AMERICAN JOURNAL OF PHARMTECH RESEARCH

Journal home page: http://www.ajptr.com/

COLLOIDAL DRUG DELIVERY SYSTEMS: A FUTURE PROSPECTIVE FOR TREATMENT OF TUBERCULOSIS

Ankur Bhardwaj*, Lalit Kumar, Veenu

1. Department of Pharmaceutics, ISF College of Pharmacy, Moga, Punjab142001, India

ABSTRACT

Colloidal Drug Delivery system is an advancing technology expected to bring revolutionary changes in the field of pharma and health sciences including drug delivery, diagnostics and treatment. The advancement in colloidal drug delivery systems helps in preparing newer formulations which become useful for treatment of tuberculosis. Development of Metered dose inhaler (MDT) and Directly Observed Therapy (DOTS) also proves to helpful in treatment of tuberculosis. Various colloidal drug delivery systems liposomes, niosomes, nanoparticles and microparticles proves to be a successful tool for tuberculosis treatment. One of the preparations like microemulsions results in theimprovement of bioavailability of the drugs. Similarly corticosteroids also found to be an interesting tool here because corticosteroids reduced the risk of pleural thickening in tuberculosis patients. These various colloidal drug delivery systems minimize the problems of conventional therapy like poor penetration, drug resistance, systemic toxicity and also main the improved drug delivery. This article describes the applications of various formulations along with their future aspects in treatment of tuberculosis.

Keywords: Tuberculosis, Liposomes, Nanoparticles, Niosomes, DOTS.

*Corresponding Author Email: ankurpharma1947@gmail.com

Received 01 October 2011, Accepted 12 October 2011

Please cite this article in press as: Patel HB *et al.*, Colloidal Drug Delivery Systems: A Future Prospective for treatment of Tuberculosis American Journal of PharmTech Research 2011.

INTRODUCTION

Tuberculosis (TB) is one of the major infectious diseases worldwide and its incidence is increasing particularly in association with AIDS pandemic. Among various forms of tuberculosis, pulmonary tuberculosis is most commonly characterized by the involvement of alveolar macrophages harbouring a large number of tubercle bacilli. The tubercle bacilli penetrate inside the macrophages subsequently to protectorate through intracellular harbouring. The bacilli secrete molecules that prevent phagosome–lysosome fusion. Moreover, due to very hydrophobic waxy cell wall, bacilli are resistant to digestion by lysosomal enzymes and hence resist the killing effects of macrophage (Bermudez, 1994)[1]. TB bacilli reside and proliferate within lung macrophages, the very cells that have evolved to engulf and destroy microorganisms that reach the surface of the lungs along with inhaled air. Several researchers, including Hickey and colleagues[2, 3, 4, 5] Khuller's group[6, 7, 8] Terada and colleagues[9, 10, 11, 12] and the Shen and Sharma R.[13, 14] have proposed the use of inhalable or respirable particulate delivery systems for chemotherapy of TB. This proposal is premised upon the uptake of inhaled particles by lung macrophages, where TB bacteria find sanctuary. It is well established that inhaled particulate or vesicular delivery systems enhance the efficacy of anti-TB drugs presumably by targeting macrophages and building up high intracellular drug concentrations. Most of the anti-tubercular drugs presently in use, fail to penetrate macrophages within which bacilli lurk and that derives researchers to persue delivery systems and their engineered versions in order to be therapeutically effective. Although drugs to combat a wide range of genetic, malignant and infectious diseases are available, their efficacy is often compromised by their inability to reach target sites at an appropriate concentration. Effective chemotherapy can be practically implemented in pulmonary infections using liposomes, through drug targeting to alveolar macrophages (AMs)[15, 16]. Consequently, much attention has been focused on the use of drug delivery systems, which are expected to optimise the action of the drugs already in existence by targeting or by facilitating their release where they are needed.

CONVENTIONAL SYSTEM

First drug used for treatment of tuberculosis (TB) was streptomycin in 1947 after this isoniazid was introduced in 1952.

Basically, antiTB drugs can be divided into two types depending on their efficacy and toxicity as given in Table 1

Table 1: Classification of Anti-Tubercular Drugs along with their side effects

Drugs	AntiTuberculosis efficacy	Toxicity	Side effects
First Line			
Isoniazid (INH)	High	Low	Peripheral neuritis, mental disturbances, rarely convulsion.
Rifampicin (RIF)	High	Low	Hepatitis, heamolysis, shock, renal failure.
Pyrazinamide (PYZ)	High	Low	Hepatotoxicity, hyperuricemia.
Ethambutol (E)	High	Low	Nausea, rashses, fever, neurological changes.
Streptomycin (S)	High	Low	Ototoxicity,nephrotoxicity.
Second Line			
Thiacetazone (Tzn)	Low	High	Hepatitis, dermatitis.
Para-amino salisylic acid (PAS)	Low	High	Anorexia, epigastric pain
Ethionamide	Low	High	Impotence, Optic neuritis
Cycloserine (CYS)	Low	High	Tremors, psychosis, tremors.
New Drugs			
Ciprofloxacin	Low	High	Anorexia, dermatitis.
Clarthromycin	Low	High	Ototoxicity
Azithromycin	Low	High	Epigastric pain, impotence

Limitations of Conventional Therapy

1. Poor penetration.
2. Systemic toxicity.
3. Higher dosing.
4. Failure rates are high.
5. Drug resistance is the main problem.
6. Poor patient compliance.
7. Non-specific drug delivery.

MDR AND DOTS

Multidrug-resistant (MDR) tuberculosis is defined as disease caused by strains of *Mycobacterium tuberculosis* that are at least resistant to treatment with isoniazid and rifampicin; extensively drug-resistant (XDR) tuberculosis refers to disease caused by multidrug-resistant strains that are also resistant to treatment with any fluoroquinolone and any of the injectable drugs used in treatment with second-line anti-tuberculosis drugs (amikacin, capreomycin, and kanamycin). This therapy depends on the drug used, previous regimen, dosage form, other diseased condition and sensitivity of patient to pathogen and various drugs.

