

We are IntechOpen, the world's leading publisher of Open Access books Built by scientists, for scientists

4,800

Open access books available

122,000

International authors and editors

135M

Downloads

Our authors are among the

154

Countries delivered to

TOP 1%

most cited scientists

12.2%

Contributors from top 500 universities



WEB OF SCIENCE™

Selection of our books indexed in the Book Citation Index
in Web of Science™ Core Collection (BKCI)

Interested in publishing with us?
Contact book.department@intechopen.com

Numbers displayed above are based on latest data collected.

For more information visit www.intechopen.com



Polyurethane as Carriers of Antituberculosis Drugs

Yerkesh Batyrbekov and Rinat Iskakov

Additional information is available at the end of the chapter

<http://dx.doi.org/10.5772/35896>

1. Introduction

Polyurethanes (PU) are an important class of polymers that have found many applications as biomaterials due to their excellent physical properties and relatively good biocompatibility. Basically, PU may be produced by two chemical processes: by polycondensation of a diamine with bischloroformates or by reaction between a diol and a diisocyanate. Many biomedical devices are made from segmented PU such as catheters, blood pumps, prosthetic heart valves and insulation for pacemakers (Lelah & Cooper, 1986, Lamba et al., 1997). A promising approach for the development of new controlled-releasing preparations is use of PU as the carriers in drug delivery systems.

Drug delivery systems have been progressively developed in the field of therapeutic administration owing to their advantages: providing drug concentration over a period of prolonged action, decreasing the total therapeutic dose and reducing the undesirable side effects, and, hence, improving the pharmaceutical efficiencies. These are achieved by the use of the controlled-release drug delivery systems (Hsien, 1988). Controlled release dosage forms consist of the pharmacological agent and the polymer carrier that regulate its release. In general two types of drug delivery systems have been used: diffusion-controlled systems and dissolution-controlled systems. In the first case the drug is usually dispersed or dissolved in the solid reservoir or membrane and the kinetics of drug release are generally controlled by diffusion through the polymer. In the second case the drug is generally incorporated into a water-soluble or water-swelling polymer and the release of drug is controlled by swelling and dissolution of polymer. In both cases polymer function is a principal component which controls the transport and the release rate of drug molecule. To be a useful drug carrier, a polymer needs to possess certain features. The polymeric carrier has to be non-toxic, non-immunogenic and biocompatible; the carrier must contain an effective dose of active agent; the material of system must be biodegradable and

form biologically acceptable degradation products; the rate of drug release from the carrier must occur at an acceptable rate; the carrier must be able to be easily sterilized.

The design of the PU controlled-release forms for therapeutic drug administration is the subject of intense interest. Such systems are being used for sustained and controlled delivery of various pharmaceutical agents such as prednisolon (Sharma et al., 1988), morphine, caffeine (Graham et al., 1988), prostaglandin (Embrey et al., 1986) and theophylline (Reddy et al., 2006). The PU carrier is utilized to deliver iodine-containing drugs (Touitou & Friedman, 1984). Urethane-based hydrogels were prepared based on the reaction of diisocyanates with amphiphilic ethylene oxide and triol crosslinker to deliver propranolol hydrochloride, an antihypertensive drug (Van Bos & Schacht, 1987). Drug delivery systems on a PU base with various antitumorous drugs, such as cyclophosphane, thiophosphamide and vincristine, have been prepared (Iskakov et al., 1998, 2000). An *in vitro* technique was used to determine the release characteristics of the drugs into model biological media. It was shown the drug release occurs in accordance with first-order kinetics.

PU-based drug delivery systems have considerable potential for treatment of tuberculosis. Tuberculosis is widely spread disease in most developing countries. The main method of tuberculosis treatment is chemotherapy. Although current chemotherapeutic agents for tuberculosis treatment are therapeutically effective and well tolerated, a number of problems remain. The chemotherapy is burden some, extends over long periods and requires continuous and repeated administration of large drug doses. Thus, traditional drug chemotherapy has serious limitations because of increasing microbial drug resistance and toxico-allergic side effects. One of the ultimate problems in effective treatment of tuberculosis is patient compliance. These problems of increasing drug resistance, toxico-allergic side effects, patient compliance can be approached by the use of long-acting polymeric drug delivery systems (Sosnik et al., 2010). The design of implantable systems containing the antituberculosis drugs in combination with biocompatible polymers would make possible to achieve the significant progress in treatment of this global debilitating disease (Shegokar et al., 2011).

Biodegradable microsphere drug delivery systems have shown application for oral and parenteral administration. Administration of microparticles to the lungs (alveolar region) may provide the opportunity for the prolonged delivery active agent to tuberculosis infected macrophages. Microspheres can be produced to meet certain morphological requirements such as size, shape and porosity by varying the process parameters. However, the morphology of the lung is such that to achieve effective drug deposition it is necessary to control the particle size of microparticles.

The objective of the chapter is to develop an effective polymeric drug delivery systems based on PU for the treatment of tuberculosis. Polyurethane materials are investigated as carriers for sustained and controlled release of antituberculosis drugs. The synthesis and characterization of PU microcapsules are studied making use various molecular weight polyethylene glycol and tolylene-2,4-diisocyanate. Antituberculosis drug isoniazid (Is), rifampicin, ethionamide and florimicin were incorporated into the PU microcapsules and

foams. The effects of nature and concentration of drugs and diols, molecular weight (Mw), morphology of polyurethanes on release behavior from polymeric systems were studied. The possibility of application of the polymeric drug delivery systems based on polyurethane for tuberculosis treatment was shown by some medical and biological tests.

2. Polymeric microparticles for tuberculosis treatment

Recent trends in polymeric controlled drug delivery have seen microencapsulation of pharmaceutical substances in biodegradable polymers as an emerging technology. Extensive progressive efforts have been made to develop various polymeric drug delivery systems to either target the site of tuberculosis infection or reduce the dosing frequency (Toit et al., 2006). Carriers as microspheres have been developed for the sustained delivery of antituberculosis drugs and have demonstrated better chemotherapeutic efficacy when investigated in animal models. Antituberculosis drugs have been successfully entrapped in microparticles of natural and synthetic polymers such as alginate (ALG), ALG-chitosan, poly-lactide-co-glycolide and poly-butyl cyanoacrylate (Gelperina et al., 2005, Pandey & Khuller, 2006).

ALG, a natural polymer, has attracted researchers owing to its ease of availability, compatibility with hydrophobic as well as hydrophilic molecules, biodegradability under physiological conditions, lack of toxicity and the ability to confer sustained release potential. The ability of ALG to co-encapsulate multiple antitubercular drugs and offer a controlled release profile is likely to have a major impact in enhancing patient compliance for better management of tuberculosis (Ahmad & Khuller, 2008).

Spherical microspheres able to prolong the release of Is were produced by a modified emulsification method, using sodium ALG as the hydrophilic carrier (Rastogi et al., 2007). The particles were heterogeneous with the maximum particles of an average size of 3.719 μm . Results indicated that the mean particle size of the microspheres increased with an increase in the concentration of polymer and the cross-linker as well as the cross-linking time. The entrapment efficiency was found to be in the range of 40-91%. Concentration of the cross-linker up to 7.5% caused increase in the entrapment efficiency and the extent of drug release. Optimized Is-ALG microspheres were found to possess good bioadhesion. The bioadhesive property of the particles resulted in prolonged retention in the small intestine. Microspheres could be observed in the intestinal lumen at 4h and were detectable in the intestine 24h post-oral administration. Increased drug loading (91%) was observed for the optimized formulation suggesting the efficiency of the method. Nearly 26% of Is was released in simulated gastric fluid pH 1.2 in 6h and 71.25% in simulated intestinal fluid pH 7.4 in 30h.

ALG microparticles were developed as oral sustained delivery carriers for antituberculosis drugs in order to improve patient compliance (Qurrat-ul-Ain et al., 2003). Pharmacokinetics and therapeutic effects of ALG microparticle encapsulated Is, rifampicin and pyrazinamide were examined in guinea pigs. ALG microparticles containing antituberculosis drugs were evaluated for in vitro and in vivo release profiles. These microparticles exhibited sustained

release of Is, rifampicin and pyrazinamide for 3-5 days in plasma and up to 9 days in organs. Peak plasma concentration, elimination half-life and infinity of ALG drugs were significantly higher than those of free drugs. The encapsulation of drug in ALG microparticles resulted in up to a nine-fold increase in relative bioavailability compared with free drugs. Chemotherapeutic efficacy of ALG drug microspheres against experimental tuberculosis not detectable at 1:100 and 1:1000 dilutions of spleen and lung homogenates. Histopathological studies further substantiated these observations, thus suggesting that application of ALG-encapsulated drugs could be useful in the effective treatment of tuberculosis.

Pharmacokinetics and tissue distribution of free and ALG-encapsulated antituberculosis drugs were evaluated in mice at different doses (Ahmad et al., 2006). ALG nanoparticles encapsulating Is, rifampicin, pyrazinamide and ethambutol were prepared by controlled cation-induced gelification of ALG. The formulation was orally administered to mice at two dose levels. A comparison was made in mice receiving free drugs at equivalent doses. The relative bioavailabilities of all drugs encapsulated in ALG nanoparticles were significantly higher compared with free drugs. Drug levels were maintained at or above the minimum inhibitory concentration until 15 days in organs after administration of encapsulated drugs, whilst free drugs stayed at or above 1 day only irrespective of dose. The levels of drugs in various organs remained above the minimum inhibitory concentration at both doses for equal periods, demonstrating their equiefficiency.

