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NOVEL DRUG DELIVERY SYSTEMS: DESIRED FEAT FOR TUBERCULOSIS

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ABSTRACT

Tuberculosis has claimed its victims throughout much of known human history and is currently the most devastating human bacterial disease. The ability to infect human population on a global scale, combined with the widespread emergence of multi-drug resistant strains, has led to the placement of *Mycobacterium tuberculosis* on the National Institute of Allergy and Infectious Diseases (NIAID) list of Biodefence and Emerging Infectious Disease Threats Agents. The resurgence of interest in tuberculosis (TB) has stemmed because of increased evidences from developed countries. Contrary to expectations, no country has reached the phase of elimination and in no subsection of society TB has been completely eliminated. A deeper understanding of the process will assist in the identification of the host and mycobacterial efforts involved and provide targets for therapeutic strategies against tuberculosis. The article presents a view on pathogenesis of tuberculosis and its diverse manifestations, host defense evasion, mechanisms of microbial persistence, emergence of Multiple Drug Resistance and Extensive Drug Resistance, conventional therapy used and the possible novel systems which are under extensive investigation as drug carriers for improving the cytosolic concentration of the anti-tubercular agents.

Keywords: Tuberculosis, Novel drug delivery system, *Mycobacterium tuberculosis*, Therapy.

INTRODUCTION

'Tuberculosis is a social disease, and presents problems that transcend the conventional medical approach. On one hand, its understanding demands that the impact of social and economic factors on the individual be considered as much as the mechanisms by which tubercle bacilli cause damage to the human body. On the other hand, the disease modifies in a peculiar manner the emotional and intellectual climate of the societies that it attacks.' Rene Dubos (1952 one of the Giants of the 20th century medicine).

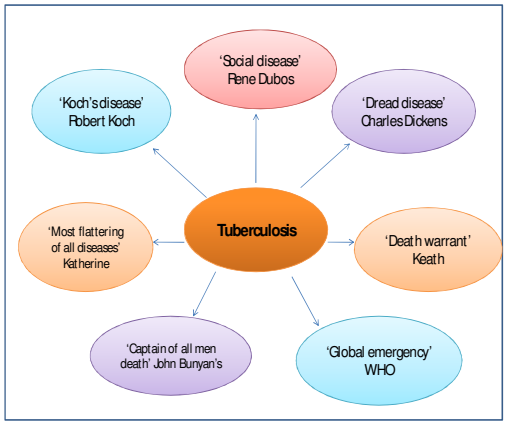

Fig. 1: Designation of Tuberculosis by various renowned Scientists.

Tuberculosis is an ancient scourge [1] and a global health problem causing an increase in mortality and morbidity [2]. The synergistic pathology of co-infection with the human immune deficiency virus has fuelled the disease, as well as the continued resistance of *Mycobacterium tuberculosis* strains to multiple antibiotics is the cause for physician's armamentarium for treating and preventing tuberculosis being limited. It is the most common opportunistic infection in Acquired-Immuno Deficiency Syndrome. Tuberculosis (TB) is a disease caused by an obligate intracellular pathogen. It is an infectious disease, therefore transmitted from one person to another person. The TB germ (*Mycobacterium tuberculosis*) invades lungs and causes the onset of disease. The germ either sleeps quietly (in the host body) without being noticed (this is called a TB infection) or it can wake up and make patient sick (this is called TB disease). In addition, there are now two more serious types of TB disease. The first is called multidrug-resistant TB, or MDR TB. MDR TB is not easy to treat because the two best medicines for TB don't get rid of the germ. The second is called extensively drug-resistant TB, or XDR TB. XDR TB is a rare kind of MDR TB that is very complicated to treat. Most of the medicines used to get rid of the TB germ do not work very well. The description of Tuberculosis is below:

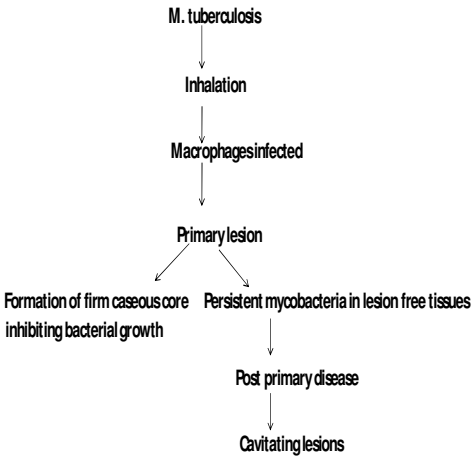

Fig. 2: Description of Tuberculosis

There are nearly 60 commonly recognized species of mycobacterium but most are saprophytic inhabitants of soil. Tuberculosis is an infectious (contagious) disease caused by Mycobacterium tuberculosis (in humans mainly) is a microscopic, rod shaped bacterium. Mycobacteria are

aerobic, non-spore forming, non-motile bacilli with a waxy coat that causes them to retain the red dye when treated with acid (red snappers) in the acid fast stains [3]. Mycobacterias- *M. bovis (cattle), M. africanum, M. canetti, M. microti , M.smegmatis, M. leprae , M. fortuitum, M. brumae (*less common in humans). Tuberculosis spreads by droplet infection, in which a person breathes the bacilli released by a TB patient through coughing, exhaling or sneezing. Once inhaled, water in the droplets evaporates and the tubercule bacilli may reach the alveoli. The causative organism and the disease caused along-with the risk factors for Tuberculosis is discussed ahead.

Table 1: Causative organism, host, source and the disease [4]

Organism	Host	Source	Disease
M. tuberculosis	Diseased persons	Infective droplets	Tuberculosis
M. bovis	Diseased cows	milk	Intestinal or tonsillar lesions
M. avium	No virulence in normal host		Disseminated infections
M. intracellular	Patients with AIDS		Disseminated infections

M.- Mycobacterium

There are various risk factors which may enhance or propagate the onset of disease i.e. tuberculosis, some of them are human immunodeficiency virus infection, low socioeconomic status, alcoholism, homelessness, crowded living conditions, diseases that weaken the immune system, migration from a country with a high number of cases.

Pathogenesis

The pathogenesis of tuberculosis is complex and its manifestations are diverse, reflecting a lifetime of dynamic interactions between Mycobacterial virulence factors and the human immune system. TB infection begins when the mycobacterium reaches the alveolar macrophages. *Mycobacterium tuberculosis* (Mtb) is promiscuous in its use of multiple cell surface receptors to gain entry into macrophages [5]. The receptors on which microbe adhere are mannose, Fc, complement etc. Once inside the host M. tuberculosis resides in a membrane bound vacuole. Attributes of the bacteria are:

Modifies the phagosome maturation in order to enhance its intracellular survival [6].

Alteration in the Rab GTPase protein composition [7].

Exclusion of vacuolar protein ATPase with consequent lack of acidification [8].

Retention of a protein Tryptophan aspartate containing coat TACO [9].

The inhaled bacilli get lodged in the terminal air spaces of the lungs

because of aerodynamic reasons close to the pleura where they replicate.