MDR tuberculosis and XDR tuberculosis are serious threats to the progress that has been made in the control of tuberculosis worldwide over the past decade[17, 18]. In 2008, an estimated 440,000 cases of MDR tuberculosis emerged globally. India and China carry the greatest estimated burden of MDR tuberculosis, together accounting for almost 50% of the world's total cases. More than three quarters of the estimated cases of MDR tuberculosis occur in previously untreated patients. In some countries, the incidence of tuberculosis is rising, and the incidence of MDR tuberculosis appears to be rising even faster (e.g., in Botswana and South Korea). However, in Estonia, Hong Kong, the United States, and Orel and Tomsk Oblasts (in the Russian Federation), the incidence of tuberculosis is falling, and the incidence of MDR tuberculosis appears to be falling even faster[17, 18, 19]. This trend is the result of high-quality care and control practices that result in high rates of case detection and cure, drug-susceptibility testing for all patients, and the provision of appropriate treatment for all patients carrying drug-resistant strains. In short, preventing initial infection with MDR tuberculosis and managing the treatment of existing cases appropriately are the keys to containing the spread of this disease. The WHO-recommended Stop TB Strategy[20] provides the framework for treating and caring for those who are sick and controlling the epidemic of drug-susceptible and drug-resistant disease. The DOTS (Directly Observed Therapy) approach, which underpins the Stop TB Strategy, calls for political commitment to national programs designed to control disease by means of early diagnosis with the use of bacteriologic testing, standardized treatment with supervision and patient support, and provision and management of the drugs used in treatment; the approach also includes the monitoring of treatment and evaluation of its effectiveness. Between 1995 and 2008, a total of 36 million people were treated successfully with the use of the DOTS approach, and 6 million lives

Table 2: Different regimen have been recommended for the treatment of tuberculosis (TB) in case of smear positive adult patients[23]

Regimen	Phase	Under 50 kg	Over 50 kg
Regimen-1 RIF/INH/PYZ/ETH 120/60/300/200mg daily for 5 days/week combined tablet	Intensive Phase	4 tablet	5 tablet
Regimen-2 RIF/INH 150/100 mg and 300/150mg combined tablets	Continuous Phase	3 tablet	2 tablet

were saved[21]. Specific guidelines for controlling drug susceptible and drug-resistant disease already exist and the Global Plan to Stop TB, 2006 through 2015, developed by the Stop TB Partnership, specifies the scale at which these interventions need to be funded and implemented to achieve global targets[22]. There are different regimens for treatment of tuberculosis have been used which are shown in Table 2.

Problems in combination therapy

Problems encountered with the combination of various drugs are as

1. It may cause liver disease to patient.
2. Combination may results in the increase of convulsion to the patient.
3. Kidney disease may occur.
4. Combination may results in gout disease.
5. Drug interaction between rifampicin (RIF) and isoniazid (INH) results in the decreased bioavailability of rifampicin by 32% when used in fixed dose combination (FDC). So it is compensated by giving higher dose of rifampicin as the FDC products.
6. Similarly, combination of isoniazid and ciprofloxacin results in delay of absorption of INH.
7. Also, bioavailability of INH decreased because of FDC between pyrazinamide (PYZ) and isoniazid (INH).

COLLOIDAL DRUG DELIVERY SYSTEM

Colloidal Drug Delivery system (CDDS) play important role for effective transportation of loaded drug to the target site. Colloidal drug delivery systems (CDDS) are particulate or vesicular dosage form in nanometer size range. They include liposomes, niosomes, nanospheres, multiple emulsion and ceramics. Colloidal drug carrier is one of the most important entities essentially required for successful transport of loaded drugs. They are drug vectors, which sequester, transport and retain the active drug to route, while they elute or deliver it within or in the vicinity of target. Targeting the drug to the desired site of action would not only improve the therapeutic efficacy but also enable a reduction of the amount of drug, which must be administered to achieve a therapeutic response, thus minimizing unwanted toxic effect. The overall drug consumption and side-effects can be lowered significantly by depositing the active agent in the morbid region only and in no higher dose than needed. This highly selective approach reduces systemic side effects to a great degree. Colloidal drug carriers such as liposomes and nanoparticles are able to modify the distribution of an associated substance. They

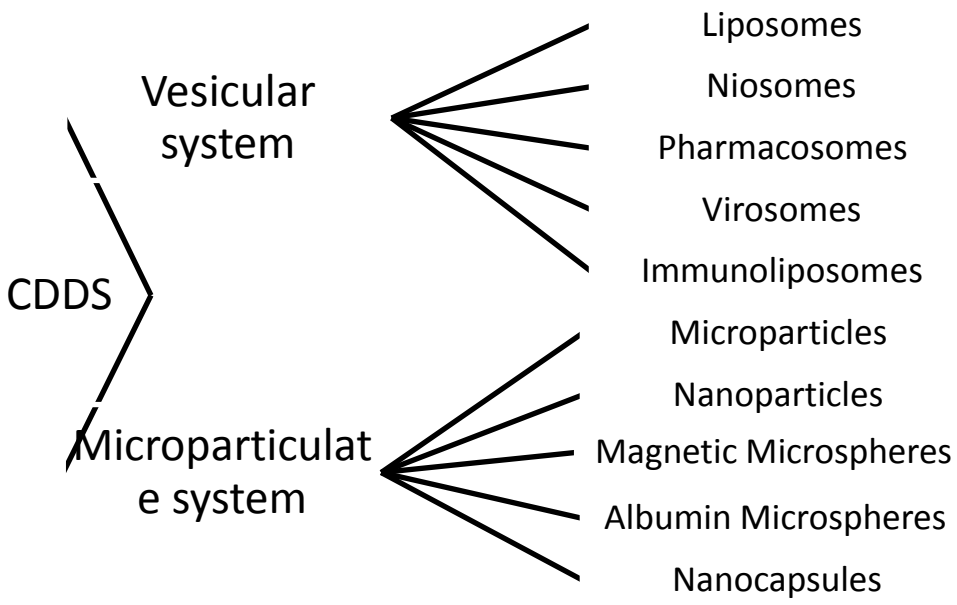
can therefore be used to improve the therapeutic index of drugs by increasing their efficacy and/or reducing their toxicity. Colloidal drug carrier systems such as micellar solutions, vesicle and liquid crystal dispersions, as well as nanoparticle dispersions consisting of small particles of 10–400 nm diameter show great promise as drug delivery systems. When developing these formulations, the goal is to obtain systems with optimized drug loading and release properties, long shelf-life and low toxicity. The incorporated drug participates in the microstructure of the system, and may even influence it due to molecular interactions, especially if the drug possesses amphiphilic and/or mesogenic properties[24].

Properties of an ideal CDDS

An ideal colloidal drug carrier should be engineered to have the following features[25]:

- It must be able to cross anatomical barriers.
- It must be recognized specifically and selectively by the target cells and must maintain the avidity and specificity of the surface ligands.
- The linkage of the drug and the directing unit (ligand) should be stable in plasma, interstitial and other biofluids.
- Carrier should be non-toxic, non-immunogenic and biodegradable particulate or macromolecule and after recognition, and internalization.
- The biomodules used for carrier navigation and site recognition should not be ubiquitous; otherwise the CDDS may cross over to other sites, defeating the concept of targeting.

Classification of colloidal drug delivery systems (CDDS): There are two ways for classification of CDDS.



However, therapeutic applications of intravenously injected liposomes have been limited due to several factors, such as leakage of their contents into the plasma compartment before they reach the target tissue, rapid clearance from the bloodstream and their uptake by the macrophages of the liver and spleen. Pressurised packed or aerosolised liposomes for pulmonary targeting of drugs have been well documented[1, 15].

