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TARGETING OF ANTILEISHMANIAL DRUGS PRODUCED BY
NANOTECHNOLOGIES

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BIBLIOGRAPHY

Agnihotri S.A., Mallikarjuna N.N., Aminabhavi T. M. Recent advances on chitosan-based micro-and nanoparticles in drug delivery. *Journal of Controlled Release*. 2004; 100: 5-28.

Ahsan F., Rivas I. P., Khan M.A., Torres Suárez A.I. Targeting to macrophages: role of physicochemical properties of particulate carriers-liposomes and microspheres-on the phagocytosis by macrophages. *Journal of Controlled Release*. 2002; 79: 29-40.

Aksungur P., Sungur A., Ünal S., Iskit A. B., Squier C.A. and Senel S. Chitosan delivery systems for the treatment of oral mucositis: *in vitro* and *in vivo* studies. *Journal of Controlled Release*. 2004; 98(2): 269-279.

Al Jaser M., El-Yasigi A., Croft S.L. Pharmacokinetics of antimony in patients treated with sodium stibogluconate for cutaneous leishmaniasis. *Pharmaceutical Research*. 1995; 12(1): 113-116.

Alvar Ezquerro J.P. Las leishmaniasis de la biología al control. 1ª edición. Junta Castilla y León. Zamora. 1997.

Alvar J., Corachán M. Infecciones causadas por protozoos flagelados hemotisulares. Farreras. Rozman. Medicina interna. Decimoquinta edición. Elsevier. Madrid, 2004; Volumen 2, Capítulo 297: 2414-2418.

Andersson M. Chitosan compositions. WO/2006/067626.

Artemyev M.V., Woggon U., Wannemacher R., Jaschinski H. and Langbein W. Light Trapped in a Photonic Dot: Microspheres Act as a Cavity for Quantum Dot emission. *Nano letters*. 2001; 1(6): 309-314.

Banerjee G., Nandi G., Mahato S.B., Pakrashi A. and Basu M.K. Drug delivery system: targeting of pentamidines to specific sites using sugar grafted liposomes. *Journal of Antimicrobial Chemotherapy*. 1996; 38: 145-150.

Basu M.K.; Lala S. Macrophage specific drug delivery in experimental leishmaniasis. *Current molecular medicine*. 2004; 4(6): 681-689.

Belliard A.M., Leroy C., Banide H., Farinotti R., and Lacour B. Decrease of intestinal P-glycoprotein activity by 2-n-propylquinoline, a new oral treatment for visceral leishmaniasis. *Experimental Parasitology*. 2003; 103: 51-56.

Benita S. Microencapsulation: Methods and industrial applications. *Drugs and the pharmaceutical sciences*. Marcel Dekker, Inc. New York. Baser. North Carolina, 1996; 73: 21-25.

Bhandari B. R., D'Arcy B.R. and Padukka I. Encapsulation of lemon oil by paste method using beta-cyclodextrin: encapsulation efficiency and profile of oil volatiles. *J. Agric. Food. Chem.* 1999; 47: 5194-5197.