Chemotherapeutic potential of ALG nanoparticle-encapsulated econazole and antituberculosis drugs were studied against murine tuberculosis (Ahmad et al., 2007). Econazole (free or encapsulated) could replace rifampicin and Is during chemotherapy. Eight doses of ALG nanoparticle-encapsulated econazole or 112 doses of free econazole reduced bacterial burden by more than 90% in the lungs and spleen of mice infected with *Mycobacterium tuberculosis*. ALG nanoparticles reduced the dosing frequency of azoles and antitubercular drugs by 15-fold.

Is was encapsulated into microspheres of ALG-chitosan by means of a complex coacervation method in an emulsion system (Lucinda-Silva & Evangelista, 2003). The particles were prepared in three steps: preparation of a emulsion phase and adsorption of the drug. The results showed that microspheres of ALG-chitosan obtained were of spherical shape. The emulsion used for microparticle formation allows the preparation of particles with a narrow size distribution. The adsorption observed is probably of chemical nature, i.e. there is an ionic interaction between the drug and the surface of the particles.

ALG-chitosan microspheres encapsulating rifampicin, Is and pyrazinamide, were formulated (Pandey & Khuller, 2004). A therapeutic dose and a half-therapeutic dose of the microsphere-encapsulated were orally administered to guinea pigs for pharmacokinetic and chemotherapeutic evaluations. The drug encapsulation efficiency ranged from 65% to 85% with a loading of 220-280 mg of drug per gram microspheres. Administration of a single oral dose of the microspheres to guinea pigs resulted in sustained drug levels in the plasma for 7 days and in the organs for 9 days. In *Mycobacterium tuberculosis* H₃₇Rv-infected guinea

pigs, administration of a therapeutic dose of microspheres spaced 10 days apart produced a clearance of bacilli equivalent to conventional treatment for 6 weeks.

Poly(lactide-co-glycolide) (PLG) polymers are biodegradable and biocompatible, they have been the most commonly used as carriers for microparticle formulations. Monodispersed poly(lactic-co-glycolic acid) (PLGA) microspheres containing rifampicin have been prepared by solvent evaporation method (Makino et al., 2004, Yoshida et al., 2006). The microspheres were spherical and their average diameter was about 2 μm . The loading efficiency of rifampicin was dependent on the molecular weight of PLGA. The higher loading efficiency was obtained by the usage of PLGA with the lower Mw, which may be caused by the interaction of the amino groups of rifampicin with the terminal carboxyl groups of PLGA. PLGA with the monomer compositions of 50/50 and 75/25, of lactic acid/glycolic acid, were used in this study. From rifampicin-loaded PLGA microspheres formulated using PLGA with the Mw of 20,000, rifampicin was released with almost constant rate for 20 days after the lag phase was observed for the initial 7 days at pH 7.4. On the other hand, from rifampicin-loaded PLGA microspheres formulated using PLGA with the molecular weight of 5000 or 10,000, almost 90% of rifampicin-loaded in the microspheres was released in the initial 10 days. Highly effective delivery of rifampicin to alveolar macrophages was observed by the usage of rifampicin-loaded PLGA microspheres. Almost 19 times higher concentration of rifampicin was found to be incorporated in alveolar macrophages when rifampicin-loaded PLGA microspheres were added to the cell culture medium than when rifampicin solution was added.

Controlled release rifampicin-loaded microspheres were evaluated in nonhuman primates (Quenelle et al., 2004). These microspheres were prepared by using biocompatible polymeric excipients of lactide and glycolide copolymers. Animals received either 2.0 g of a large formulation (10–150 μm , 23 wt% rifampicin) injected subcutaneously at Day 0 (118–139 mg rifampicin/kg), 4.0 g of a small formulation (1–10 μm , 5.8 wt% rifampicin) administered intravenously in 2.0 g doses on Day 0 and 7 (62.7–72.5 mg rifampicin/kg), or a combination of small and large microspheres (169–210 mg rifampicin/kg). Extended rifampicin release was observed up to 48 days. Average rifampicin concentrations remaining in the liver, lung, and spleen at 30 days were 14.03, 4.09, and 1.98 $\mu\text{g/g}$ tissue, respectively.

PLG nanoparticles encapsulating streptomycin were prepared by the multiple emulsion technique and administered orally to mice for biodistribution and chemotherapeutic studies (Pandey & Khuller, 2007). The mean particle size was 153.12 nm with 32.12 \pm 4.08% drug encapsulation and 14.28 \pm 2.83% drug loading. Streptomycin levels were maintained for 4 days in the plasma and for 7 days in the organs following a single oral administration of PLG nanoparticles. There was a 21-fold increase in the relative bioavailability of PLG-encapsulated streptomycin compared with intramuscular free drug. In *Mycobacterium tuberculosis* (*M.tuberculosis*) H₃₇Rv infected mice, eight doses of the oral streptomycin formulation administered weekly were comparable to 24 intramuscular injections of free streptomycin.

PLG nanoparticle-encapsulated econazole and moxifloxacin have been evaluated against murine tuberculosis (drug susceptible) in order to develop a more potent regimen for tuberculosis (Ahmad et al., 2008). PLG nanoparticles were prepared by the multiple emulsion and solvent evaporation technique and were administered orally to mice. A single oral dose of PLG nanoparticles resulted in therapeutic drug concentrations in plasma for up to 5 days (econazole) or 4 days (moxifloxacin), whilst in the organs (lungs, liver and spleen) it was up to 6 days. In comparison, free drugs were cleared from the same organs within 12-24h. In *M. tuberculosis*-infected mice, eight oral doses of the formulation administered weekly were found to be equipotent to 56 doses (moxifloxacin administered daily) or 112 doses (econazole administered twice daily) of free drugs. Furthermore, the combination of moxifloxacin+econazole proved to be significantly efficacious compared with individual drugs. Addition of rifampicin to this combination resulted in total bacterial clearance from the organs of mice in 8 weeks. PLG nanoparticles appear to have the potential for intermittent therapy of tuberculosis, and combination of moxifloxacin, econazole and rifampicin is the most potent.

Antituberculosis drugs Is, rifampicin, streptomycin and moxifloxacin have been encapsulated in poly(butyl cyanoacrylate) nanoparticles (Anisimova et al., 2000, Kisich et al, 2007). Incorporation of drugs in polymeric nanoparticles not only increased the intracellular accumulation of these drugs in the cultivated human blood monocytes but also produced enhanced antimicrobial activity of these agents against intracellular *M. tuberculosis* compared with their activity in extracellular fluid. Encapsulated moxifloxacin accumulated in macrophages approximately three-fold times more efficiently than the free drug, and was detected in the cells for at least six times longer than free moxifloxacin at the same extracellular concentration.

This brief review suggested that micro- and nanoparticles based delivery systems have a considerable potential for treatment of tuberculosis. Their major advantages, such as improvement of drug bioavailability and reduction of the dosing frequency, may create a sound basis for better management of the disease, making directly observed treatment more practical and affordable.

3. Polyurethane microparticles as carriers of drug

PU microspheres can be prepared by interfacial polycondensation in emulsions. These techniques include polycondensation of two or more complimentary monomers at the interface of two-phase system, carefully emulsified for obtaining little drop-lets in emulsion phase. Usually, the interfacial polycondensation carried out by two steps: emulsification step (emulsion formation using a mechanical stirring during few minutes and one of the monomers is dissolved in the emulsion drops; polycondensation step (the second complementary monomer is added to the external phase of the emulsion and the polycondensation reaction takes place at the liquid-liquid emulsion interface). Interest in the PU microparticles in each day has being increased since products presents numerous advantages in biomedical, pharmaceutical and cosmetic applications.

PU microparticles could be interesting matrices for controlled drug delivery. Aliphatic PU Tecoflex was evaluated as microsphere matrix for the controlled release of theophylline (Subhaga et al., 1995). PU microspheres were prepared using solvent evaporation technique from a dichloromethane solution of the polymer containing the drug. A dilute solution of poly(vinyl alcohol) served as the dispersion medium. Microspheres of good spherical geometry having theophylline content of 35% could be prepared by the technique. The release of the drug from the microspheres was examined in simulated gastric and intestinal fluids. While a large burst effect was observed in gastric fluid, in the intestinal fluid a close to zero-order release was seen.

Microencapsulation of theophylline in PU was developed with 4, 4'-methylene-diphenylisocyanate, castor oil and ethylene diamine as chain extender (Rafienia et al., 2006). PU microspheres were prepared in two steps pre-polymer preparation and microspheres formation. Particle size investigation with optical microscopy revealed size distribution of 27–128 μm . Controlled release experiment of theophylline was performed in phosphate buffered saline at pH 7.4 with UV-spectrometer at 274 nm. Drug release profiles showed initial release of 2–40% and further release for more than 10 days.

The effect of chain-extending agent on the porosity and release behavior of biologically active agent diazinon from PU microspheres were studied (Jabbari & Khakpour, 2000). Microsphere was prepared using a two-step suspension polycondensation method with methylene diphenyl diisocyanate, polyethylene glycol 400 and 1,4-butanediol as the chain-extending agent. Chain-extending agent was used to increase the ratio of hard to soft segments of the PU network, and its effect on microsphere morphology was studied with SEM. According to the results, porosity was significantly affected by the amount of chain-extending agent. The pore size decreased as the concentration of chain-extending agent increased from zero to 50 mole%. With further increase of chain-extending agent to 60 and 67%, PU chains became stiffer and formation of pores was inhibited. Therefore, pore morphology was significantly affected by variations in the amount of chain-extending agent. The release behavior of microspheres was investigated with diazinon as the active agent. After an initial burst, corresponding to 3% of the incorporated amount of active agent, the release rate was zero order.

