Kheawfu et al., 2018 prepared curcumin- nanoemulsion containing 10% and 20% of clove oil and 5% surfactant (Triton X-100, polysorbate 20, or polysorbate 80) in water. Phase separation occurs in formulations that contain polysorbate 80 with both 10% and 20% clove oil after storage at an ambient temperature for 24hrs while polysorbate 20 containing formulations shows no phase separation.[29]

Measurement of Droplet Size and Polydispersity Index: The particle size and polydispersity index of nanoemulsion was measured by photon correlation spectroscopy using a Malvern Zetasizer. Samples were diluted appropriately with the aqueous phase of the formulation to get optimum kilo counts per second (Kcps) of 50 - 202.8 for measurements, and the pH of diluted samples ranged from 6.9 to 7.2. The measurements were carried out at 25 ºC in 75% - 100% intensity. The samples were analyzed.[30]

Determination of Entrapment Efficiency: Entrapment efficiency (EE %) was determined by measuring the concentration of free drug (unentrapped) in aqueous medium. This is the prime importance, as it influences the release characteristics of drug molecule. The amount of drug encapsulated per unit weight of nanoparticles is determined after separation of the entrapped drug from the nanoemulsion formulation.

EE = Weight of total drug in formulation – Weight of drug in aqueous phase × 100 / Weight of total drug in formulation

Drug Content: Accurately weighed quantities of nanoemulsion were mixed with 100 ml of 0.1M HCl. The filtrate was analysed spectrophotometrically at 262 nm for drug content against 0.1 M HCl. Corresponding drug concentrations in the samples were calculated from the calibration plot generated by regression of the data. Drug content was calculated as detected amount of itraconazole with respect to theoretical amount of drug used for the preparation of nanoemulsion. Each determination was carried out in triplicate.[31]

In-vitro Drug Release: In vitro percent drug release studies were carried out by using franz diffusion cell. Cellophane membrane was used as filtration purpose. Membrane was soaked in phosphate buffer for 12 hours before mounting it on cell. Itraconazole formulation was placed in the donor compartment and recipient compartment was filled with diffusion medium phosphate buffer pH 7.4. The content of the cell was stirred with the help of magnetic stirrer at 37ºC. Serial sampling were performed after 0.5, 1, 2, 3, 4, 5, 6 h. Fresh phosphate buffer was placed at receptor compartment to maintain constant volume. Samples were analyzed by spectrophotometrically at 262 nm.[32]

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