Mannose receptors expressed abundantly in the liver, spleen and AMs have been most widely utilised for targeting bioactive molecules to the macrophages[16]. Drugs are released from the liposomes following intralysosomal degradation. AMs form a first-line defence against microorganisms entering the lung via the airways. In contrast to the interstitial macrophages in the lung, AMs, which are located in the disalveolar space, have direct access to liposomes administered via the airways, for example by intra-tracheal instillations, intra-nasal administration or by the application of aerosolised liposomes. Various colloidal drug delivery systems are given below:

1. LIPOSOMES

Liposomes are concentric bilayered vesicles in which aqueous volume is enclosed mainly composed of natural or synthetic phospholipids. Liposomal drug delivery systems are useful as drug delivery vehicles for delivery of drug to the target site. Effective chemotherapy for pulmonary tuberculosis can be attained by targeting drugs to lung tissue by tagging specific markers or homing devices onto the surface of liposomes. Liposomes, as well as delivering drugs to the infected site, could also act as drug reservoirs to provide a slow and sustained release of the drug. Rifampicin-loaded aerosolised liposomes were evaluated for their selective presentation to AMs, the most dense site of tuberculosis infection. Egg phosphatidylcholine- and cholesterol-based liposomes were modified by imparting negative charge (using dicetylphosphate) or by coating them with alveolar macrophage-specific ligands (maleylated bovine serum albumin [MBSA] and *O*-steroyl amylopectin [*O*-SAP])[26]. Ligand-anchored liposomal aerosols are not only effective in the rapid attainment of a high drug concentration in the lung (population of AMs), but also in maintaining this over a prolonged period of time[27].

Liposomes have been considered as a potential drug and/or gene carrier due to enabling the loading capacity for a variety of compounds, allowing chemical modification for a wide range of applications, minimizing the systemic toxicity of the incorporated drugs and improving their stability[28, 29]. Since mannose receptors, a 175 kDa transmembrane protein of the C-type lectin family, are exclusively expressed on the surface of alveolar macrophages that can recognize

mannose terminal molecules with high affinity, mannosylation of liposomes is an attractive approach for cell-selective targeting to alveolar macrophages. It has been reported that the efficient uptake of carrier systems is affected by the ligand density and physiological environment[25, 30]. The aim of this study was to evaluate the targeting efficiency of Man-liposomes to alveolar macrophages by direct pulmonary delivery. Man-liposomes composed of 1, 2-distearoyl-sn-glycero-3 phosphocholine (DSPC), Cholesterol (Chol) and Man-C4-Chol with different molar ratios were characterized in a series of in vitro and in vivo studies. In vitro uptake of man liposomes was investigated in primary cultured rat alveolar macrophages. In vivo targeting of Man liposomes was also studied after intratracheal administration in rats. They have demonstrated the efficient targeting to alveolar macrophages of Man-liposomes by increasing the mannose residues expressed on the surface of liposomes. Man-liposomes with a high content of Man-C4-Chol exhibit high affinity for mannose receptors resulting in extensive uptake by alveolar macrophages after intratracheal administration. In addition, Man-liposomes are moderately stable to prevent the release of incorporated drugs in lung microenvironment. These observations suggest that mannosylated liposomes are promising carrier systems for targeting drugs to alveolar macrophages following intra-tracheal administration[31].

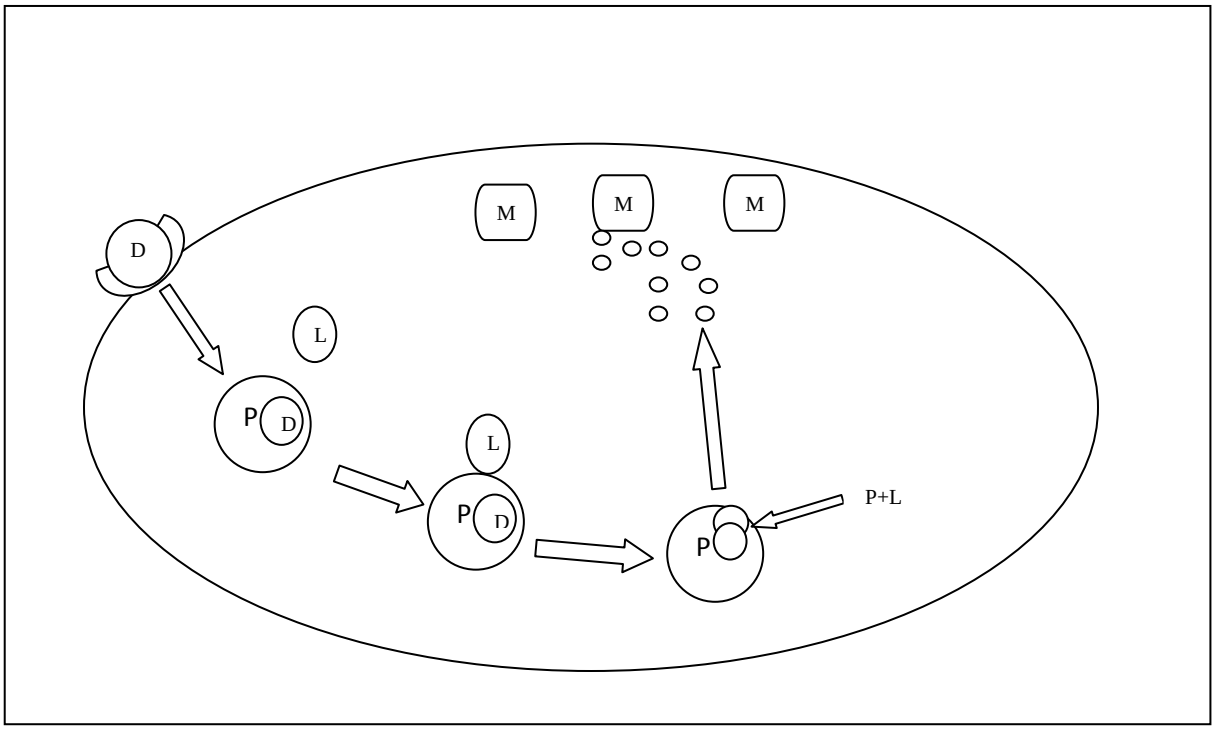
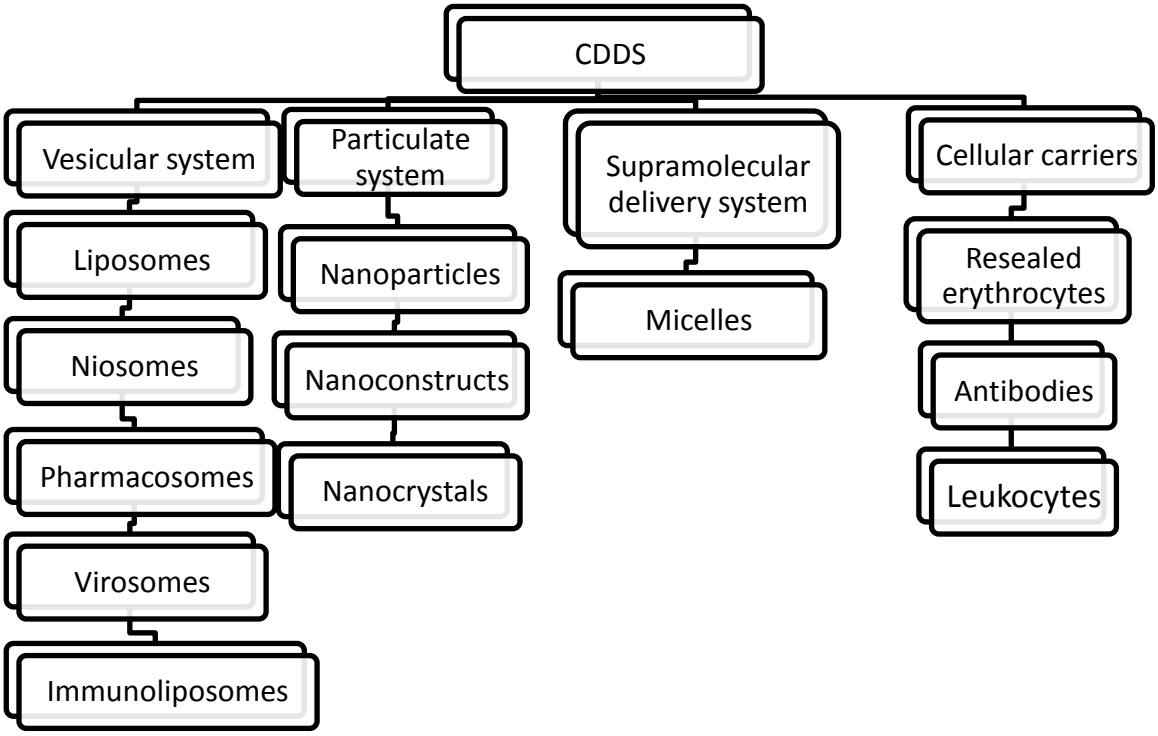