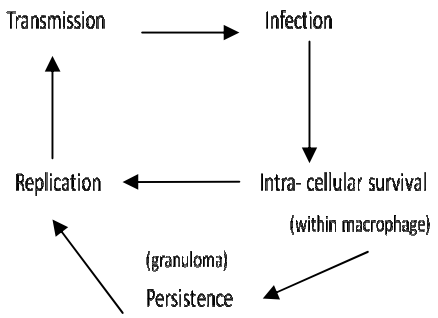

Fig. 3: The transmission and persistance of Mycobacteria

The primary infection involves replication within the endosome of macrophages, then spread to the lymph nodes and then eventual dissemination to the remote sites of the body. In spite of successful initial parasitization of the human host the primary infection is asymptomatic in adults. Even after the activation of human immune response, the organism is never completely eradicated. Macrophages, T-lymphocytes, B-lymphocytes and fibroblasts are among the cells that aggregate to form a granuloma surrounding the infected macrophages. The granuloma functions not only to prevent dissemination of the mycobacteria, but also provides a local environment for communication of cells of the immune system. Within the granuloma, T lymphocytes secrete cytokine like interferon γ which activates macrophages to destroy the bacteria with which they are infected. Bacteria are not always eliminated within the granuloma, but can become dormant, resulting in a latent infection. Another feature of the granulomas of human tuberculosis is the development of cell death, also called necrosis, in the center of tubercles. Thus, mycobacterium is foremost among the bacterial pathogens in its ability to establish and maintain latency. The only clinical evidence of Mtb infection during latency is delayed type hypersensitivity against mycobacterial antigens, demonstrated by a tuberculin skin test and the hematogenous spread of Mtb is detected in tissue by in-situ Polymerase Chain Reaction. Reactivation of TB mostly occurs in the lungs but may involve other organs also. Secondary TB lesions can develop in the lungs (particularly the apex of the upper lobes that is the high oxygen pressure areas), peripheral lymph nodes, kidneys, brain, and bone. All parts of the body can be affected by the disease, though it rarely affects heart, skeletal muscles, pancreas and thyroid. The signs and symptoms of the disease are cough lasting for more than 2-3 week, progressive increase in production of mucus ,discolored or bloody sputum, chest pain ,tissue destruction (liquefies infected portioin of lungs), chills, fever, fatigue, ssevere headache , shortness of breath, weight

loss, loss of appetite, night sweats, ttiredness or weakness

Expression of Bacterial Virulence Regulatory Proteins (Genes)

Complementation of *Mycobacterium tuberculosis* (Mtb) H□□Ra by a cosmid library of Mtb identified a number of clones responsible for the pathogenesis of tuberculosis [10]. *In-vivo* complementation assay provided evidence for involvement of katG and rpoV in the virulence of Mtb [11]. Substractive hybridization revealed specifically or differentially expressed proteins in virulent mycobacterium [12]. The sequence of gene from Mtb H□□Ra designated as virS encoding a 38kDa protein belonging to AraC family of transcriptional regulators bears homology with the virulence regulating proteins of other species i.e. Yersinia, Shigella etc.

Therapy

The history of tuberculosis changed dramatically with the introduction of the anti-tubercular agents. The drug discoverers and the year of invention with the inference are listed below.

TB prevention and control takes two parallel approaches. In the first, people with TB and their contacts are identified and then treated. Identification of infections often involves testing high-risk groups for TB. In the second approach, children are vaccinated to protect them from TB. Unfortunately, no vaccine is available that provides reliable protection for adults. However, in tropical areas where the levels of other species of Mycobacteria are high, exposure to nontuberculous mycobacteria gives some protection against TB. The World Health Organization declared TB a global health emergency in 1993, and the Stop TB Partnership developed a Global Plan to Stop Tuberculosis that aims to save 14 million lives between 2006 and 2015 Since humans are the only host of *Mycobacterium tuberculosis*, eradication would be possible: a goal that would be helped greatly by an effective vaccine.

Table 2: Example of genes as well as there proteins in the pathogenesis of few disease i.e. the causative organism

S. No	Organism	Gene	Regulation	Reference
1	Shigella	virB	Transcriptional activator. Necessary for invasion and spread of infection to other cells	[11]
2	Yersinia	virFy	Invasion and intracellular survival.	[12]
3	*Mycobacterium tuberculosis*	virS	Virulence of the pathogen.	[10]

Table 3: Drugs discovery [1]

S. No.	Drug	Discoverer	Year	Inference
1	Tuberculin (isolated substance)	Robert Koch	1890	Discredited as ineffective
2	BCG (for use as a vaccine)	Albert Calmette	1921	herculean effort to attenuate M. bovis
3	PAS(para amino salicylic acid)	Jorgen Lehmann	1943	first bactericidal agent
4	Streptomycin	Albert Schatz, Elizabeth Bugie, and Selman Waksman	1944	Effective anti-tubercular agent
5	Thiosemicarbazone	Gerhard Domagk	1945	Use diminshed
6	Isoniazid	Czech biochemist	1952	first oral mycobactericidal agent
7	Rifamycins		1957	First-line agent in tuberculosis treatment regimen