PU polymers and poly(ether urethane) copolymers were chosen as drug carriers for α -tocopherol (Bouchemal et al., 2004). This active ingredient is widely used as a strong antioxidant in many medical and cosmetic applications, but is rapidly degraded, because of its light, heat and oxygen sensitivity. PU and poly(ether urethane)-based nanocapsules were synthesized by interfacial reaction between two monomers. Interfacial polycondensation combined with spontaneous emulsification is a new technique for nanoparticles formation. Nanocapsules were characterized by studying particle size (150-500 nm), pH, yield of encapsulation and morphologies. Polyurethanes were obtained from the condensation of isophorone diisocyanate and 1,2-ethanediol, 1,4-butanediol, 1,6-hexanediol. Poly(ether urethane) copolymers were obtained by replacing diols by polyethylene glycol oligomers Mw 200, 300, 400 and 600. Mw of di- and polyols have a considerable influence on

nanocapsules characteristics cited above. The increase of M_w of polyols tends to increase the mean size of nanocapsules from 232 ± 3 nm using ethanediol to 615 ± 39 nm using PEG 600, and led to the agglomeration of particles. We also noted that the yield of encapsulation increases with the increase of polyol length. After 6 months of storage, polyurethanes nanocapsules possess good stability against aggregation at 4 and 25° C. Comparing results obtained using different monomers, it reveals that the PU based on hexanediol offers good protection of alpha-tocopherol against damaging caused by the temperature and UV irradiation (Bouchemal et al., 2006).

Ovalbumin (OVA)-containing PU microcapsules were successfully prepared by a reaction between toluene diisocyanate and different polyols such as glycerol, ethane diol, and propylene glycol (Hong & Park, 2000). The structural and thermal properties of the resultant microcapsules and the release profile of the OVA from the wall membranes were studied. In conclusion, the microcapsules from the glycerol showed the highest thermal stability, with the formation of many hydrogen bonds. From the data of release profiles, it was confirmed that the particle size distribution and morphologies of microcapsules determined the release profiles of the OVA from the wall membranes.

Bi-soft segmented poly(ester urethane urea) microparticles were prepared and characterized aiming biomedical application (Campos et al., 2011). Two different formulations were developed, using poly(propylene glycol), tolylene 2,4-diisocyanate terminated pre-polymer and poly(propylene oxide)-based tri-isocyanated terminated pre-polymer (TI). A second soft segment was included due to poly(ϵ -caprolactone) diol. Infrared spectroscopy, used to study the polymeric structure, namely its H-bonding properties, revealed a slightly higher degree of phase separation in TDI-microparticles. TI-microparticles presented slower rate of hydrolytic degradation, and, accordingly, fairly low toxic effect against macrophages. These new formulations are good candidates as non-biodegradable biomedical systems.

The synthesis of PU microsphere-gold nanoparticle "core-shell" structures and their use in the immobilization of the enzyme endoglucanase are described (Phadtare et al., 2004). Assembly of gold nanoparticles on the surface of polymer microspheres occurs through interaction of the nitrogens in the polymer with the nanoparticles, thereby precluding the need for modifying the polymer microspheres to enable such nanoparticle binding. Endoglucanase could thereafter be bound to the gold nanoparticles decorating the PU microspheres, leading to a highly stable biocatalyst with excellent reuse characteristics. The immobilized enzyme retains its biocatalytic activity and exhibits improved thermal stability relative to free enzyme in solution.

Microencapsulation of the water soluble pesticide monocrotophos (MCR), using PU as the carrier polymer, has been developed using two types of steric stabilizers polymethylacrylate (PLMA) macrodiol and PLMA-g-PEO graft copolymer (Shukla et al., 2002). The microencapsulation process is carried out in non-aqueous medium and at a moderate temperature to avoid any chemical degradation of monocrotophos during the encapsulation process. Microcapsules were characterized by optical microscopy and SEM for particle size and morphology, respectively. The effects of loading of MCR, crosslinking density of PU,

and nature of steric stabilizer on the release of MCR from PU microcapsules have been studied.

Poly(urea-urethane) microcapsules containing oil-soluble dye dioctyl phthalate as core material were prepared by the interfacial polymerization with using mixtures of tri- and di-isocyanate monomers as wall forming materials (Chang et al., 2003, 2005). The time course of the dye release in dispersing tetrahydrofuran was measured as a function of the weight fraction of tri-isocyanate monomer in the total monomer weight and the core/wall material-weight ratio. The dye release curves were well represented by an exponential function $C=C_{eq}(1-e^{-t/\tau})$, where C is the concentration of the dye in the dispersing medium, C_{eq} that at equilibrium state, t the elution time and τ is a time constant. τ increased linearly against weight at high concentration, suggesting controllability of the release rate of microcapsules by varying tri-isocyanate/di-isocyanate ratio

4. Polyurethane microparticle as carrier of antituberculosis drug

New polyurethane microcapsules incorporated with antituberculosis drug Is have been synthesized by interfacial polyaddition between toluene-2,4-diisocyanate (TDI) and various poly(ethylene glycol)s (PEG). Drug Is is hydrophilic water-soluble compound, and it is insoluble in toluene. Thus Is could be capsulated by interfacial polycondensation technique using water-in-toluene emulsion, which prevents transferring of Is to the external phase. And drug encapsulation is possible during the process of the polymer wall formation (Batyrbekov et al., 2009; Iskakov et al., 2004).

Isocyanate groups react with hydroxyl groups of PEG to form polyurethane chains according to the Scheme (Fig.1 a). TDI can also reacts with molecules of water at the border of reaction to form unstable NH-COOH group, which dissociates into amine and carbon dioxide (Fig.1 b). Chains with amine end-group reacts with the isocyanate groups of growing polymer with urea segments formation.

Polycondensation was carried out in a 1 L double-neck flask fitted with a stirrer. Polyethylene glycol with 4 various molecular weights 400, 600, 1000 and 1450 (Sigma, USA) - PEG 400, PEG 600, PEG 1000 and PEG 1450 respectively were used as diol monomers. TDI (Sigma, USA) was applied as a bifunctional monomer for the polycondensation. Three solutions were prepared separately. Solution A: 10 mg surfactant Tween 40 was dissolved in 100 ml of toluene; solution B: x mmol diol and Is were added in y ml of water; amount of Is was 10, 20, and 30 mol % from PEG; solution C: $2.5x$ mmol TDI was dissolved in 10 ml of solution A. Water/oil ratio was 1:10 vol.%. Solution B was poured into the reaction flask, containing 90 ml of solution A under the stirring at 1000 rpm during 15 minutes. After the formation of microemulsion, solution C was added dropwise. After 180 min the polymerization was stopped. Microparticles were filtered, carefully washed with distilled water and dried at ambient conditions. Yield of polymers was estimated from the total amount of introduced monomers compared to the weight of polycondensation products.

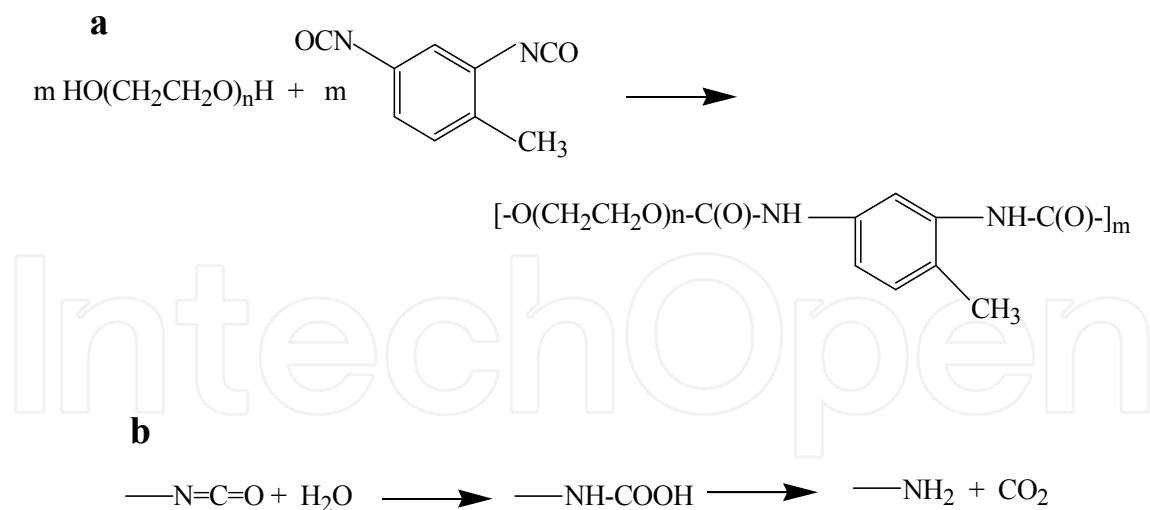


Figure 1. Scheme of reaction between PEG and TDI with polyurethane formation.

The completion of polycondensation process was estimated by IR-spectra from decreasing of the absorption band at $2270\text{--}2320\text{ cm}^{-1}$, which correspond to —N=C=O isocyanate group. IR spectra were obtained by a Nicolet 5700 FT-IR (USA) infrared spectrophotometer in KBr.

In the IR-spectra of microparticles the N-H stretching vibration were observed at $3450\text{--}3300\text{ cm}^{-1}$, absorption bands at $1740\text{--}1700\text{ cm}^{-1}$ for the C=O stretching of urethane and at $1690\text{--}1650\text{ cm}^{-1}$ for urethane-urea formation were also present (Fig.2). Absorption bands are present at 1100 cm^{-1} for C-O-C ether group and at $2850\text{--}2950\text{ cm}^{-1}$ for C-H. In FT-IR spectra of microparticles containing Is, the new stretching vibrations band appeared at 1350 cm^{-1} , 1000 cm^{-1} and 690 cm^{-1} , which were also present in FT-IR spectra of pure Is that indicates the physical mechanism of Is capsulation.