Figure 1: Action of Drug In contact with the macrophage where D: Drug, L: Lysosomes, P: Phagosomes, M: Mycobacteria, P+L: Phagosome and Lysosomes fusion

Whenever a Mycobacteria enters into the body, it is engulfed by macrophage (their role is to phagocytose i.e. engulf and then digest cellular debris and pathogens either as stationary or mobile cells and stimulate lymphocytes and other immune cells to respond to pathogen). When a macrophage ingest a pathogen, pathogen becomes trapped in a phagosome which is then fuse with lysosome within phagolysosome, enzyme and toxic peroxide digest pathogen. Because of fusion of phagosome and lysosome drug is released due to the formation of phagolysosome (as in diseased condition mycobacteria prevent the phagosome and lysosome fusion) which is responsible for killing of mycobacteria tuberculosis as explained in Figure 1.

Mannosylated liposomes

Mannosylated liposomes have been considered as promising non-live vectors for targeted delivery purposes. In the past few decades several strategies have been developed to promote an adequate coating of liposomes, used as drug/antigen carrier, with the mannose derivative that specifically recognizes its receptor. Baldeschweiler and co-workers[32] described the capacity of mannosylated liposomes to target cells of the monocyte–macrophage system using 6-aminomannose covalently linked to cholesterol. Later, Barratt and co-workers[33] demonstrated that fluorescently labelled mannosylated liposomes were more rapidly taken up by mouse peritoneal macrophages than by rat alveolar macrophages. This uptake rate was saturable at high liposome concentrations, although it was not inhibited by the presence of conventional liposomes. In addition, the rate of association was also related to the size of mannosylated liposomes. Thus, liposomes with a diameter of about 1.4 μm were taken up more quickly than those of 400 – 700 nm diameter. In an interesting study, it was shown that the most effective particle size of mannosylated liposomes for ciprofloxacin (CPFX) targeting to alveolar APCs, following pulmonary administration is 1000 nm[34]. Uptake of liposomes by these cells increased by introducing surface mannose modification[35, 36]. More recently, Chono and co-workers[37] confirmed that the efficient antibacterial effects of mannosylated CPFX liposomes against intracellular parasites in alveolar APCs may be exhibited at a lower dose than that used in clinical situations. This study, which was carried out by intratracheal administration of liposomes in rats, clearly indicated that the pulmonary administration of mannosylated CPFX liposomes could be an efficient drug delivery system for the treatment of respiratory intracellular parasitic infections, including *M. tuberculosis*, *C. pneumoniae*, *Listeria monocytogenes*, *Legionella pneumophila* and *Francisella tularensis*[38].



2. NIOSOMES

Basically, niosomes are non-ionic surfactant vesicles which are formed in aqueous media with or without the presence of cholesterol (CHOL) or other lipids[39]. Niosomes have been suggested to be a safe vesicular system and as an alternative to liposomes, especially for controlled drug delivery. They behave similarly to liposomes but have better stability[40]. They can prolong the circulation of an entrapped drug, resulting in an altered distribution and metabolic stability[41, 42]. The use of polymerizable monomeric building molecules and their subsequent polymerization following vesiculation have been suggested as a method to improve stability[43]. Basically, Niosomes are vesicles mainly consisting of non-ionic surfactants that encloses and encompasses the drug molecules.

Advantages of niosomes[44] includes:

1. Osmotically active and stable, increase the stability of entrapped drug.
2. Handling and storage of surfactants require no special conditions.
3. Improve oral bioabilability of poorly absorbed drugs and can enhance skin penetration of drugs.
4. Niosomal surfactants are biodegradable, biocompatible, non-immunogenic and non-toxic.
5. They can prolong the circulation of the entrapped drug.

Niosomes of rifampicin and gatifloxacin were prepared by lipid hydration technique using rotary flash evaporator. The prepared rifampicin and gatifloxacin niosomes showed a vesicle size in the

range of 100-300nm, the entrapment efficiency were 73% and 70% respectively. The *in vitro* release study showed that 98.98% and 97.74% of release of rifampicin and gatifloxacin niosomes respectively. The bactericidal activities of the niosomal formulation were studied by BACTEC radiometric method using the resistant strains (RF 8554) and sensitive strains (H37Rv) of *Mycobacterium tuberculosis* which showed greater inhibition and reduced growth index. The study showed that the drugs loaded in niosome vesicles exhibited improved bactericidal activity against the tubercle bacilli. The diffusion study of the rifampicin niosome and gatifloxacin niosomes gave extended release of the drug, which suffices to decreased dose, lesser days of treatment and more patient compliance. The duration of treatment under DOTS strategy may also be reduced to the greater extent[45].