BCG- Bacillus Calmette Guerine

Table 4: Classification of Drugs

S. No.	Category	Drugs	Intellectual property Status	Dose (mg)	BCS Class
1	First-line oral antituberculosis drugs	Isoniazid ,	Generic	300	III
		Rifampicin,	Generic	300	II
		Ethambutol HCl,	Generic	400	III
		Pyrazinamide,	Generic	500	III
		Streptomycin	Generic	500	N/A (i.v./ i.m.)
		Rifabutin	Pfizer	150	II
2	Injectable antituberculosis drugs	Kanamycin A,	Generic	1000	III N/A (i.v./ i.m.)
		Amikacin,	Generic	1000	N/A (i.v./ i.m.)
		Capreomycin,	Generic	1000	N/A (i.v./ i.m.)
		Streptomycin	Generic	500	N/A (i.v./ i.m.)
3	Fluoroquinolones	Levofloxacin,	Generic	500	N/A (i.v./ i.m.)
		Moxifloxacin,	Bayer	400	Na
		Gatifloxacin	Kyorin Pharmaceutical Co.	400	Na
4	Oral bacteriostatic second-line	Ethionamide,	Generic	500	II
		Cycloserine,	Generic	500	IV/ II
		p-aminosalicylic acid	Generic	500	Na

BCS- Biopharmaceutical Classification System ,ISH- Isoniazid, RIF- Rifampicin, PYZ- Pyrazinamide, ETH- Ethambutol, STP- Streptomycin.

i.v.- Intra- venous, i.m.- Intra- muscular, Na- not available

The standard therapy regimen for uncomplicated drug- sensitive TB: Isoniazid (ISH) (5mg/kg) maximum upto 300mg/day, Rifampicin (RIF) (10mg/kg) maximum upto 600mg/kg, Pyrazinamide (PYZ) (15-30mg/kg) maximum upto 2g/day, Fourth agent– a.) either Ethambutol (ETH) (15mg/kg/day) b.) or Streptomycin (1g/day). During pregnancy- The standard multidrug regimen (of ISH, RIF, ETH) is safe [13]. Various supportive treatments are Diet- Whole food diet including raw foods, fluids and particularly pears, Nutritional Therapy- Vitamins (A, beta-carotene, E, C, B complex), essential fatty acids, multiminerals and zinc, Herb Therapy- Tincture of Echinacea, elecampane, and mullein, garlic capsules, Hydrotherapy, Juice Therapy- Raw potato juice, carrot juice, Topical Treatment- Eucalyptus packs etc. Vaccines- Bacillus Calmette-Guerin (BCG) is of dubious efficacy and is used by many countries as a part of there TB control programme. This was the first vaccine for TB and developed at the Pastuer Institue in France. The first recombinant TB vaccine Rbcg30, entered clinical trials in the united state in 2004, sponsored by NIAID. A very promising TB vaccine, MVA85A is currently in the phase -II South Africa by a group led by the Oxford University. DOTS (Directly Observed Treatment short course) – DOTS is the most effective strategy available for controlling TB. TB drugs are provided under the observation of health care provider/ DOT (Directly observed treatment) provider. DOT provider will also take care of any side effects of the medicine and be a source of moral support to the patient. The five components of the DOTS strategy are: Government commitment to sustained TB control activities, Case detection by sputum smear microscopy among symptomatic patients self- reporting to health services, Standardized treatment regimen of 6-8 months for at least all confirmed sputum smear positive cases, with directly observed treatment (DOT) for at least the initial 2 months, A regular, uninterrupted study of all essential anti- tuberculosis drugs, A standardized recording and reporting system that allows assessment of treatment results for each patient and of the TB control program overall. The Case detection rate (all new cases, %) for India till the year 2007 summarized in a graphical form and the treatment success of the therapy for the above detection cases in India till 2007.

Most side effects of the Anti- Tubercular Drugs are minor in nature. The serious side effects are; yellowish skin or eyes, fever for 3 or more days, abdominal pain, tingling fingers or toes, easy bleeding, aching joints, dizziness, tingling or numbness around the mouth, easy bruising, blurred or

changed vision, ringing in the ears, and hearing loss.

Multi-Drug Resistance and Extensive Drug Resistance

MDR-TB describes strains of tuberculosis that are resistant to at least the two main first-line TB drugs - isoniazid and rifampicin. XDR-TB is MDR-TB that is also resistant to three or more of the six classes of second-line drugs. The description of XDR-TB was first used earlier in 2006, following a joint survey by World Health Organization (WHO) and the US Centers for Disease Control and Prevention.