- Borovskaya E. and Shur M.S. Quantum Dots. World Scientific. 2002. 25:1-10.
- Bragg, W.L. The Diffraction of Short Electromagnetic Waves by a Crystal. Proceedings of the Cambridge Philosophical Society. 1914; 17: 43–57.
- Brugerolle.G., Clarmont-Ferrand. Encyclopedic reference of Parasitology. Second edition. Springer. Düsseldorf, 2000a; Biology, Structure,Function: 334-335.
- Brugerolle G., Clarmont-Ferrand. Encyclopedic reference of Parasitology. Second edition Springer. Düsseldorf, 2000b; Diseases, Treatment, Therapy: 277-289.
- Buckner F.S. and Wilson A.J. Colorimetric assay for screening compounds against *Leishmania* amastigotes grown in macrophages. Am. J. Trop. Med. Hyg., 2005; 72(5): 600-605
- Burgess D.J., Duffy E., Etzler F. and Hickey A.J. Particle size analysis: AAPS workshop report, cosponsored by the Food and Drug Administration and the United States Pharmacopeia. The AAPS Journal. 2004; 6(3): article 20.
- Burgess D.J., Hussain A.S., Ingallinera T.S., Chen M.L. Assuring quality and performance of sustained and controlled release parenterals: AAPS Workshop report, co-sponsored by FDA and USP. Pharmaceutical Research. 2002; 19(11): 1761-1768.
- Cabrera-Serra M.G., Lorenzo-Morales J., Romero M., Valladares B., Piñero J.E. In vitro activity of perifosine: a novel alkylphospholipid against the promastigote stage of *Leishmania* species. Parasitol Res. 2007; 100 (5):1155-7.
- Callahan H.L. and Beverley S. M. Heavy Metal Resistance: A new role for P-glycoproteins in *Leishmania*. The journal of biological chemistry. 1991; 266(28): 18427-18430.
- Cantos G., Barbieri CL., Lacomini M., Gorin PA., Travassos LR. Synthesis of antimony complexes of yeast mannan and mannan derivatives and their effect of *Leishmania*-infected macrophages. Biochemical Journal. 1993; 289(1):155-160.
- Carrió J., de Colmenares M., Riera C., Gállego M., Arboix M., and Portús M. *Leishmania infantum*: Stage-Specific Activity of Pentavalent Antimony Related with the assay conditions. Experimental Parasitology, 2000a; 95: 209-214.
- Carrió J., Riera C., Gállego M., Arboix M. and Portús M. *In vitro* susceptibility of *Leishmania infantum* to meglumine in isolates from repeated leishmaniasis episodes in HIV-coinfected patients. Journal of Antimicrobial Chemotherapy, 2000b; 47: 113-124.
- Carrió J., Riera C., Gállego M., Portús M. *In vitro* activity of pentavalent antimony derivatives on promastigotes and intracellular amastigotes of *Leishmania infantum* strains from humans and dogs in Spain. Acta Tropica, 2001; 79: 179-183.
- Carrió J. and Portús M. *In vitro* susceptibility to pentavalent antimony in *Leishmania infantum* strains is not modified during *in vitro* or *in vivo* passages but is modified after host treatment with meglumine antimoniate. BioMedCentral Pharmacology. 2002; 2(11).

Chang E., Thekkekk N., Yu W. W., Colvin V. L., and Drezek R. Evaluation of Quantum Dot Cytotoxicity based on Intracellular Uptake. *Small*. 2006; 2: 1412-1417.

Chen H., Langer R. Oral particulate delivery: status and future trends. *Advanced drug Delivery Reviews*. 1998; 34: 339-350.

Chirkov SN. The antiviral activity of chitosan (review) *Prikl Biokhim Mikrobiol*. 2002 Jan-Feb;38(1):5-13.

Christensen K.L., Pedersen G.P., Kristensen H.G. Preparation of redispersible dry emulsions by spray drying. *International Journal of Pharmaceutics*. 2001a; 212: 187-194.

Christensen K.L., Pedersen G.P., Kristensen H.G. Technical optimisation of redispersible dry emulsions. *International Journal of Pharmaceutics*. 2001b; 212: 195-202.

Chu M., Zhou L., Song X., Pan M., Zhang L., Sun Y., Zhu J. and Ding Z. Incorporating quantum dots into polymer microspheres via a spray-drying and thermal-denaturing approach. *Nanotechnology*. 2006; 17: 1791-1796.

Chulay JD., Fleckenstein L., Smith DH. Pharmacokinetics of antimony during treatment of visceral leishmaniasis with sodium stibogluconate or meglumine antimoniate. *Trans. R.Soc.Trop.Med.Hyg*. 1988; 82: 69-72.

Chulay JD., Spencer HC., Mugambi M. Electrocardiographic changes during treatment of leishmaniasis with pentavalent antimony (sodium stibogluconate). *Am.J.Trop.Med.Hyg*. 1985; 34(4):702-9.

Coppi G., Iannuccelli V., Sala N. and Bondi M. Alginate microparticles for Polymyxin B Peyer's patches uptake: microparticles for antibiotic oral administration. *J. Microencapsulation*. 2004; 21: 829-839.

Cordero del Campillo M., Rojo Vázquez F.A. *Parasitología Veterinaria*. Mc.Graw-Hill-Interamericana. 1999; Parte VI: Parasitosis del perro y del gato. Capítulo 36. Parasitosis sistémicas: 652- 693.

Cornaire G., Woodley J., Hermann P., Cloarec A., Arellano C., Houin G. Impact of excipients on the absorption of P-glycoprotein substrates *in vitro* and *in vivo*. *International Journal of Pharmaceutics*. 2004; 278: 119-131.