3. NANOPARTICLES

Nanoparticles are sub nanosized colloidal structures composed of synthetic or semisynthetic polymers. Nanospheres are solid core spherical particulates which are nanometric in size ranging from 10 to 1000 nm. Generally, nanoparticles include not only the particles like nanopellets as described by Birrenbach and Speiser[46] but also contain nanocapsules and polymer lattices. They contain drug embedded within the matrix or adsorbed on to the surface. Nanocapsules are vesicular system in which drug is essentially encapsulated with in the central volume surrounded by an embryonic polymeric sheath. In nanocrystals drug is mainly encapsulated in the solution system[47, 48].

Nanoparticles results in the reduction in the dosing frequency of antituberculosis drugs (ATDs) by applying drug delivery technology has the potential to improve the patient compliance in tuberculosis (TB). Alginate (a natural polymer) based nanoparticulate delivery system was developed for frontline ATDs (rifampicin, isoniazid, pyrazinamide and ethambutol) by Zahoor Ahmad[49]. Alginate nanoparticles were prepared by the controlled cation induced gelification method and administered orally to mice. The drug levels were analysed by high performance liquid chromatography (HPLC) in plasma/tissues. The therapeutic efficacy was evaluated in *M. tuberculosis* H37Rv infected mice. High drug encapsulation efficiency was achieved in alginate nanoparticles, ranging from 70%-90%. A single oral dose resulted in therapeutic drug concentrations in the plasma for 7-11 days and in the organs (lungs, liver and spleen) for 15 days. In comparison to free drugs (which were cleared from plasma/organs within 12-24 h), there was a significant enhancement in the relative bioavailability of encapsulated drugs. In TB-infected mice three oral doses of the formulation spaced 15 days apart resulted in complete

bacterial clearance from the organs, compared to 45 conventional doses of orally administered free drugs. Alginate nanoparticles appear to have the potential for intermittent therapy of TB. The added advantages of nanoparticles over microparticles include the ability to improve drug encapsulation, pharmacokinetics, bioavailability as well as therapeutic efficacy[50].

Sharma *et al.* (2004)[51] conducted a study to explore lectin-functionalized poly (lactide-co-glycolide) nanoparticles (PLG-NPs) as bio adhesive drug carriers against tuberculosis (TB), in order to reduce the drug dosage frequency of anti-tubercular drugs and thus improve patient compliance in TB chemotherapy. In this study they observed the presence of drugs in plasma for 6–7 days for rifampicin and 13–14 days for isoniazid and pyrazinamide after administration of lectin coated PLG-NPs through the oral/aerosol route. They also observed that upon administration of uncoated PLG-NPs (oral/aerosolized) rifampicin was detectable in plasma for 4–6 days, whereas isoniazid and pyrazinamide were detectable for 8–9 days. All three drugs were present in lungs, liver and spleen for 15 days. Obtaining these results they concluded that WGA-functionalized PLG-NPs could be potential drug carriers for antitubercular drugs through the oral as well as aerosol route for effective TB control[52].

Johnson *et al.*, (2005)[53] evaluated the efficacy of nanoparticle-encapsulated anti-tuberculosis drugs administered every 10 days versus that of daily non encapsulated drugs against *Mycobacterium tuberculosis* aerosol infection in guinea pigs. In both cases the treatments significantly reduced the bacterial count. This finding suggested that the nanoparticle drug delivery system has potential in intermitted treatment of tuberculosis.

The following are among the important technological advantages of nanoparticles as drug carriers: high stability (i.e., long shelf life); high carrier capacity (i.e., many drug molecules can be incorporated in the particle matrix); feasibility of incorporation of both hydrophilic and hydrophobic substances; and feasibility of variable routes of administration, including oral administration and inhalation. These carriers can also be designed to enable controlled (sustained) drug release from the matrix[54]. Various antitubercular drug delivery systems and their formulations along with their in vivo parameters have been shown in Table 3.

4. MICROEMULSION

Microemulsions are thermodynamically stable, isotropic clear dispersions of oil, water, and surfactant (and/or co-surfactant) which have high stability, low viscosity, and transparency. SMEDDS is a pre-concentrate of microemulsion containing drug, oil, and surfactant (and/or co-surfactant). When used as drug delivery system (DDS), microemulsion help in enhancing

solubility and dissolution rate and improve bioavailability of a drug[60]. Easy administration, increased absorption, improved clinical potency, and decreased toxicity of microemulsion have encouraged many researchers to explore the ability of microemulsion as DDS[61].

A microemulsion is a system of water, oil and amphiphilic compounds (surfactant and co-surfactant) which is a transparent, single optically isotropic, and thermodynamically stable liquid[62].

Table 3: Major data on various drug delivery systems and their formulations

Drug Release and Therapeutic Efficacy of the various Drug Delivery Formulations of the Antituberculous Drugs	Animal Model	Administration Route	Duration of Drug Release (*d*) d: days		Regimen Producing Sterilizing Effect in Lungs and Spleen	Reference
			Plasma	Organs		
PLG nanoparticles	Mice	Orally	6–9	9–11	5 doses every 10 d	55
	Mice	subcutaneous injection	32	36	Single injection	52
	Guinea pigs	Aerosolic form	4–9	up to 10 d (each drug)	5 doses every 10 d	51
	Guinea pigs	Orally	4–9	up to 10 d (each drug)	5 doses every 10 d	51
Mannosylated Liposomes	Adult Alwino Rat	DPI	5	Up to 5 d (each day)	1 dose every d	56
Mannosylated Nanoparticles	Dawley rats (6 to 8 weeks old,	subcutaneous injection		12 hrs	20.0 mg kg^{-1} 0.16% (*m*/*V*)	57
Galactosylated liposomes	Mice	intra venous injection	1 hr		0.5% dose	58
Lectin-functionalized PLG nanoparticles	Guinea pigs	Orally	7–13	up to 15 d (each drug)	3 doses fortnightly	51
	Guinea pigs	Aerosolic form	6–14	up to 15 d (each drug)	3 doses fortnightly	51
Solid lipid nanoparticles (SLN)	Guinea pigs	Aerosolic form	5	7	7 doses weekly	59

The concept of microemulsion was first introduced by Hoar and Schulman in 1943. They prepared the first microemulsion by dispersing oil in an aqueous surfactant solution and adding an alcohol as a co-surfactant, leading to a transparent, stable formulation[60].

Microemulsion are formed when and only when (i) the interfacial tension at the oil/water interface is brought to a very low level and (ii) the interfacial layer is kept highly flexible and fluid. These two conditions are usually met by a careful and precise choice of the components and of their respective proportions, and by the use of a "co-surfactant" which brings flexibility to the oil/water interface.

In topical formulations, microemulsion have been proved to increase the cutaneous absorption of both lipophilic and hydrophilic API's when compared to conventional vehicles (emulsions, pure oils, aqueous solutions, etc.). In an extensive review of this type of applications, Kreilgaard et. al.[61] attribute this performance to a generally higher solubility of the API's in microemulsions, generating an increased concentration gradient towards the skin. The role of penetration enhancers played by the amphiphilic components of the microemulsion and the internal mobility of the drug within the vehicle also contribute to the overall performance of microemulsions in dermal or transdermal drug delivery.