Resistance to anti-TB drugs in populations is a phenomenon that occurs primarily due to poorly managed TB care. Problems include incorrect drug prescribing practices by providers, poor quality drugs or erratic supply of drugs, and also patient non-adherence. Multidrug-resistant tuberculosis, defined as TB caused by organisms that are resistant to isoniazid and rifampicin, continues to threaten the progress made in controlling the disease. The emergence of extensively drug-resistant TB (XDR-TB), defined as MDR-TB that is resistant as well to anyone of the fluoroquinolones and to at least one of three injectable second-line drugs (amikacin, capreomycin or kanamycin), has heightened this threat. XDR-TB has been identified in all regions of the world since 2006. Treatment outcomes are significantly worse in XDR-TB patients than in MDR-TB patients. Outbreaks of XDR-TB in populations with high prevalence of HIV have caused alarmingly high mortality rates. The emergence of XDR-TB as a new threat to global public health demands that health officials and health-care providers respond with a coordinated strategy drawing on the Stop TB Strategy.

Table 5: (WHO 2007-2008 XDR & MDR Tuberculosis Global Response Plan)

Indicator	2007	2008	Total
Cultures performed	1,800,000	2,200,000	4,000,000
Drug susceptibility tests performed	750,000	900,000	1,650,000
New laboratories established	21	22	43
MDR-TB cases enrolled on treatment(excluding XDR-TB)	60,000	100,000	160,000
XDR-TB cases enrolled on treatment	6,000	10,000	16,000
% of estimated MDR-TB cases enrolled intreatment per year (excluding XDR-TB)	16%	28%	
% of estimated XDR-TB cases enrolled intreatment per year	25%	43%	
Lives Saved	49,000	85,000	134,000

W.H.O. – World Health Organization, XDR- Extensive Drug Resistance, MDR- Multiple Drug Resistance TB- Tuberculosis

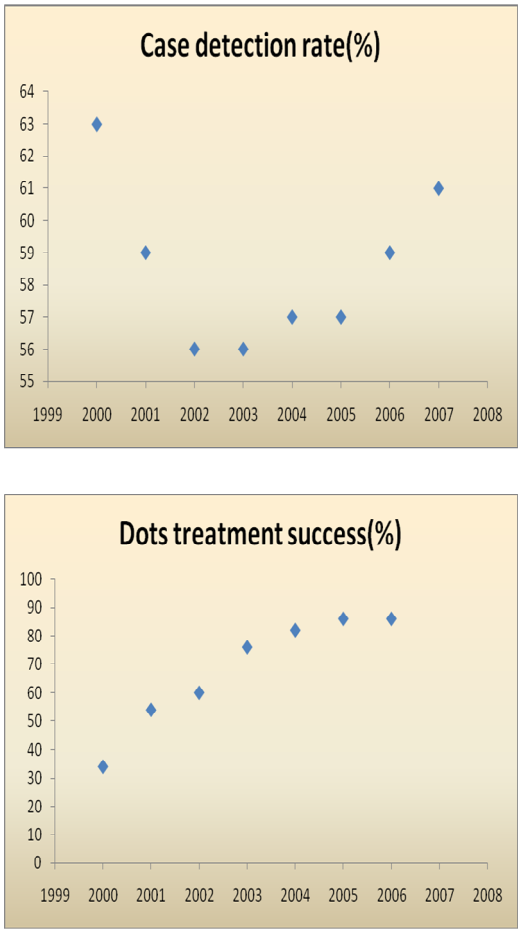

Fig. 4: Case detection rate and DOTS treatment success

Novel Delivery Systems

Inhalation of aerosolized drugs is a well established modality [14] in the treatment of localized disease states within the lungs. A significant disadvantage of many existing inhaled drugs is the relatively short duration of resultant clinical effects and most medicines in aerosol form require inhalation at least 3-4 times daily [15]. This often leads to poor patient compliance with the therapeutic regime and increases the possibility of associated side-effects due to the risk of self- administration of the drug by the patient. A number of methods are used for potential pulmonary sustained release systems. Example of few promising candidates are-

(1) Nanoparticles and Microparticles- Nanoparticles are colloidal structures composed of synthetic or semi-synthetic polymers. The bioactives are entrapped in the polymer matrix as particulates enmesh or solid solution or may be bound to the particle surface by physical adsorption or chemical reactions. Inhalation is the most significant route for the delivery of airborne nanoparticles [16]. The human lungs contain about 2300 Km of airways and 500 million alveoli [17]. The surface area of lungs is estimated to be approximately 75-140 m^2 in adults [18].