Coutinho M.T., Bueno L.L., Sterzik A., Fujiwara T.R., Botelho R.J., De Maria M., Genaro O. and Linardi M.P. Participation of *Rhipicephalus sanguineus* (Acari: Ixodidae) in the epidemiology of canine visceral leishmaniasis. *Veterinary Parasitology*. 2005; 128 (1-2): 149-155.

Croft S.L., Davidson R.N., Thornton E.A. Liposomal amphotericin B in the treatment of visceral leishmaniasis. *J.Antimicrob.Chemother*. 1991; 28 (Suppl.B): 111-8.

Cruz A., Rainey P. M., Herwaldt B.L., Stagni G., Palacios R., Trujillo R., and Saravia N.G. Pharmacokinetics of Antimony in Children Treated for Leishmaniasis with Meglumine Antimoniate. *JID*. 2007; 195: 603.

Delgado J., Macías J., Pineda J. A., Corzo J. E., González-Moreno M.P., de la Rosa R., Sánchez-Quijano A., Leal M., Lissen E. High Frequency of serious side effects from meglumine antimoniate given without an upper limit dose for the treatment of visceral leishmaniasis in human immunodeficiency virus type-1-infected patients. *Am.J.Trop.Med.Hyg.* 1999; 61(5): 766-769.

Demicheli C., de Figueiredo T.L., Carvalho S., Sinesterra R.D., Lopes J.C.D. and Frézard F. Physico-chemical characterization of meglumine antimoniate. *BioMetals*. 1999; 12: 63-66.

Demicheli C., Ochoa R., Da Silva J.B.B., Falção C.A.B., Rossi-Bergmann B., De Melo A. L., Sinesterra R.D., and Frézard F. Oral Delivery of Meglumine Antimoniate- β -cyclodextrin complex for treatment of leishmaniasis. *Antimicrobial agents and chemotherapy*. 2004; 48 (1): 100-103.

Demicheli C., Ochoa R., Silva Lula I., Gozzo F.C., Eberlin M. N. and Frézard F. Pentavalent organoantimonial derivatives: two simple and efficient synthetic methods for meglumine antimoniate. *Applied Organometallic Chemistry*. 2003; 17: 226-231.

Desai K.G.H. and Park H.J. Preparation of cross-linked chitosan microspheres by spray-drying: Effect of cross-linking agent on the properties of spray dried microsphere. *Journal of Microencapsulation*. 2005; 22(4): 377-395.

Desai K.G.H. and Park H.J. Effect of manufacturing parameters on the characteristics of vitamin C encapsulated tripolyphosphate-chitosan microspheres prepared by spray-drying. *Journal of Microencapsulation*. 2006; 23(1): 91-103.

Desjeux P. Leishmaniasis. Public health aspects and control. *Clin Dermatol*. 1996; 14: 417-23.

Desjeux P, Alvar J. Leishmania/HIV co-infections: epidemiology in Europe. *Ann. Trop. Med. Parasitol*. 2003; 97(Suppl. 1): 3-15.

Dini E., Alexandridou S., Kiparissides C. Synthesis and characterization of cross-linked chitosan microspheres for drug delivery applications. *J. Microencapsulation*. 2003; 20 (3): 375-385.

Dollo G., Le Corre P., Guérin A., Chevanne F., Burgot J.L., Leverge R. Spray-dried redispersible oil-in-water emulsion to improve oral bioavailability of poorly soluble drugs. *European Journal of Pharmaceutical Sciences*. 2003; 19: 273-280.

Donbrow M. Microcapsules and nanoparticles in medicine and pharmacy. CRC press. Boca Raton. London. 1992: 3-11.

Dorea J.G., Costa J.M., Holzbecher J., Ryan D.E., Marsden P.D. Antimony accumulation in hair during treatment of leishmaniasis. *Clin.Chem*. 1987; 33(11): 2081-2.

Dorea JG., Merchan-Hamann E., Ryan D.E., Holzbecher J. Retention of antimony in skin biopsias of leishmaniasis patients after treatment with N-methylglucamine antimoniate. Clin.Chem. 1990; 36(4): 680-2.