Many topical formulations currently marketed are based on microemulsions. Microemulsions enhance the bioavailability of poorly soluble drugs by maintaining them in molecular dispersion in the GI tract and extending the absorption window available in the GI lumen.

This lead to a faster absorption allowing a more rapid onset of drug action. But microemulsions also overcome food effect and reduce subject to subject variability by levelling the differences in digestive capabilities. Many examples of microemulsion based formulations are now on the market ; Among them, the performances of microemulsions are well demonstrated in the reformulation of Cyclosporin A by Novartis into a microemulsion based formulation marketed under the trade mark Neoral®: this has increased the bioavailability nearly by a factor 2. In addition, Neoral shows a much faster onset of action than the earlier version Sandimmune®, a reduced inter/intra-subject variability and a much lower impact of food intake on cyclosporin pharmacokinetics.

The microemulsion composed of oleic acid, phosphate buffer, ethanol, and Tween (20, 40, 60, and 80) has been investigated in the presence of antitubercular drugs of extremely different solubilities, viz. isoniazid (INH), pyrazinamide (PZA), and rifampicin (RIF) by S. K. Mehta et al., in 2010. in his work the emphasis has been laid on the formulation of microemulsions with

different Tween surfactants. Phase studies have been performed and the influence of structure of surfactant on the isotropic region has been studied. Among the four surfactants, Tween 80 has been used to load and perform the comparative analysis of all the three antitubercular drugs, viz., rifampicin, isoniazid, and pyrazinamide. Conductivity and viscosity measurements reveal that physicochemical properties do not alter with change in surfactant. No significant effect on the microstructure of microemulsion has been observed in the presence of drug. The microemulsion remains stable after the incorporation of drug (in terms of optical texture and phase separation). In addition, the particle size analysis indicates that the microemulsion changes into o/w emulsion at infinite dilution. The spectroscopic studies have been carried out to elucidate the position of drug molecule in microemulsion (along with the partition coefficient) and reveal that most of the INH molecules are present in the continuum region of an o/w microemulsion, RIF in the oil droplet, and PZA in the palisade layer of the droplet toward the outer side. Optical microscopy has been carried out with dilution of Tween 80 microemulsion, and the images clearly show the presence of "percolation phenomena" along with changes occurring in the microstructure, w/o to discontinuous to o/w. Furthermore, the effect of the presence of drug on microstructure has also been studied through optical microscopy. Dissolution studies infer that the release of drug follows INH>PZA>RIF. In the present system, the release of INH and PZA from microemulsion has been found to be non-Fickian, whereas RIF release is Fickian in nature. The present Tween-based microemulsion appears beneficial for the delivery of all the three drugs in terms of easy preparation, low cost, controlled release, most importantly stability, and no precipitation of drugs. Such a microemulsion formulation can be used for fixed dose combination of first-line antitubercular drugs in future[63].

5. CORTICOSTEROIDS

Tamilarasu Kadhiravan et al[64] studied that corticosteroids are often used as an adjunct in the treatment of various forms of tuberculosis (TB) and for the prevention of complications, such as constrictive pericarditis, hydrocephalus, focal neurological deficits, pleural adhesions and intestinal strictures . Notwithstanding, they have been proven in clinical trials to improve the following outcomes only—death or disability in human immunodeficiency virus (HIV)-seronegative patients with tubercular meningitis and tubercular pericarditis. Despite a lack of specific evidence for efficacy in HIV co-infected patients with tubercular meningitis or pericarditis, corticosteroids are generally recommended in them as well. Corticosteroids significantly decrease the risk of pleural thickening in patients with tubercular pleural effusion.

Recently, it has been demonstrated that use of corticosteroids improve the morbidity in HIV co-infected patients with paradoxical TB immune reconstitution inflammatory syndrome (IRIS). However, evidence favouring the use of corticosteroids in other clinical situations is sparse or lacking. Likewise, the biological mechanisms underlying their beneficial effect in TB meningitis and pericarditis remain poorly understood. Adverse outcomes are common among patients with extrapulmonary TB despite the availability of effective anti-tubercular treatment. More evidence is required on the efficacy of corticosteroids in other forms of extrapulmonary TB. Corticosteroids seem to have a potential benefit in patients with tubercular pericarditis. Meanwhile, it is prudent to use corticosteroids in patients with tubercular pericarditis (both effusive and constrictive) irrespective of the HIV serostatus. On the other hand, although it has been found that corticosteroids reduced the risk of pleural thickening, clinical significance of this benefit is unclear[63]. Various colloidal drug delivery systems along with their one advantage over the other systems have been shown in Table 4.

Table 4: Various Colloidal Drug Delivery Systems

Delivery system	Drug	Method	Advantages	Reference
Liposomes	Ciprofloxacin (CPFX)		Improved targeting to alveolar APCs	31
Niosomes	Rifampicin (RIF), gatifloxacin	Lipid hydration technique	They exhibited improved bactericidal activity against the tubercle bacilli.	45
Nanoparticles	RIF		Nanoparticle drug delivery system has potential in intermitted treatment of tuberculosis.	53
Microemulsions	RIF		Improved bioavailability.	63
Corticosteroids			corticosteroids reduced the risk of pleural thickening	64

CONCLUSION

According to WHO reports Tuberculosis is becoming life threatening disease especially in the developing countries. The main reason for this is the severe drawbacks of conventional therapy and development of resistance by microbes towards the conventional therapy. Treatment of this disease becomes more difficult when it get associated with disease like AIDS. MDT and DOTS are found to be the two main therapy available to overcome the drug resistance problems. The

colloidal drug delivery system like liposomes, niosomes, nanoparticles, microemulsion etc are also found to helpful in term of targeting, more encapsulation, good release and resistance problems. The ligand appended liposomes like mannosylated liposomes shows distinct advantage of releasing the drug only at alveolar macrophage (target site) in a controlled fashion, over the conventional system. So these can be effective choice of drug delivery system for the treatment of tuberculosis. Nanoparticles produced by controlled cation induced gelification method may show high drug encapsulation efficiency thus can give better therapeutic level of drug in body and can excessively reduce the dosing frequency of drug. Niosomes can be also used as an alternative to liposome as they show better stability as compared to liposomes. So nisomes are also good choice for delivery of antitubercular drugs. Microemulsion can be also used to deliver antitubercular drugs. Microemulsion may enhance the bioavailability of the antitubercular drugs by maintaining them in molecular dispersion form in GIT and can avoid their side effects. Thus we can say that colloidal drug delivery systems can play an important role in effective treatment of Tuberculosis.