The large surface area of the alveoli and the intimate air- blood contact in this region makes the alveoli less well protected against inhaled substances, such as nanoparticles as compared to the airways [19]. Microparticles are spherical particles with size range from 50nm to 2 mm, containing a core substance. They are generally injected either intraperitoneally, or directly to the target organs and because of there size they provide a sustain release depot of the drug. They entail the need

for diversification of natural course of colloidal carrier biodisposition i.e., passive accumulation. They impart hydrophilicity to the surface and contributes a distinctive steric barrier. Therapeutic applications of Nanoparticles include- Intracellular Targeting-Nanoparticles can be prepared by using dreivatized polymers, which orient projecting their hydrophilic segment exposed to aqueous bulk while hydrophobic segment are shielded, thus the resultant surface tends to be hydrophilic and evade recognition from reticulo- endothelial system [20]. Avoidance of Multi-Drug resistance- Nanoparticle loaded drugs have resulted in effective treatment of diseases both in animal and clinical models [21]. Alongwith cell sensitization, nanoparticulate drug delivery may help over come a broader range of drug resistance due to favourable pharmacokinetics.

(2) Liposomes

Liposomes are concentric bilayer vesicles in which an aqueous volume is entirely enclosed by a membranous lipid bilayer.These are the most extensively investigated systems for controlled delivery of drugs to the lungs, since they can be prepared with phospholipids endogenous to the lungs as surfactants. They can entrap a wide range of hydrophilic as well as hydrophobic drugs. Pulmonary delivery has been improved and even tested in animals and human subjects [22]. Incorporation of drugs in liposome enhances bactericidal activity as compared to free drug, especially for the treatment of monocytes and macrophages [23]. Drug distribution depends upon the drug release from the liposome which could serve to retain drugs in the lungs and minimize their distribution to other organs. When given intratracheally to sheep, amikacin in solution exhibited a half life of about 2 h with a maximum plasma level of 8.3µg/ml, whilst the half life of drug encapsulated in phosphatidylcholine/ phosphatidylglycerol /cholesterol (4:3:3) liposome was found to be greater than 10 h with 3.3µg/ml plasma level [24]. Application of liposomes include- relatively low toxicity, prepared in wide size range (20nm-1mm), ability to solublize poorly water soluble drugs, facilitating there nebulization, they serve as a biodegradable pulmonary reservoir with prolonged residence time, they decrease mucociliary clearance of drugs due to their surface viscosity, can be exploited as a targeting device to individual population within the lung, specifically to the infected or impaired alveolar macrophages and the lung epithelium. Novel delivery systems can be administered to the lungs by various modes of delivery i.e. Nebulization, Instillation, Insufflations etc. The tabular representation is as follows:

Table 6: Table for illustration of various delivery systems with the mode of delivery, percentage of drug loaded into the system

S. No.	Delivery System	Mode of Delivery	Drug Loading	Reference
1	Liposomes conventional	Nebulization	Rifampicin22% Isoniazid 14%	[25]
2	Liposome ligand appended	Nebulization	Rifampicin40%	[26]
3	Liposomes	Nebulization	Amikacin 15-21%	[27]
4	Liposome	Instillation	Amikacin 40%	[24]
5	Liposome	Nebulization	Rifampicin 69.3%	[28]
6	Liposome	Nebulization	Rifampicin85.3%	[29]
7	Microparticles PLG	Nebulization/ Insufflation	Rifampicin 30%	[30]
8	Microparticles PLA dry powders	Inhalation	Rifampicin11% Isoniazid 4%	[31]
9	Microparticles DPP	Insufflation	PAS, 95%	[32]
10	Microparticles	Inhalation	Rifampicin20.8±2.4%	[33]
11	Nanoparticles PLG	Nebulization	Rifampicin60-70%	[34]
12	Lectin PLG	Nebulization	Rifampicin60-70%	[35]
13	Solid lipid nanoparticles	Nebulization	Rifampicin40-50%	[36]
14	Microspheres	Dry powder inhaler	Capreomycin sulphate 6.2±2%	[37]