In the process of interfacial polycondensation, two PU products of reaction were detected: the main product - microparticles, and the secondary product - linear precipitated polyurethane. The increase of PEG content in water phase resulted in increased amount of the secondary product, and as the PEG content in water phase reached 60 vol.%, maximum of the secondary product was observed (about 40%).

Decreasing PEG concentration in water phase leads to increased yield of polyurethane microparticles. Maximum of yield was reached at PEG concentration 22 - 27 vol.% and in that condition whole oligomer reacted at surface of emulsion drops with microparticles formation. Reduction of microparticle yield after the maximum is due mainly to increasing contribution of the hydrolysis process of isocyanate groups.

Appearance of the secondary product and increase of its yield, probably, can be attributed to the increase of PEG concentration and results in PEG partially transfer from the water phase to the internal phase of toluene and the process of polycondensation between PEG and TDI takes place with linear polyurethane formation. At the end of reaction rate of PEG diffusion to surface, namely at the reaction region, seems to be a limit stage of the process. Reducing of PEG concentration causes to decrease of system viscosity. Effectiveness of Is capsulation in PU microparticles ranged from 3.4 to 41.7 % and significantly depended on water/PEG ratio in the water phase of emulsion.

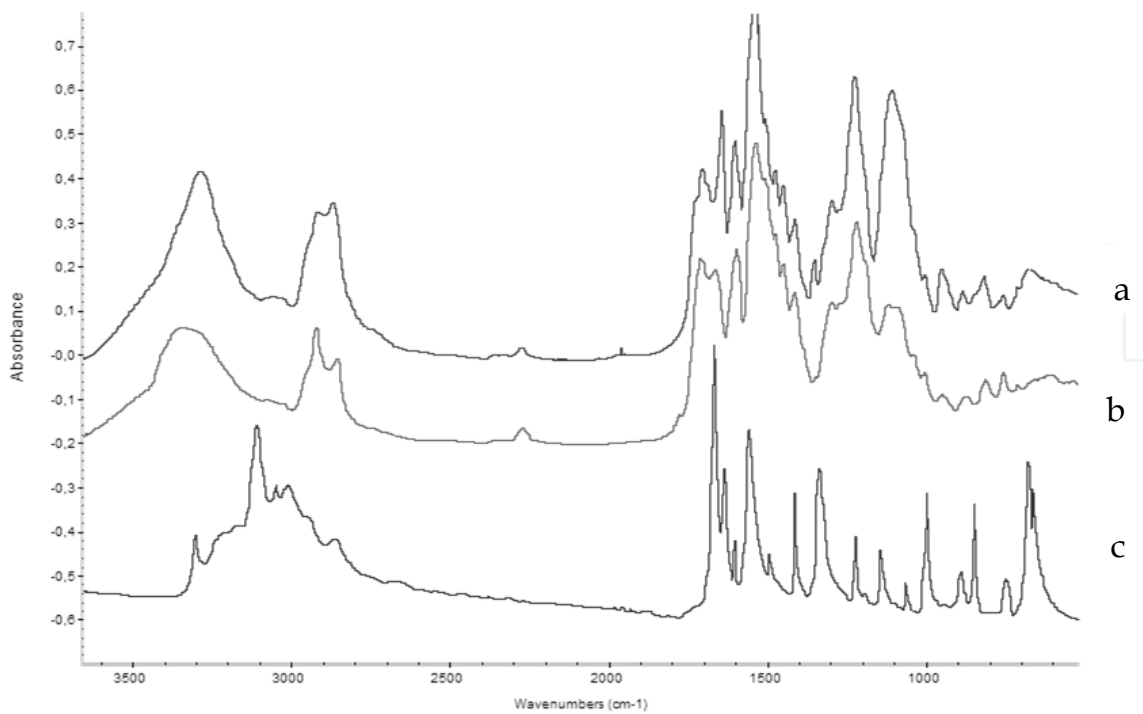


Figure 2. FT-IR-spectra of polyurethane microparticles containing isoniazid (a), polyurethane microparticles (b) and isoniazid (c).

Fig. 3 shows that composition of the water phase influences upon effectiveness of capsulation. Increase of PEG concentration results in decreasing effectiveness of capsulation and decrease of Is loading correspondingly. The high PEG concentration promotes miscibility of Is in the internal oil phase - toluene. Morphology of the surface of microparticles is very important factor, which affects release behavior of active agent. The wall structure depends on the conditions of interfacial polycondensation process, such as Mw and chemical structure of diol, the concentration of the monomers and other. The effect of water/PEG ratio in aqueous phase on morphology of microparticle was investigated. Microparticles prepared from PEG solutions of higher concentration have dense surface so that Is diffused much slower. At the high concentration of PEG reaction between PEG and TDI is significantly limited on the interface of the drops. Furthermore excessive PEG transfers to the external surface of microparticles and reacts with TDI and less penetrable wall was formed.

Fig.4 shows SEM photos of interfacial polycondensation products prepared by reaction between TDI and PEG 400 at water/PEG ratio 11,8 : 88,2 vol.% in water phase. According to Figs. 4a and 4b two products of polycondensation with different structure were formed. PU microparticles have spherical shape and size about 5 - 10 μm (Fig. 4a). The secondary product has fibril structure with diameter less then 500 nm (Fig 4b). The effect of water/PEG ratio on morphology of microparticle walls is shown in Figs. 4c and 4d. PU microparticles prepared at water/PEG ratio 82,4 :17,6 (Fig. 4c) have rough surface. On the contrary the surface of PU microparticles prepared at water/PEG ratio 11,8 : 88,2 (Fig 4d) were dense and smooth.

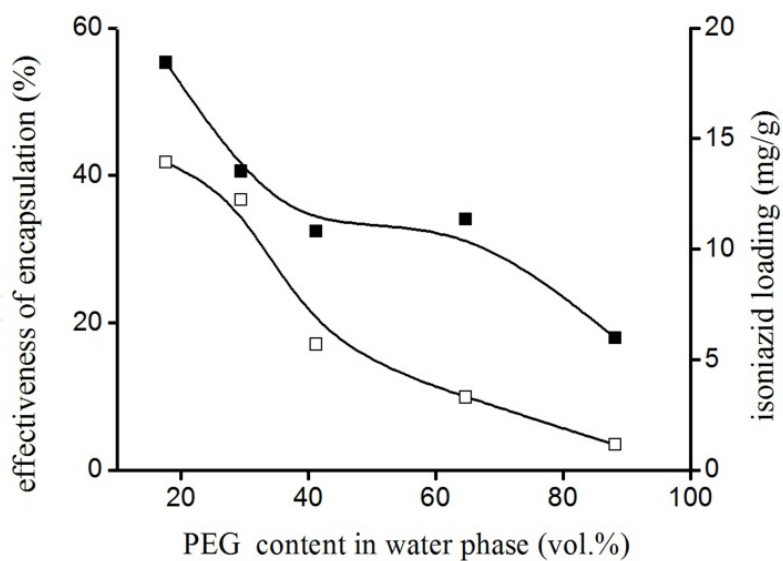


Figure 3. The effect of PEG content in water phase on effectiveness of encapsulation (□) and Is loading in PU microparticles (■).

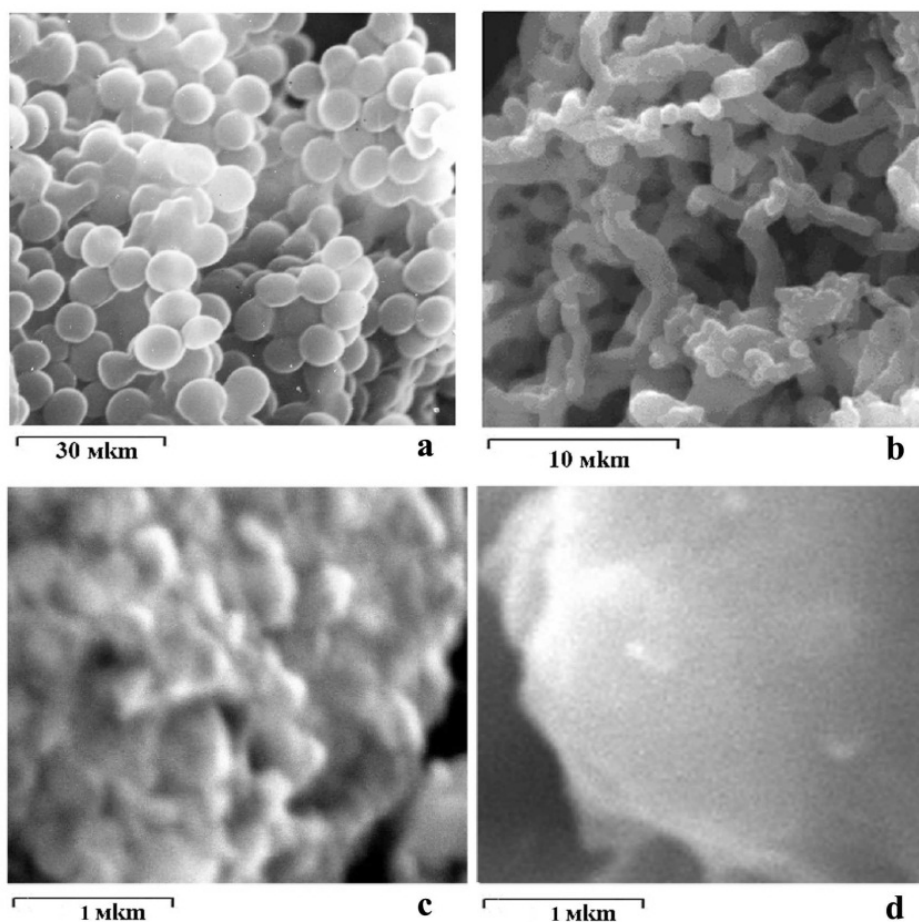


Figure 4. SEM photographs of products of interfacial polycondensation . between TDI and PEG 400 at 60°C. PU microparticles (a) and PU secondary product (b) synthesized at water/PEG ratio 11.8 : 88.2 in water phase. Surface of PU microparticles prepared at water/PEG ratio 82.4 :17.6 (c) and 11.8 : 88.2 (d) in water phase.