D'Souza S.S., DeLuca P.P. Methods to assess *in vitro* drug release from injectable polymeric particulate systems. Pharmaceutical Research. 2006; 23(3): 460-474.

Dubertret B., Skourides P., Norris D.J., Noireaux V., Brivanlou A.H., Libchaber A. *In vivo* imaging of quantum dots encapsulated in phospholipid micelles. Science. 2002; 298 (5599): 1759 – 1762.

Edris A. and Bergnstahl B. Encapsulation of orange oil in a spray dried double emulsion. Nahrung/Food. 2001; 2: 133-137.

Einstein R., Jones R.S., Knifton A., Starwer G.A. Principles of Veterinary Therapeutics. Longman Scientific & Technical. England, 1994; 452-452.

Ellenhorn M.J. Ellenhorn's Medical Toxicology. Diagnosis and Treatment of Human Poisoning. Williams & Williams. USA, 1997; Chapter 67: Metals and Related Compounds: 1537-1538.

El Fadili K., Messier N., Leprohon P., Roy G., Guimond C., Trudel N., Saravia NG., Papadopoulou B., Legare D., Ouellette M. Role of the ABC transporter MRPA (PGPA) in antimony resistance in *Leishmania infantum* axenic and intracellular amastigotes. Antimicrob. Agents Chemother. 2005; 49: 1988–1993.

European Pharmacopeia. 5th edition, 2007 (5.8).

Fang N., Chan V., Mao H.-Q. and Leong K.W. Interactions of phospholipid bilayer with chitosan: effect of molecular weight and pH. Biomacromolecules. 2001; 2: 1161- 1168.

Faraut-Gambarelli F., Piarroux R., Deniau M., Giusiano B., Marty P., Michel G., Fauge' re B. and Dumon H. *In Vitro* and *In vivo* Resistance of *Leishmania infantum* to Meglumine Antimoniate: a Study of 37 Strains Collected from Patients with Visceral Leishmaniasis. Antimicrobial Agents and Chemotherapy. 1997. 41(4): 827–830.

Farmacopéia brasileira ; Comissão Permanente de Revisão da Farmacopéia Brasileira. 4. ed. São Paulo: Atheneu Editora São Paulo. 2002; 175-175.1,175.2.

Faulí i Trillo C. Tratado de Farmacia Galénica. 1^a Ed. Luzán 5. 1993; Capítulo XLII: 593.

Felt O., Carrel A., Baehni P., Buri P., Gurny R. Chitosan as tear substitute: a wetting agent endowed with antimicrobial efficacy. J. Ocul. Pharmacol. Ther. 2000; 16(3): 261-70.

Feng J., Zhao L., and Yu Q. Receptor-mediated stimulatory effect of oligochitosan in macrophages. Biochemical and Biophysical Research Communications. 2004; 317: 414-420.

Fernandez-Urrusuno, R., Calvo P., Remunan-Lopez, C., Vila-Jato, J.L., Alonso, M.J. (1999). Enhancement of nasal absorption of insulin chitosan nanoparticles. *Phar. Res.* 16:1576-1581.

Ferreira I.C., Lonardoni M.V., Machado G.M., Leon L.L., Gobbi Filho L., Pinto L.H., de Oliveira A.J. Anti-leishmanial activity of alkaloidal extract from *Aspidosperma ramiflorum*. *Mem. Inst. Oswaldo Cruz.* 2004; 99(3): 325-7.

Fisa R., Gállego M., Castillejo S., Aisa M.J., Serra T., Riera C., Carrió J., Gállego J., Portús M. Epidemiology of canine leishmaniosis in Catalonia (Spain) the example of the Priorat focus. *Vet. Parasitol.* 1999; 83(2): 87-97.

Fischer S., Foerg C., Ellenberger S., Merkle H.P., Gander B. One-step preparation of polyelectrolyte-coated PLGA microparticles and their functionalization with model ligands. *Journal of Controlled Release.* 2006; 111: 135-144.

Fischer S., Foerg C., Merkle H.P., Gander B. Chitosan Coated PLGA-Microspheres-A modular system for targeted drug delivery. *European cells and materials.* 2004; 7 (Suppl.2): 11-12.

Foglia Manzillo V., Oliva G., Pagano A., Manna L., Maroli M. and Gradoni L. Deltamethrin-impregnated collars for the control of canine leishmaniasis: Evaluation of the protective effect and influence on the clinical outcome of *Leishmania* infection in kennelled stray dogs. *Veterinary Parasitology.* 2006; 142 (1-2): 142-145.