PLG- Poly (lactide- co- gycolide), PLA- Polylactic acid, DPP- Dipalmitoylglycerophosphocholine

(3) Niosomes

Non-ionic surfactant based vesicles (niosomes) are the structures formed from the self assembly of non-ionic amphiphiles in an aqueous media resulting in a closed bilayer structure. The assembly is rarely spontaneous [38] and usually involves some input of energy such as physical agitation or heat. The result is an assembly in which the hydrophobic parts of the molecule are shielded from the aqueous solvent and the hydrophilic head groups enjoy maximum contact with same. Rifampicin encapsulated within Span 85 (sorbitan tri-oleate) based noisome in the 8-15 mm size range were found to accumulate in the lung of mice [39] thus offering the possibility of improved anti-tuberculosis therapy.

(4) Biodegradable Microspheres

These drug carriers can be prepared over a wide range of particle sizes, which is a decisive factor in the in vivo deposition of particulate carriers. Drugs can be easily incorporated with relatively high efficiency and manipulation of the synthetic process procedure different drug release rates can be achieved. They are more physicochemically stable both in vitro and in vivo. Drugs entrapped have a slower release rate and a longer duration of action. The higher stability enables easy formlation. A number of biodegradable microspheres have proved to be non-toxic, biodegradable and non-immunogenic following systemic injection [14]. Model microspheres coated with a polaxamine-980 block copolymer demonstrated increased circulatory half life in the vascular compartment after intravenous injection with little or no RES uptake and high deposition levels in lungs [40].

(5) Nanocapsule

These are the vesicular systems in which drug is essentially encapsulated within the central volume surrounded by an embryonic continuous polymeric sheath. These are a hybrid structure between polymer nanucapsule and liposomes. Liposomes preparation involves organic solvents and are leaky, unstable in biological fluids, lung nanocapsule are prepared by solvent free, soft energy procedure and present a great stability (with physical stability upto 18 months). They have generally an oily core, corresponding to medium – chain triglycerides suurounded by a membrane made from a mixture of lecithin and a pegylated surfactant. Their formulation is based on the phase inversion temperature phenomenon of an emulsion leading to lipid nanocapsule formation with good mono-dispersion [41]. Extensive work has been reported using anti- tubercular agents, some of the novel drug delivery systems which have been formulated are summarized below. Following are few systems with various parameters mentioned.

Challenges & Future Prospects

"Age and prior exposure bring no such immunity against TB as they establish against many of the acute infections"– Wade Hampston Frosts [53]. Pulmonary TB is the commonest form of TB and alveolar macrophages are the abode of *Mycobacterium tuberculosis* the administration of anti- tubercular drugs via the respiratory route is an exciting possibility. The objective to eliminate the transmission of causative organism is currently out of reach due to difficulty of diagnosis, multi-drug resistance and treatment adherence. The main reasons for the failure to control the treatable disease are Demographic growth- cases and case fatality have risen more

sharply, because of Human Immuno deficiency virus pandemic [54], Drug resistance- rates are high in many countries (especially to rifampicin, which is too expensive to be included in many of the regimens). The major mechanisms of resistance are inactivation of the drug, altered cell wall permeability or drug efflux, drug titration due to target overproduction, alteration of the target by mutation appear to be employed by Mtb and its resistance to short course chemotherapy regimens [55] and Economic power is political power, and sufferers from TB tend to be from the poorest section of society- whether in developed or developing countries.

The BCG vaccine is of dubious efficacy and the currently available anti-tubercular drugs should be modified in such a way to release drugs in a slow and sustained manner, thus it would be possible to reduce the dosing frequency thereby improving compliance. Plain liposomes and other colloidal carriers are largely unsuccessful in drug targeting due to their difficulties in gaining access to targeted tissues, penetrating vascular barriers and evading phagocytic capture by the reticulo- endothelial system.

The advent of the novel drug delivery systems holds the key for the prevention of tuberculosis disease.