The release behavior of Is from PU microparticles was carried out and different conditions of synthesis such as water/PEG ratio, molecular weight of PEG and isoniazid concentration was investigated. The release behavior of microparticles loaded with isoniazid was studied with ultraviolet (UV) spectroscopy. For calibration, physiological solutions of isoniazid with concentration ranging from 0.004 to 0.05 mg/ml were prepared and their absorption was measured at 263.5 nm with Jasco UV/VIS 7850 spectrophotometer (Japan). 10 mg of isoniazid-loaded microparticles were dispersed in 10 ml of physiological solution under light stirring at constant temperature 37°C. After fixed time interval 2 ml of solution was taken out by the squirt equipped with the special filter. The efficiency of capsulation was calculated as ratio of introduced isoniazid to solution B compared with amount of delivered isoniazid into water during 3 weeks. Isoniazid loading was weight of isoniazid (mg) contained in 1 g of microparticles.

Fig. 5 shows the release behavior of Is from PU microparticles, synthesized at different water/PEG ratio. The most part of the drug delivered during the first three hours, then slow release of the residual Is was observed during the next two weeks. Microparticles prepared with less concentration of PEG in the water phase demonstrated faster diffusion of Is through walls of microparticles. The increased PEG content in water phase of reaction, results in decreasing Is diffusion, due to formation of PU microparticles with denser polymer wall. Microparticles prepared with PEG concentration 17.6, 29.4 and 41.2 vol.% showed the release 58 - 66 % of Is during 3 h. However, due to denser wall of microparticles prepared with PEG 64.7 и 88.2 vol. % demonstrated the release no more 35% of the drug within the same time.

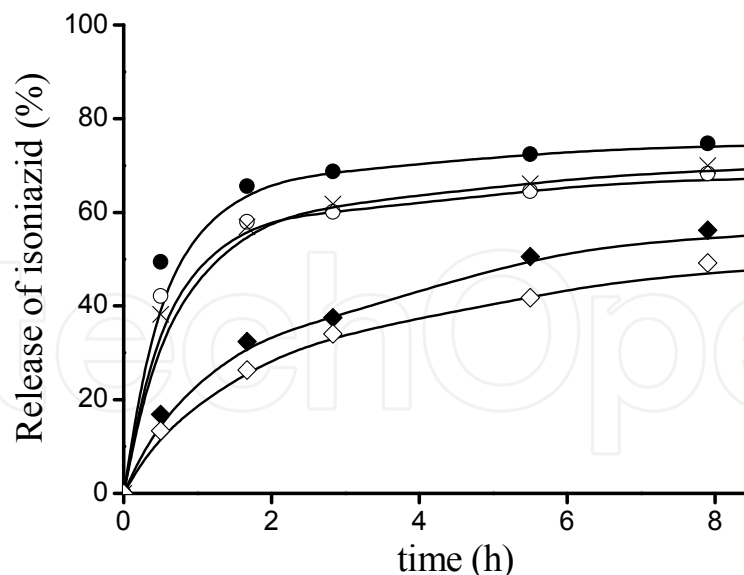


Figure 5. Release of Is from PU microparticles synthesized at various water/PEG ratio: ● - 82.4:17.6, ○ - 70.6:29, × - 58.8:41.2, ◆ - 35.3:64.7 and ◇ - 11.8:88.2.

The effect of molecular weight of PEG on release of Is from PU microparticles was investigated (Fig 6). Microparticles were prepared by using PEG with Mw 400, 600, 1000 and 1450. Increasing molecular weight of soft segments (PEG) results in the increase of diffusion

rate of Is into solution. This phenomenon can be attributed to increasing Mw of PEG which leads to accelerating diffusion of water-soluble Is through hydrophilic PEG chains.

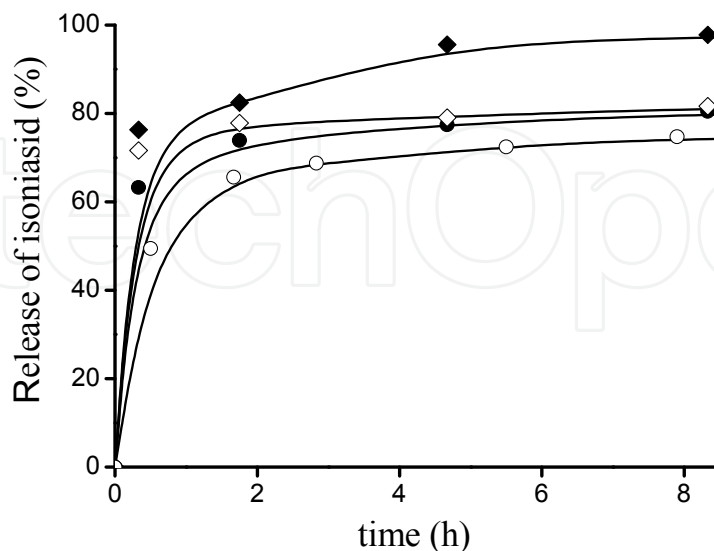


Figure 6. Release of Is from PU microparticles synthesized at various Mw of PEG. Mw = 400 (o), 600 (●), 1000 (◇) and 1450 (◆).

Microparticles with different Is loading, namely 18.4, 35.3 and 65.6 mg/g were produced. In Fig 7 release behavior of Is is shown.

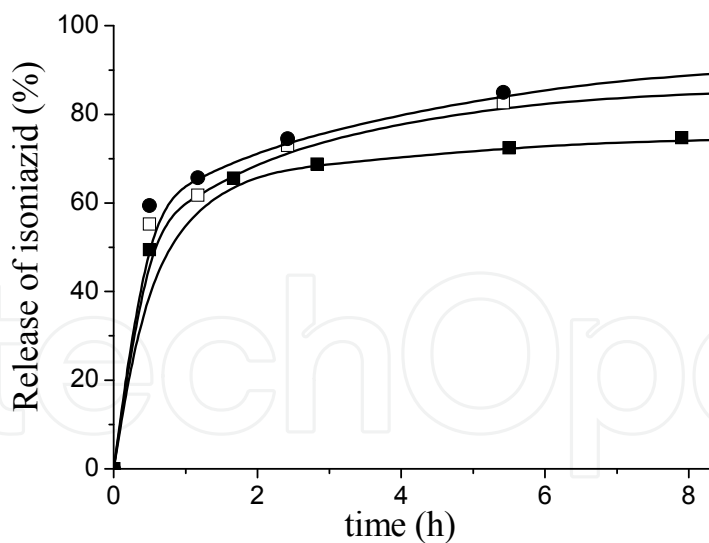


Figure 7. Release of Is from PU microparticles with different Is loading: 18.4 (■), 35.3 (□) and 65.6 mg/g (●).

Microparticles with higher Is loading demonstrate faster release rate of the drug due to increased gradient of concentrations between the external solution and core of microparticles.

PU microparticles were administrated subcutaneously to mice BL/6. Histologic analyses of the underskin tissue was carried out at a different period of microparticles administration in the mice by using electron microscope LEO F360, equipped with X-ray analyzer EDS Oxford ISI 300.

Fig 8 shows histologic analyses of tissue under skin. Within 5 days of the microparticles deposition, the thickening of the surrounding tissue due to primary macrophage reaction and fibrillar tissue formation were detected as shown in Fig. 8b. On day 21, some enzymatic lysis of polyurethane – C(O)–NH – group probably took place (Fig. 8c) and partial biodegradation of PU microparticles was observed. For all experimental animals no casting-off or necrosis of tissue were observed.

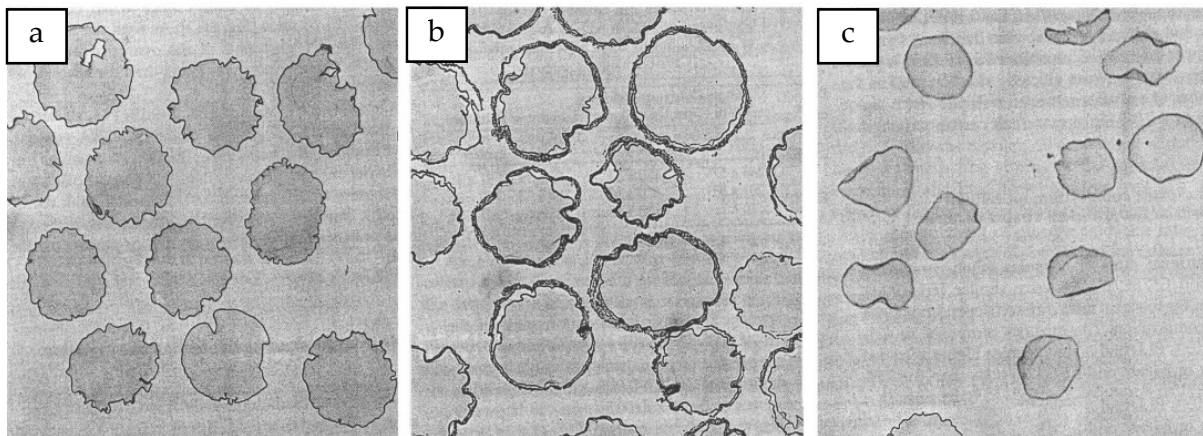


Figure 8. Histological slices of tissue under mice skin 1 (a), 5 (b), and 21 (c) days after deposition of isoniazid-containing PU microparticles to BL/6 mice provided by transparent electron microscope with 400x magnification.