Franco M.A., Barbosa A.C., Rath S., Dorea J.G. Antimony oxidation states in antileishmanial drugs. *Am. J. Trop. Med. Hyg.* 1995; 52(5): 435-437.

Freiberg S. and Zhu X. X. Polymer microspheres for controlled drug release. *International Journal of Pharmaceutics.* 2004; 282 (1-2): Pages 1-18

Frézard F., Martins P.S., Bahia A.P., le Moyec L., de Melo A.L., Pimenta A.M., Salerno M., Silva J.B., Demicheli C. Enhanced oral delivery of antimony from meglumine antimoniate/beta-cyclodextrin nanoassemblies. *Int. J. Pharm.* 2007; 23: Epub ahead of print.

Frézard F., Michalick M.S.M., Soares C.F. and Demicheli C. Novel methods for the encapsulation meglumine antimoniate into liposomes. *Brazilian Journal of Medical and Biological Research.* 2000; 33: 841-846.

Fusai T., Boulard Y., Durand R., Paul M., Bories C., Rivollet D., Astier A., Houin R., Deniau M. Ultrastructural changes in parasites induced by nanoparticle-bound pentamidine in a *Leishmania major*/mouse model. *Parasite.* 1997; 4(2): 133-9.

Gallaher D.D., Gallaher C.M., Mahrt G.J., carr T.P., Hollingshead C.H., hesslink R. Jr., Wise J. A glucomannan and chitosan fiber supplement decreases plasma cholesterol and increases cholesterol excretion in overweight normocholesterolemic humans. *J. Am. Coll. Nutr.* 2002; 21(5): 428-33.

Gao X., Yang L., Petros J. A., Marshall F.F., Simons J.W. and Nie S. *In vivo* molecular and cellular imaging with quantum dots. *Current opinion in Biotechnology*. 2005; 16: 63-72.

Garcia-Fuentes M., Torres D., Alonso M.J. New surface-modified lipid nanoparticles as delivery vehicles for salmon calcitonin. *International Journal of Pharmaceutics*. 2005; 296: 122-132.

Gavini E., Chetoni P., Cossu M., Alvarez M.G., Saettone M.F., Giunchedi P. PLGA microspheres for the ocular delivery of a peptide drug, vancomycin using emulsification/spray-drying as the preparation method: *in vitro/in vivo* studies. *Eur. J. Pharm. Biopharm.* 2004; 57(2): 207-12.

Gelb J.Jr. Microencapsulation process using supercritical fluids. USP 5766637. US Patent Issued on June 16, 1998.

Genta I., Conti B., Perugini P., Pavanetto F., Spadaro A., Puglisi G. Bioadhesive microspheres for ophthalmic administration of acyclovir. *J. Pharm. Pharmacol.*, 1997; 49:737-742.

George E.P. BOX, Hunter W.G., Stuart junter J. *Estadística para investigadores. Introducción al diseño de experimentos, análisis de datos y construcción de modos.* Editorial Reverté, S.A. Barcelona.1989.

Gerasimenko D.V., Avdienko I.D., Bannikova G.E., Zueva O., Varlamov V.P. Antibacterial effects of water-soluble low-molecular-weight chitosans on different microorganisms. *Prikl. Biokhim. Mikrobiol.* 2004; 40(3): 301-6.

Gourbal B., Sonuc N., Bhattacharjee H., Legare D., Sundar S., Ouellette M., Rosen BP., Mukopadhyay R. Drug uptake and modulation of drug resistance in *Leishmania* by an aquaglyceroporin. *J. Biol. Chem.* 2004; 279: 31010–31017.

Gramiccia M., Gradoni L., Orsini S. Decreased sensitivity to meglumine antimoniate (Glucantime) of *Leishmania infantum* isolated from dogs after several courses of drug treatment. *Ann. Trop. Med. Parasitol.* 1992; 86(6): 613-20.

Grenha A., Seijo B., Remuñan-López C. Microencapsulated chitosan nanoparticles for lung protein delivery. *European Journal of pharmaceutical Sciences*. 2005; 25: 427-437.