Table 7: Novel delivery systems of Anti- tubercular drugs with some parameters

S/ No.	Delivery System	Polymer	Method	Size	In- vitro	In- vivo	Reference
				Rifampicin			
1	Microparticles	PLGA	Spray drying	RIF-PLGA, 2.76/1.57; PLGA, 2.87/1.45; (VMD/ SD)		Animals treated with single and double doses of RIFPLGA microspheres – reduced numbers of viable bacteria, inflammation and lung damage compared with RIF-only treated animals 28 days post-infection. Two doses of RIF-PLGA reduced splenic enlargement.	[42]
2	Microspheres	PLG	Solvent evaporation	3 to 4 µm,	21 and 12% cumulative *in vitro* drug release, respectively, after 6 days	significant decrease in numbers of CFU at 7 days	[43]
3	Microparticles	PLGA	Solvent evaporation and spray drying	shriveled morphology, spherical particles	3.45 µm (solvent evaporation) and 2.76 µm (spray dried)		[44]
4	Aerosolised	Cast	Egg PC,	MBSA-		7–11% (ligand-anchored	[26]

	liposomes	film method	Cholesterol	coated liposomes size: 3.64 ± 0.65 µm, *O*-SAP-coated vesicles size: 3.85 ± 0.59 µm.		liposomal aerosols) %viability of *Mycobacterium smegmatis* inside macrophages	
				Isoniazid			
5	Porous, non-porous and hardened microparticles	PLG	Double emulsification solvent evaporation	Mean volume diameters were: 62.11 µm, 71.95 µm and 11.75 µm for porous	Non-porous 6 days Porous 3 days Hardened 7 weeks	Porous and non-porous microparticles up to 2 days. Hardened PLG microparticles sustained release of up to 7weeks (plasma)	[45]
6	Implant	PLGA	PLGA polymer rods			Concentrations of INH ≥ 0.2 µg/ml were found both in serum and urine up to 63 days after implant	[46]
				Combination			
INH, RIF, PZA and RIF, INHPYZ ETB	Nanoparticles	alginate	Cation-induced gelification of alginate	235.5 ± 0 nm	elative bioavailabilities o higher compared with oral free drugs	Drug levels were maintained at or above the MIC90 post nebulisation until Day 15	[47, 48]
IF, INH, PYZ, ETB	Microparticles	PLG	Double emulsification solvent evaporation	1.11 µm for INH, 1.40 µm for RIF and 2.20 µm for PZA	up to 20 days (intestinal fluid)	Entrapped drugs remained in circulation up to 72 h	[49]
RIF, INH, PYZ	Nanoparticles	PLG	Multiple emulsion technique	186–290 nm	initial (up to 48 h) burst release (plasma)	no tubercle bacilli could be detected in the tissues after 5 oral doses of treatment	[34]
RIF, INH and PYZ	Nebulised SLNs	nanocrystalline lipid suspensions in water	Emulsion solvent diffusion technique	Suitable for bronchoalveolar drug delivery		Plasma (5 days), organs (7 days)	[36]
RIF, INH	Osmotically regulated capsular multi-drug oral delivery system	HPMC and NaCMC	Phase inversion process	porous structure of the membranes was evident (SEM)	initial burst release	first order kinetics	[50]
INH, RIF	Microparticles	PLG	Double emulsification solvent evaporation	11.75 µm INH and 11.64 µm RIF	up to 7 and 6 weeks	One dose of PLG microparticles cleared bacteria more effectively from lungs and liver in experimental murine model of TB	[51]
INH, RIF	Microspheres	PLG	Combination of	0.5–3 µm	particles delivered to	intracellular drug concentrations	[31]

			solvent extraction and evaporation		the bronchiopulmonary system	lower
INH, PYZ	Single implants	PLGA	Depot drug preparation			sustained levels up to 54 days. [52]

PLG- Poly (lactide- co- gycolide), PLGA- Poly (lactic- co- gycolic) acid, PLA- Polylactic acid, DPP- Dipalmitoylglycerophosphocholine, PC- Phosphatidylcholine, HPMC- Hydroxy Propyl Methyl Cellulose, Na CMC- Sodium Carboxy Methyl Cellulose, CFU- Colony forming unit, MIC- Minimum Inhibitory Concentration, SEM- Scanning Electron Microscopy.

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