Thus, the data obtained in the present work have demonstrated the possibility of using PU microparticles as a carrier for the controlled delivery of antituberculosis drug Is. PU microparticles were prepared by interfacial reaction between PEG and TDI in water in toluene emulsion. The effect of water/PEG ratio on the morphology of microparticles and release behavior was shown. The low PEG content in aqueous phase results in the formation of microparticles with rough surface, which demonstrate faster diffusion of Is in comparison to PU microparticles produced from more concentrated PEG solutions, they have smooth surface and less penetrable walls for Is. Increased Mw of PEG and Is loading leads to increased diffusion rate of isoniazid from polyurethane microparticles. For PU microparticles administered in mice BL/6 subcutaneously, biodegradation was observed due to enzymatic lysis of polyurethane group. Preliminary data indicate that PU microparticles could be perspective carriers for controlled delivery and respirable administration of antituberculosis drug Is.

5. Polyurethane foams as carriers of antituberculosis drugs

The use of soft PU foams as carriers of antituberculosis drugs is of considerable interest. In such systems pharmaceutical agents are dispersed or dissolved in the PU carrier and the

kinetics of drug release are generally controlled by diffusion phenomena through the polymer. Such systems are being used for treatment of tuberculosis-infected cavities (wounds, pleural empyema, bronchial fistula). It is the purpose of this chapter to show the possibility of using polyurethane foams as carriers of some antituberculosis agents for tuberculosis treatment.

PU foams were synthesized by reaction of pre-polymer with isocyanate terminal groups with a small amount of branching agent and water. Other ingredients, such as catalyst and chain extenders, were not used in order to preserve medical purity. The scheme of synthesis is presented below in Fig.9.

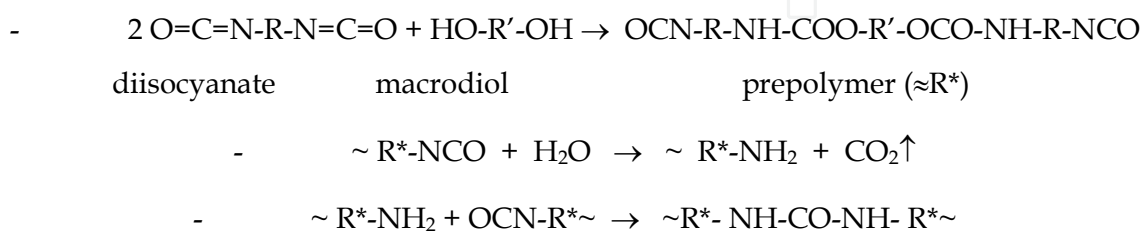


Figure 9. Scheme of PU foams synthesis.

Antituberculosis drugs Is, ethionamide (Eth), florimicin (Fl) and rifampicin (Rfp) were incorporated as fine crystals in the polymeric matrix at the stage of PU synthesis. The PU contained 100-300 mg of heterogeneously dispersed antituberculosis drugs.

The release of drugs from PU was examined by immersing polymeric samples in a model biological medium (physiological solution, phosphate buffer pH 7.4 and Ringer-Locke solution) at 37°C. The amount of drug released was determined UV-spectrophotometrically by measuring the absorbance maximum characteristic for each drug.

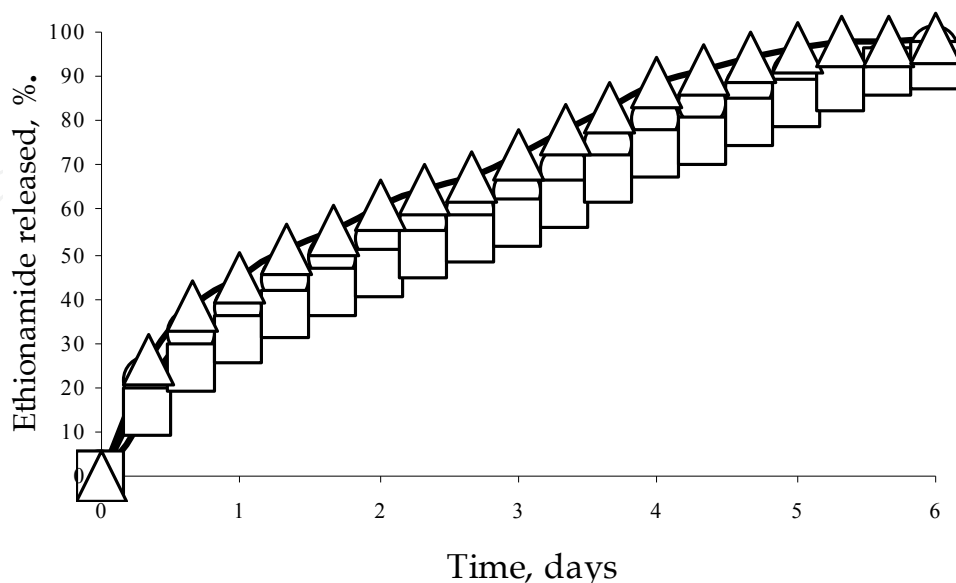


Figure 10. Release of Eth from polyurethane foam into Ringer-Locke solution at 37°C. Drug loadings (mg/g PU): 100(O), 200(Δ), 300(□).

All the release data show the typical pattern for a matrix-controlled mechanism. The cumulative amount of drugs released from the PU was linearly related to the square root of time and the release rate decreased with time. The process is controlled by the dissolution of the drug and by its diffusion through the polymer. The release is described by Fick's law and proceeds by first-order kinetics (Philip & Peppas, 1987). The structure of the drugs and their solubility influences the rate of release: the total amount of Is is released in 3-4 days, Eth in 5-6 days (Fig.10), Fl and Rfp in 14-16 days (Fig.11). The release time for 50% of Is is 22-26 h, for Eth 28-30 h, for Fl and Rfp 72-76 h, respectively. The rapid release of Is and Eth in comparison with Fl and Rfp is due to the higher solubility of these drugs in the dissolution medium. Increasing the drug loading from 100 to 300 mg/g resulted in an increase in the release rate.

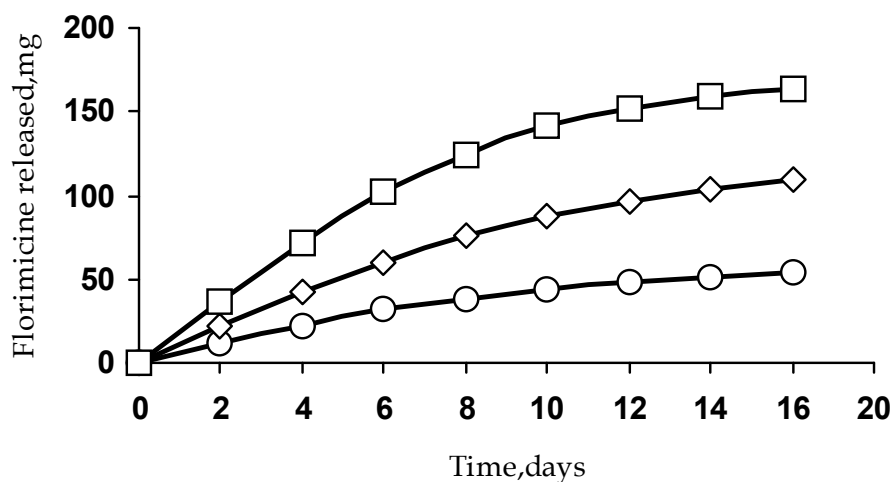


Figure 11. Release of Fl from PU foam into Ringer-Locke solution at 37°C. Drug loadings (mg/g PU): 100(O), 200(Δ), 300(\square).

Table 1 presents the values of the diffusion coefficients for drug release into different media, calculated for the initial release stage by a modified Higuchi equation (Higuchi, 1963). With increase of drug loading, the diffusion coefficient is not significantly decreased. This is connected with the plasticizing action of the drug, resulting in the deterioration of the mechanical properties of the polymeric matrix. The medium into which the drugs are released has no significant effect upon the diffusion coefficient.

The release results show that the use of PU as a carrier of antituberculosis drugs provides a controlled release of drugs suitable for use in practical medicine, i.e. it allows prolonged action of drugs over some days.

The tuberculostatic activity of drugs released from the PU was determined by diffusion into dense Levenshtein-Iensen nutrient medium compared with a museum strain of *M. tuberculosis*.

It has been shown that drugs introduced into a polymeric matrix have tuberculostatic activity on the level of free drugs. Is formed a microorganism growth delay zone of 41 mm, Eth 35 mm and Fl 29 mm.