Guerin P. J., Olliaro P., Sundar S., Boelaert M., Croft S.L., Desjeux P., Wasunna M.K., and Brycesoniero A.DM.. Visceral leishmaniasis: current status of control, diagnosis, and treatment, and a proposed research and development agenda. *The Lancet*. 2002; 2: 494-501.

Guo Z. Xing R. Liu S. Zhong Z. Ji X. Wang L. Li P. The influence of the cationic of quaternized chitosan on antifungal activity. *Int. J. Food Microbiol.* 2007 Jul 19;

Gupta K.C. and Jabrail F.H. Glutaraldehyde and glyoxal cross-linked chitosan microspheres for controlled delivery of centchroman. *Carbohydrate Research*. 2006; 341: 744-756.

Guru P.Y, Agrawal A.K., Singha U.K, Singhal A., Gupta C.M. Drug targeting in *Leishmania donovani* infections using tuftsin-bearing liposomes as drug vehicles. FEBS Lett. 1989; 245(1-2): 204-8.

Gustafson S.B., Fulkerson P., Bildfell R., Aguilera L., Hazzard T.M. Chitosan dressing provides hemostasis in swine femoral arterial injury model. Prehosp. Emerg. Care. 2007; 11(2): 172-8.

Hadinoto K., Phanapavudhikul P., Kewu Z., Tan R.B. Dry powder aerosol delivery of large hollow nanoparticulate aggregate as prospective carriers of nanoparticulate drugs: effects of phospholipids. Int. J. Pharm. 2007; 333(1-2):187-98.

Han Y., Zhao L., Yu Z., Feng J., Yu Q. Role of mannose receptor in oligochitosan-mediated stimulation of macrophage function. International Immunopharmacology. 2005; 5: 1533-1542.

Hansen T., Holm P., Schultz K. Process characteristics and compaction of spray-dried emulsions containing a drug dissolved in lipid. International Journal of Pharmaceutics. 2004; 287: 55-66.

Hantson P., Luyasu S., Haufroid V., Lambert M. Antimony excretion in a patient with renal impairment during meglumine antimoniate therapy. Pharmacotherapy. 2000; 20(9): 1141-1143.

Hasegawa U., Nomura S.I. M., Kaul S. C., Hirano T., Akiyoshi K. Nanogel-quantum dot hybrid nanoparticles for live cell imaging. Biochemical and Biophysical Communications. 2005; 331: 917-921.

He P., Davis S. S., Illum L. Chitosan microspheres prepared by spray drying. International Journal of Pharmaceutics. 1999a; 187: 53-65.

He P., Davis S.S. and Illum L. Sustained release chitosan microspheres prepared by novel spray drying methods. J.Microencapsulation. 1999b; 16(3): 343-355.

Heinzelmann K., Franke K. Using freezing and drying techniques of emulsions for the microencapsulation of fish oil to improve oxidation stability. Colloids and Surfaces B: Biointerfaces, 1999; 12 (3): 223-229.

Hejazi R., Amiji M. Chitosan-based gastrointestinal delivery systems. Journal of Controlled Release. 2003; 89: 151: 165.

Herwaldt B.L., Berman J.D. Recommendations for treating leishmaniosis with sodium stibogluconate (Pentostam) and review of pertinent clinical studies. J. Trop. Med. Hyg. 1992; 46:296-306.

Higuchi T. Rate of release of medicaments from ointment bases containing drugs in suspension. J. Pharm. Sci. 1961; 50: 874-875.

Higuchi T. Mechanism of sustained-action medication: theoretical analysis of rate of release of solid drugs dispersed in solid matrices. J.Pharmaceut Sci. 1963; 52: 1145–1148.

Hoekstra A., Struszczyk H., Kivekäs O. Percutaneous microcrystalline chitosan application for sealing arterial puncture sites. *Biomaterials*. 1998; 19(16):1467-71.

Hong B.-S., Meadows D.L., Ketelson H. A., Owen G.R. Contact lens care compositions containing chitosan derivatives. WO/2004/061063.

Huang Y.C., Yeh M.K., Chiang C.H. Formulation factors in preparing BTM-chitosan microspheres by spray-drying method. *International Journal of Pharmaceutics*. 2002; 242: 239-242.

Illum L. Chitosan and its use as pharmaceutical excipient. *Pharmaceutical research*. 1998; 15 (9): 1326-1331.