REFERENCES

1. Bermudez LE. Use of liposome preparation to treat mycobacterial infections. Immunobiology 1994; 191: 578–583.
2. O'Hara P, Hickey AJ. Respirable PLGA microspheres containing rifampicin for the treatment of tuberculosis: manufacture and characterization. Pharm Res 2000; 17: 955–961.
3. Suarez S, Kazantseva M, Bhat M, Costa D, Hickey AJ. The influence of suspension nebulization or instillation on particle uptake by guinea pig alveolar macrophages. Inhal Toxicol 2001 a; 13: 773–788.
4. Suarez S, O'Hara P, Kazantseva M, Newcomer CE, Hopfer R, McMurray DN, Hickey AJ. Airways delivery of rifampicin microparticles for the treatment of tuberculosis. J Antimicrob Chemother 2001 b; 48: 431–434.
5. Suarez S, O'Hara P, Kazantseva M, Newcomer CE, Hopfer R, McMurray DN, Hickey AJ. Respirable plga microspheres containing rifampicin for the treatment of tuberculosis: screening in an infectious disease model. Pharm Res 2001 c; 18: 1315–1319.
6. Pandey R, Khuller GK. Antitubercular inhaled therapy: opportunities, progress and challenges. J Antimicrob Chemother 2005; 55: 430–435.

7. Pandey R, Khuller GK. Solid lipid particle-based inhalable sustained drug delivery system against experimental tuberculosis. Tuberculosis (Edinb) 2005; 85: 227–234.
8. Zahoor A, Sharma S, Khuller GK. Inhalable alginate nanoparticles as antitubercular drug carriers against experimental tuberculosis. Int J Antimicrob Agents 2005; 26: 298–303.
9. Hino M, Oda M, Yoshida A, Nakata K, Kohchi C, Nishizawa T, Inagawa H, Hori H, Makino K, Terada H, Soma G . Establishment of an in vitro model using NR8383 cells and *Mycobacterium bovis* calmette-guerin that mimics a chronic infection of mycobacterium tuberculosis. In Vivo 2005; 19: 821–830.
10. Hirota K, Hasegawa T, Hinata H, Ito F, Inagawa H, Kochi C, Soma GI, Makino K, Terada H. Optimum conditions for efficient phagocytosis of rifampicin-loaded PLGA microspheres by alveolar macrophages. J Controlled Rel 2007; 119: 69–76.
11. Makino K, Nakajima T, Shikamura M, Ito F, Ando S, Kochi C, Inagawa H, Soma G, Terada H. Efficient intracellular delivery of rifampicin to alveolar macrophages using rifampicin-loaded PLGA microspheres: effects of molecular weight and composition of PLGA on release of rifampicin. Colloids Surf B: Biointerf 2004; 36: 35–42.
12. Yoshida A, Matumoto M, Hshizume H, Oba Y, Tomishige T, Inagawa H, Kohchi C, Hino M, Ito F, Tomoda K, Nakajima T, Makino K, Terada H, Hori H, Soma G. Selective delivery of rifampicin incorporated into poly(dl-lactic-*co*-glycolic) acid microspheres after phagocytotic uptake by alveolar macrophages, and the killing effect against intracellular mycobacterium bovis calmette-guerin. Microbes Infect 2006; 8: 2484–2491.
13. Sen H, Jayanthi S, Sinha R, Sharma R, Muttil P. Inhalable biodegradable microparticles for target-specific drug delivery in tuberculosis and a process thereof. PCT/IB 03/04694.
14. Sharma R, Saxena D, Dwivedi AK, Misra A. Inhalable microparticles containing drug combinations to target alveolar macrophages for treatment of pulmonary tuberculosis. Pharm Res 2001; 18: 1405–1410.
15. Farr SJ, Kellaway IW, Carman-Meaking B. Assessing the potential of aerosol generated liposomes from pressurized pack formulations. J Controlled Rel 1987; **5**: 119-127.
16. Vyas SP, Sakthivel T. Pressurized pack-based liposomes for pulmonary targeting of isoprenaline--development and characterization. J Microencapsulation 1994; 11(4): 373-380.

17. World Health Organization. Multidrug and extensively drug-resistant TB (M/XDR-TB): 2010 global report on surveillance and response. 2010. (Accessed August 16, 2010, at http://whqlibdoc.who .int/publications/2010/9789241599191_eng.pdf.)
18. Raviglione MC, Smith IM. XDR tuberculosis—implications for global public health. N Engl J Med 2007; 356: 656- 659.
19. Dye C. Doomsday postponed? Preventing and reversing epidemics of drug resistant tuberculosis. Nat Rev Microbiol 2009; 7: 81-87.
20. Raviglione MC, Uplekar MW. WHO's new Stop TB Strategy. Lancet 2006; 367: 952-955.
21. Lönnroth K, Castro KG, Chakaya JM. Tuberculosis control and elimination 2010-50: cure, care, and social development. Lancet 2010; 375: 1814-29.
22. Nathanson E, Nunn P, Uplekar M, Floyd K, Jaramillo E, Lönnroth K, Weil D Raviglione M. MDR Tuberculosis—Critical Steps for Prevention and Control. N Engl J Med 2010; 363: 1050- 1058.
23. Tripathi KD. Essential of medical pharmacology. 5th ed., Jaypee Brother Medical Publisher (P) Ltd; 2003: 698-702.
24. Sharma J, Kalra S, Sharma A, Rani S. Colloidal Drug Carriers. Int J Fam Pract 2010; 9 (2): 562-571.
25. Abu-Dahab R, Schafer UF, Lehr C. Lectin-functionalized liposomes for pulmonary drug delivery: effect nebulization on stability and bioadhesion. Eur J Pharm Sci 2001; 14: 37–46.
26. Vyas SP, Khatri K. Liposome-based drug delivery to alveolar macrophages. Expert Opin Drug Deliv 2007; 4(2):95-99.
27. Vyas SP, Kannan ME, Jain S, Mishra V, Singh P. Design of liposomal aerosols for improved delivery of rifampicin to alveolar macrophages. An article on drug delivery to AMs using surface modified, ligand coated, aerosolised liposomes. Int J Pharm 2004; 269: 37-49.
28. Hattori Y, Kawakami S, Nakamura K, Yamashita F, Hashida M. Efficient gene transfer into macrophages and dendritic cells by in vivo gene delivery with mannosylated lipoplex via the intraperitoneal route. J Pharmacol Exp Ther 2006; 318: 828–834.