Drug	Loading (mg/g PU)	$10^7 \times D$ (cm ² s ⁻¹)		
		Physiological solution	Ringer-Locke solution	Phosphate Buffer
Is	100	7,482	7,926	7,346
	200	7,026	7,150	7,158
	300	6,845	6,890	6,804
Eth	100	6,433	6,228	6,248
	200	6,237	5,928	6,142
	300	5,972	5,768	5,636
Fl	100	2,124	2,430	2,315
	200	1,980	2,068	2,112
	300	1,642	1,786	1,720
Rfp	100	1,116	1,224	1,226
	200	0,984	1,082	1,068
	300	0,922	0,944	0,896

Table 1. Diffusion coefficient (D) values for drug release from polyurethane foams into different media at 37°C for initial stage of release.

The efficiency of tuberculosis treatment by PU containing drugs was studied in experiments on guinea pigs (Batyrbekov et al., 1998). Several groups of animals, consisting of 20-25 guinea pigs, were infected with a 6-week culture of a laboratory strain of *M. tuberculosis*. Treatment was started 2 weeks after infection. Animals were treated by weekly administration of PU containing 5-day doses of the drugs (PU-Is, PU-Eth or PU-Fl), or by daily administration of a day's dose of Is, Eth or Fl. Animals of the control group were not treated (C). The weights of the guinea pigs and the dimensions of ulcers at the site of infection were periodically determined during the experiment. All untreated animals died 1.5-2 months after infection. The animals of the other groups were killed with 2.5 months after the beginning of the treatment. Guinea pigs were dissected and damage to lungs, livers, spleens and lymphatic ganglions was determined. The efficiency of the applied therapy is presented in Table 2.

Group	Index of damage, %				
	Lung	Liver	Spleen	Lymphatic ganglion	Summary
C	36,6	25,8	22,0	6,0	90,4
Is	5,0	12,2	12,2	2,5	31,9
PU-Is	4,0	11,4	12,0	2,5	29,9
Eth	8,0	13,6	14,6	3,5	39,7
PU-Eth	7,2	13,0	14,2	3,5	37,9
Fl	20,2	14,4	16,8	4,8	56,2
PU-Fl	18,8	13,0	16,6	4,4	52,0

Table 2. Macroscopic evaluation of damage to inner organs of guinea pigs.

The experimental observations show that the treatment of tuberculosis in the animals by the polymeric systems gave the same therapeutic effect as daily treatment with single doses of the drugs. The most effective action was displayed by PU containing Is. This is related to its greater tuberculostatic activity in comparison with Eth and Fl. The animals of the PU-Is and Is groups had the dissemination nidi in their inner organs practically cured: guinea pigs lost weight slightly (4.6% and 1.2%, cf. untreated 30.6%) and had small ulcers in the place of infection (3.0 mm and 3.2 mm in diameter, cf. untreated 11.2 mm) (Batyrbekov et al., 1997)

The values of weight loss and ulcer dimensions in the place of infection in animals of the another groups are following: 8.6% and 4.4 mm (PU-Eth); 9.0% and 4.8 mm (Eth); 11.4% and 5.2 mm (PU-F1); 11.0% and 5.0 mm (Fl). The treatment of experimental tuberculosis by the polymeric systems was analogous to daily treatment with free drugs. The use of a PU carrier provides a stable bacteriostatic concentration of chemotherapeutic agents for 5-7 days. Clinical observations have shown the efficiency of PU drug delivery systems for treatment of tuberculosis-infected cavities (wounds, pleural empyema, bronchial fistula).

The results obtained in the present work have shown the possibility of using PU foams as a matrix for drug delivery systems for prolonging the action of chemotherapeutic agents in tuberculosis treatment.

6. Conclusion

PU microparticles containing antituberculosis drugs were prepared by interfacial reaction between PEG and TDI in water in toluene emulsion. Two products of polycondensation were detected: the main product is spherical microparticles with size about 5-10 μm and the second product is fibrils of linear PU, which precipitate in toluene. The increase of PEG content in water phase results in increased amount of the secondary product, and as the PEG content in water phase reaches 60 vol.%, maximum of the secondary product was observed (about 40%). Decreasing PEG concentration in water phase leads to increased yield of PU microparticles. Maximum of yield was reached at PEG concentration 22 - 27 vol.% and in that conditions whole oligomer reacted at surface of emulsion drops with microparticles formation.

The release behavior of drugs from microparticles was carried out and different conditions of synthesis such as water/PEG ratio, molecular weight of PEG and drug concentration was investigated. The increase PEG content in water phase of reaction, results in decreasing drug diffusion, due to formation of PU microparticles with densere polymer wall. Increasing molecular weight of soft segments (PEG) results in the increase of diffusion rate of drug into solution. This phenomenon can be attributed to increasing molecular weight of PEG which leads to accelerating diffusion of water-soluble drug through hydrophilic PEG chains. It was shown that microparticles with higher drug loading demonstrate faster release rate of the drug due to increased gradient of concentrations between the external solution and core of microparticles.

The tuberculostatic activity of drugs released from the PU show that drugs introduced into PU have antimicrobial activity identical of low molecular drugs. The efficiency of the

tuberculosis treatment by polyurethane drug delivery systems was shown in experiments on animals. The use of PU carrier provides a stable bacteriostatic concentration of the chemotherapeutic agents for 5-7 days. The treatment of animals infected with tuberculosis by PU systems was more effective than the treatment by free drugs. It was shown that is released from PU systems was 1.5-2 times less toxic in comparison with the low molecular drug. Minimal toxic action of PU on the native organism tissue was established histologically. Medical-biological tests show that PU ensures sustained release of antituberculosis drugs and maintains effective drug concentration for long time.

The results obtained in the present chapter have shown the possibility and outlook of PU as carriers of antituberculosis drugs for the delivery systems for prolonging the action of chemotherapeutic agents in tuberculosis treatment.

Author details

Yerkesh Batyrbekov and Rinat Iskakov
*Institute of Chemical Sciences,
Kazakh-British Technical University, Kazakhstan*

Acknowledgement

This research was financially supported by a grant from the Ministry for Education and Science of Republic of Kazakhstan. The authors thank Dr. Mariya Kim for her assistance in carrying experimental studies.

7. References

- Ahmad, Z.; Pandey, R.; Sharma, S. & Khuller, G.K. (2006). Pharmacokinetic and pharmacodynamic behaviour of antitubercular drugs encapsulated in alginate nanoparticles at two doses. *International Journal of Antimicrobial agents*, Vol.27, No.5, (May 2006), pp. 409-416
- Ahmad, Z.; Sharma, S. & Khuller, G.K. (2007). Chemotherapeutic evaluation of alginate nanoparticle-encapsulated azole antifungal and antitubercular drugs against murine tuberculosis. *Nanomedicine*, Vol.3, No.3, (March 2007), pp. 239-243
- Ahmad, Z.; Pandey, R.; Sharma, S. & Khuller, G.K. (2008). Novel chemotherapy for tuberculosis: chemotherapeutic potential of econazole- and moxifloxacin-loaded PLG nanoparticles. *International Journal of Antimicrobial agents*, Vol.31, No.2, (February 2008), pp.142-146
- Ahmad, Z. & Khuller, G.K. (2008).. Alginate-based sustained release drug delivery systems for tuberculosis. *Expert Opinion on Drug Delivery*, Vol.5, No.12, (December 2008), pp. 1323-1334
- Anisimova, Y.V.; Gelperina, S.E.; Peloquin, C.A. & Heifets, L.B. (2000). Nanoparticles as antituberculosis drugs carriers: effect on activity against *M. tuberculosis* in human

- monocyte-derived macrophages. *Journal of Nanoparticle Research*, Vol.2, No.1, (January 2000), pp. 165–171
- Batyrbekov, E.O.; Rukhina, L.B.; Zhubanov, B.A.; Bekmukhamedova, N.F. & Smailova, G.A. (1997). Drug delivery systems for tuberculosis treatment. *Polymer International*, Vol.43, No.4, (April 1997), pp. 317-320
- Batyrbekov, E.O.; Iskakov, R. & Zhubanov, B.A. (1998). Synthetic and natural polymers as drug carriers for tuberculosis treatment. *Macromolecular Symposia*, Vol.127, pp. 251-255
- Batyrbekov, E.; Iskakov, R. & Zhubanov, B. (2009). Microcaparticles on the basis of Segmented Polyurethanes for the Treatment of Tuberculosis. *Life Sciences, Medicine, Diagnostics, Bio Materials and Composites. Proceedings of 2009 NSTI Nanotechnology Conference and Trade Show*. Vol.2, pp. 96-99, Houston, Texas, USA, May 3-7, 2009
- Bouchemal, K.; Briançon, S.; Perrier, E.; Fessi, H.; Bonnet, I. & Zydowicz, N. (2004). Synthesis and characterization of polyurethane and poly(ether urethane) nanocapsules using a new technique of interfacial polycondensation combined to spontaneous emulsification. *International Journal of Pharmaceutics*, Vol.269, No.1, (January 2004), pp. 89-100
- Bouchemal, K.; Briançon, S.; Couenne, F.; Fessi, H. & Tayakout, M. (2006). Stability studies on colloidal suspensions of polyurethane nanocapsules. *Journal of Nanoscience and Nanotechnology*, Vol.6, No.9-10, (October 2006), pp. 3187-3192
- Campos, E.; Cordeiro, R.; Santos, A.C.; Matos, C. & Gil, M.H. (2011). Design and characterization of bi-soft segmented polyurethane microparticles for biomedical application. *Colloids and Surfaces. B:Biointerfaces*, Vol.88, No.1, (November 2011), pp. 477-482
- Chang, C.P.; Yamamoto, T.; Kimura, M.; Sato, T.; Ichikawa, K. & Dobashi, T. (2003). Release characteristics of an azo dye from poly(ureaurethane) microcapsules. *Journal of Controlled Release*, Vol.86, No.2-3, (January 2003), pp. 207-211
- Chang, C.P.; Chang, J.C.; Ichikawa, K. & Dobashi, T. (2005). Permeability of dye through poly(urea-urethane) microcapsule membrane prepared from mixtures of di- and tri-isocyanate. *Colloids and Surfaces. B:Biointerfaces*, Vol.44, No.4, (September 2005), pp. 187-190
- Embrey, H.P.; Graham, N.B.; McNeill, M.E. & Hiller, K. (1986). Release characteristics and long term stability of polyethylene oxide hydrogels vaginal pessaries containing prostaglandin. *Journal of Controlled Release*, Vol.3, No.1, (January 1986), pp. 39-45
- Gelperina, S.; Kisich, K.; Iseman, M.D. & Heifets, L. (2005). The Potential Advantages of Nanoparticle Drug Delivery Systems in Chemotherapy of Tuberculosis. *American Journal of Respiratory and Critical Care Medicine*, Vol.172, No. 12, (December 2005), pp. 1487-1490
- Graham, N.B.; Zulfiqar, M.; McDonald, B.B. & McNeill, M.E. (1988). Caffeine release from fully swollen polyethylene oxide hydrogel. *Journal of Controlled Release*, Vol.5, No.2, (February 1988), pp. 243-252
- Higuchi, T (1963). Mechanism of sustained-action medication. Theoretical analysis of rate of release of solid drugs dispersed in solid matrices. *Journal of Pharmaceutical Sciences*, Vol.52, No.12, (December 1963), pp.1145-1149

- Hong, K. & Park, S. (2000). Characterization of ovalbumin-containing polyurethane microcapsules with different structures. *Polymer Testing*, Vol.19, No.8, (September 2000), pp. 975-984
- Hsien, D.S. (1998). *Controlled Release Systems: Fabrication Technology*, CRC Press, Boca Raton, Florida, USA
- Iskakov, R.; Batyrbekov, E.; Zhubanov, B. & Volkova, M. (1998). Polyurethanes as Carriers of Antitumorous Drugs. *Polymers for Advanced Technologies*, Vol.9, No.2. (February 1998), pp. 266-270
- Iskakov, R.M.; Batyrbekov, E.O.; Leonova, M.B. & Zhubanov, B.A. (2000). Preparation and release profiles of cyclophosphamide from segmented polyurethanes. *Journal of Applied Polymer Sciences*, Vol.75, No.1, (January 2000), pp. 35-43
- Iskakov, R.; Batyrbekov, E.O.; Zhubanov, B.A. & Mooney, D.J. (2004). Microparticles on the basis of segmented polyurethanes for drug respiratory administration. *Eurasian ChemTechnology Journal*, Vol.6, No.1, (January 2004), pp. 51-55
- Jabbari, E. & Khakpour, M. (2000). Morphology of and release behavior from porous polyurethane microspheres. *Biomaterials*, Vol.21, No.20, (October 2000), pp.2073-2079
- Kisich, K.O.; Gelperina, S.; Higgins, M.P.; Wilson, S.; Shipulo, E.; Oganessian, E. & Heifets, L. (2007). Encapsulation of moxifloxacin within poly(butyl cyanoacrylate) nanoparticles enhances efficacy against intracellular Mycobacterium tuberculosis. *International Journal of Pharmaceutics*, Vol.345, No.1-2, (December 2007), pp. 154-162
- Lamba, N.M.K.; Woodhouse, K.A.; Stuart, L. & Cooper, S.L. (1997). *Polyurethanes in Medical Application*, CRC Press, Boca Raton, Florida, USA
- Lelah, M.D. & Cooper, S.L. (1986). *Polyurethanes in Medicine*, CRC Press, Boca Raton, Florida, USA
- Lucinda-Silva, R.M. & Evangelista, R.C. (2003). Microspheres of alginate-chitosan containing isoniazid. *Journal of Microencapsulation*, Vol.20, No.2, (February 2003), pp. 145-152
- Makino, K.; Nakajima, T.; Shikamura, M.; Ito, F.; Ando, S.; Kochi, C.; Inagawa, H.; Soma, G. & Terada, H. (2004). 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 and Surfaces. B: Biointerfaces*, Vol.36, No.1, (July 2004), pp. 35-42
- Pandey, R. & Khuller, G.K. (2004). Chemotherapeutic potential of alginate-chitosan microspheres as anti-tubercular drug carriers. *Journal of Antimicrobiology and Chemotherapy*, Vol.53, No.4, (April 2004), pp. 635-640
- Pandey, R. & Khuller, G.K. (2006). Nanotechnology based drug delivery systems for the management of tuberculosis. *Indian Journal of Experimental Biology*, Vol.44, No.5, (May 2006), pp. 357-66
- Pandey, R. & Khuller, G.K. (2007). Nanoparticle-Based Oral Drug Delivery System for an Injectable Antibiotic Streptomycin - Evaluation in a Murine Tuberculosis Model. *Chemotherapy (International Journal of Experimental and Clinical Chemotherapy)*, Vol.53, No.6, (July 2007), pp. 437-441

- Phadtare, S.; Vyas, S.; Palaskar, D.V.; Lachke, A.; Shukla, P.G.; Sivaram, S. & Sastry, M. (2004). Enhancing the reusability of endoglucanase-gold nanoparticle bioconjugates by tethering to polyurethane microspheres. *Biotechnology Progress*, Vol.20, No.6, (November-December 2004), pp. 1840-1846
- Philip, L. & Peppas N.A. (1987). A simple equation for description of solute release II. Fickian and anomalous release from swellable devices. *Journal of Controlled Release*, Vol.5, No.1, (June 1978), pp. 37-42
- Quenelle, D.C.; Winchester, G.A.; Staas, J.K.; Hoskins, D.E.; Barrow, E.W. & Barrow, W.W. (2004). Sustained Release Characteristics of Rifampin-Loaded Microsphere Formulations in Nonhuman Primates. *Drug Delivery*, Vol.11, No.4, (April 2004), pp. 239-246
- Qurrat-ul-Ain; Sharma, S.; Khuller, G.K. & Garg, S.K. (2003). Alginate-based oral drug delivery system for tuberculosis: pharmacokinetics and therapeutic effects. *Journal of Antimicrobiology and Chemotherapy*, Vol.51, No.4, (April 2003), pp. 931-938
- Rafienia, M.; Orang, F. & Emami, S.H. (2006). Preparation and Characterization of Polyurethane Microspheres Containing Theophylline. *Journal of Bioactive and Compatible Polymers*, Vol.21, No.4, (July 2006), pp. 341-349
- Rastogi, R.; Sultana, Y.; Aqil, M.; Ali, A.; Kumar S.; Chuttani, K. & Mishra, A.K. (2007). Alginate microspheres of isoniazid for oral sustained drug delivery. *International Journal of Pharmaceutics*, Vol.334, No.1-2 (February 2007), pp. 71-77
- Reddy, T.T.; Hadano, M. & Takahara, A. (2006). Controlled Release of Model Drug from Biodegradable Segmented Polyurethane Ureas: Morphological and Structural Features. *Macromolecular Symposia*, Vol.242, No.1, (October 2006), pp. 241-249
- Sharma, K.; Knutson, K. & Kirn, S.W. (1988). Prednisolon release from copolyurethane monolithic devuces. *Journal of Controlled Release*, 1988. Vol.7, No.2, (February 1988), pp. 197-205
- Shegokar, R.; Shaal, L.A. & Mitri, K. (2011). Present status of nanoparticle research for treatment of Tuberculosis. *Journal of Pharmacy & Pharmaceutical Sciences*, Vol.14, No.1, (January 2011), pp. 100-116
- Shukla, P.G.; Kalidhass, B.; Shah, A. & Palaskar, D.V. (2002). Preparation and characterization of microcapsules of water-soluble pesticide monocrotophos using polyurethane as carrier material. *Journal of Microencapsulation*, Vol.19, No.3, (May 2002), pp. 293-304
- Sosnik, A.; Carcaboso, A.M.; Glisoni, R.I.; Moretton, M.A. & Chiappetta, D.A. (2010). New old challenges in tuberculosis: Potentially effective nanotechnologies in drug delivery. *Advanced Drug Delivery Reviews*. Vol.62, No.4-5, (March 2010), pp. 547-559
- Subhaga, C.S.; Ravi, K.G.; Sunny, M.C. & Jayakrishnan, A. (1995). Evaluation of an aliphatic polyurethane as a microsphere matrix for sustained theophylline delivery. *Journal of Microencapsulation*, Vol.12, No.6, (December 1995), pp. 617-625
- Toit, L.K. ; Pillay, V. & Danckwerts, M.P. (2006). Tuberculosis chemotherapy: current drug delivery approaches. *Respiratory Research*, Vol.7 , No.1, (January 2006), pp. 118-132

- Touitou, E. & Friedman, D. (1984). The release mechanism of drug from poly-urethane transdermal delivery system. *International Journal of Pharmaceutics*, Vol.19, No.3, (March 1984), pp. 323-332
- Van Bos, M. & Schacht, E. (1987). Hydrophilic Polyurethanes for the Preparations of Drug Release Systems. *Acta Pharmaceutical Technology*, Vol.33, No.3, (March 1987), pp. 120-125
- Yoshida, A.; Matumoto, M.; Hshizume, H.; Oba, Y.; Tomishige, T.; Inagawa, H.; Kohchi, C.; Makino, K.; Hori, H. & Soma, G. (2006). 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-Guérin. *Microbes Infection*, Vol.8, No. 9-10, (August 2006), pp. 2484-2491