29. Kawakami S, Sato A, Nishikawa M, Yamashita F, Hashida M. Mannose receptor-mediated gene transfer into macrophages using novel mannosylated cationic liposomes. Gene Ther 2000; 7: 292–299.
30. Tsan M, Tsan GL, White J. Surfactant inhibits cationic liposome mediated gene transfer. Hum Gene Ther 1997; 8: 817–825.
31. Wijagkanalan W, Kawakami S, Takenaga M, Igarashi R, Yamashita F, Hashida M. Efficient targeting to alveolar macrophages by intratracheal administration of mannosylated liposomes in rats. J Controlled Rel 2008; 125: 121–130.
32. Baldeschweiler JD. Phospholipid vesicle targeting using synthetic glycolipid and other determinants. Ann NY Acad Sci 1985; 446: 349 -367.
33. Barratt G, Tenu JP, Yapo A, Petit JF. Preparation and characterisation of liposomes containing mannosylated phospholipids capable of targeting drugs to macrophages. Biochim Biophys Acta 1986; 862: 153 -156.
34. Chono S, Tanino T, Seki T, Morimoto K. Influence of particle size on drug delivery to rat alveolar macrophages following pulmonary administration of ciprofloxacin incorporated into liposomes. J Drug Target 2006; 14: 557 -566.
35. Chono S, Tanino T, Seki T, Morimoto K. Uptake characteristics of liposomes by rat alveolar macrophages: influence of particle size and surface mannose modification. J Pharm Pharmacol 2007; 59: 75 -80.
36. Wijagkanalan W, Kawakami S, Takenaga M. Efficient targeting to alveolar macrophages by intratracheal administration of mannosylated liposomes in rats. J Controlled Rel 2008; 125: 121 -130.
37. Chono S, Tanino T, Seki T, Morimoto K. Efficient drug targeting to rat alveolar macrophages by pulmonary administration of ciprofloxacin incorporated into mannosylated liposomes for treatment of respiratory intracellular parasitic infections. J Controlled Rel 2008; 127 : 50 -58.
38. Juan M Irache, Hesham H Salman, Carlos Gamazo, Socorro Espuelas. Mannose-targeted systems for the delivery of therapeutics. Expert Opin Drug Deliv 2008; 5(6):703-724.
39. Rogerson A, Cummings J, and Florence AT. Adriamycin loaded niosomes: Drug entrapment, stability and release. J Microencapsulation 1987; 4: 321-328.
40. Handjani Vila RM, Riber A, Rondot B, Vanlerberghe G. Dispersion of lamellar phases of nonionic lipids in cosmetic products. Int J Cosm Sci 1979; 1: 303-314.

41. Azmin MN, Florence AT, Handjani Vila RM, Stuart JFB, Vanlerberghe G, Whittaker JS. The effect ofnon-ionic surfactant vesicle (niosome) entrapment on the absorption and distribution of methotrexate in mice. J Pharm Pharmacol 1985; 37: 237-242.
42. Baillie AJ, Florence AT, Hume LR, Murihead GT, Rogerson A. The preparation and properties of niosomes: Non-ionic surfactant vesicles. J Pharm Pharmacol 1985; 37: 863-868.
43. Venkatesan N, Vyas SP. Polymer-Coated Vesicles: Development and Characterization. Drug Delivery 1998; 5: 251-255.
44. R.S.R. Murthy. Vesicular and Particulate Drug Delivery System. 1st ed., Nasik (MH) : Carreer Publications; 2010: 92-93.
45. Pavala Rani N, Suriyaprakash TNK, Senthamarai R. Formulation and evaluation of Rifampicin and Gatifloxacin niosomes on logarithmic-phase cultures of *Mycobacterium tuberculosis*. Int J Pharm Bio Sci 2010; 1(4): 435-442.
46. Birrenbach G, Speiser PP. Polymerized micelles and their use as adjuvant in immunology. J Pharma Sci 1976; 65: 1763-1766.
47. Kreuter J. Nanoparticles: In Colloidal Drug Delivery Systems, edited by Kreuter J. New York: Marcel Dekker; 1994: 261-276.
48. Krishna Sailaja A, Amareshwar P, Chakravarty P. Different technique used for the preparation of nanoparticles using natural polymers and their application. Int J Pharm Pharm Sci 2011; 3(Suppl 2): 2011.
49. Ahmad Z, Pandey R, Sharma S, Khuller GK. Alginate Nanoparticles as Antituberculosis Drug Carriers: Formulation Development, Pharmacokinetics and Therapeutic Potential. Indian J Chest Dis Allied Sci 2006; 48: 171-176.
50. Pandey R, Khuller GK. Polymer based drug delivery systems for mycobacterial infections. Curr Drug Deliv 2004; 1: 195-201.
51. Sharma S, Khullar GK, Sharma A. Lectin-functionalised PLGA nanoparticles as oral/aerosolized antitubercular drug carrier for treatment of tuberculosis. J Antimicrob Chemother 2004; 54(4): 761-766.
52. Schmidt C, Bodmeier R. Incorporation of polymeric nanoparticles into solid dosage forms. J Controlled Rel 1999; 57(2): 115-125.
53. Johnson CM, Pandey R, Sharma S, Khuller GK, Basaraba RJ, Orme IM, Lenaerts AJ. Oral Therapy Using Nanoparticle-Encapsulated Antituberculosis Drugs in Guinea

Pigs Infected with Myco-acterium tuberculosis. Antimicrob Chemother 2005; 49(10): 4335.

54. Gelperina S, Kisich K, Michael D, Iseman H, Leonid Am J. Respir Crit Care Med 2005; 172: 1487.
55. Pandey R, Zahoor A, Sharma S, Khuller GK. Oral solid lipid nanoparticles based antitubercular therapy. Tuberculosis (Ednib) 2005; 86(5-6): 415-420.
56. Vyas SP, Sihorkar V, Jain S. Mannosylated liposomes for bio-film targeting. Int J Pharm 2007; 330: 6–13.
57. Kaur A, Jain S, Tiwary AK. Mannan-coated gelatin nanoparticles for sustained and targeted delivery of didanosine: *In vitro* and *in vivo* evaluation. Acta Pharm 2008; 58: 61–74.
58. Kawakami S, Wong J, Sato A, HattoriY, Yamashita F, Hashida M. Biodistribution characteristics of mannosylated, fucosylated and galactosylated liposomes in mice. Biochimica et Biophysica Acta 2000; 1524: 258-265.
59. Kayser O, Olbrich C, Croft SL, Kiderlen AF. Formulation and biopharmaceutical issues in the development of drug delivery system for antiparasitic drugs. Parasitol Res 2003; 9(2): S63-S70.
60. Hoar TP, Schulman JH. Transparent water in oil dispersions: the oleopathic hydromicelle. Nature 1943; 152: 102 –103.
61. Kreilgaard M. Influence of microemulsions on cutaneous drug delivery. In Bulletin Technique Gattefossé N° 2002; 95: 79–100.
62. Attwood D. Microemulsions: In Colloidal drug delivery systems, edited by Kreuter J, New York: Marcel Dekker; 1994.
63. Mehta SK, Kaur G, Bhasin KK. Tween-Embedded Microemulsions—Physicochemical and Spectroscopic Analysis for Antitubercular Drugs. AAPS Pharm Sci Tech 2010; 11: 1. DOI: 10.1208/s12249-009-9356-5.
64. Kadhiravan T, Deepanjali S. Role of Corticosteroids in the Treatment of Tuberculosis: An Evidence-based Update. Indian J Chest Dis Allied Sci 2010; 52: 153-158.