Iowa State University. <http://mse.iastate.edu/microscopy/home.html>. Revised: October, 1th, 2007.

Jenning V., Lippacher A. and Gohla S.H. Medium scale production of solid nanoparticles by high pressure homogenization. *J. Microencapsulation*. 2002; 19(1):1-10.

Jing S.B., Li L., Ji D., Takiguchi Y., Yamaguchi T. Effect of chitosan on renal function in patients with chronic renal failure. *J. Pharm Pharmacol*. 1997; 49(7):721-3.

Johansen P., Merkle H.P., Gander B., Technological considerations related to the up-scaling of protein microencapsulation by spray-drying. *Eur. J. Pharm. Biopharm*. 2000; 50(3): 413-7.

Ju O., Grove D.I., Jaksic W.J. and Dart G.W. Visceral leishmaniasis: a trip to the Greek Islands is not always idyllic. *The Medical Journal of Australia*. 2004; 181 (8): 446-447.

Jumaa M., Furkert F.H., Müller B.W. A new lipid emulsion formulation with high antimicrobial efficacy using chitosan. *European Journal of Pharmaceutics and Biopharmaceutics*. 2002; 53: 115-123.

Kala H., Traue J., Moldenhauer H., Zessin G., The use of spray drying in pharmacy. *Pharmazie*. 1979; 34(12): 779-84.

Kamau S.W., Hurtado M., Muller-Doblies U.U., Grimm F., Núñez R. Flow cytometric assessment of allopurinol susceptibility in *Leishmania infantum* promastigotes. *Cytometry*. 2000; 40: 353-360.

Kamau S.W., Núñez R., Grimm F. Flow cytometry analysis of the effect of allopurinol and the dinitroaniline compound (Chloralin) on the viability and proliferation of *Leishmania infantum* promastigotes. *BMC*. 2001; 1: 1.

Kayser O. Nanosuspensions for the formulation of aphidicolin to improve drug targeting effects against *Leishmania* infected macrophages. *International Journal of Pharmaceutics*. 2000; 196: 253-256.

Kayser O., Olbirsch C., Croft S.L., Kiderlen A.F. Formulation and biopharmaceutical issues in the development of drug delivery systems for antiparasitic drugs. *Parasitol. Res.* 2002; 90: S63-S70.

Kayser O., Kiderlen A.F., Croft S.L. Antileishmanial activity of two gamma-pyrone from *Podolepis hieracioides* (Asteraceae). *Acta Trop.* 2003a; 86(1):105-7.

Kayser O., Olbrich C., Yardaley V., Kiderlen A.F., Croft S.L. Formulation of amphotericin B as nanosuspension for oral administration. *International Journal of Pharmaceutics.* 2003b; 254: 73-75.

Khalil E.A., El Hassan A.M., Zijlstra E.E., Mukhtar M.M., Ghalib H.W., Musa B., Ibrahim ME., Kamil AA., Elsheikh M., Babiker A., Modabber F. Autoclaved *Leishmania major* vaccine for prevention of visceral leishmaniasis: a randomised, double-blind, BCG-controlled trial in Sudan. *Lancet.* 2000; 356: 1565-69.

Kim H.J., Lee H.C., Oh J.S., Shin B.A., Oh C.S., Park R.D., Yang K.S., Cho C.S. Polyelectrolyte complex composed of chitosan and sodium alginate for wound dressing application. *J.Biomater. Sci. Polym. Ed.* 1999;10(5): 543-56.

Klinkerson U., Sophanodora P., Chinachoti P., McClements D.J. and Decker E.A. Stability of spray-dried tuna oil emulsions encapsulated with two-layered interfacial membranes. *Journal of agricultural and food chemistry.* 2005; 53: 8365-8371.

Knezevic Z., Gosak D., Hraste M., Jalsenjak I. Fluid-bed microencapsulation of ascorbic acid. *J. Microencapsul.* 1998; 15(2):237-52.

Kompella U.B., Koushik K. Preparation of drug delivery systems using supercritical fluid technology. *Crit. Rev. Ther. Drug Carrier Syst.* 2001;18(2):173-99.

Kondo A. *Microcapsule Processing and Technology.* Marcel Dekker, Inc., New York, 1979.

Korsmeyer R.W., Gurny R., Doelker E.M., Buri P., Peppas N.A. Mechanism of solute release from porous hydrophilic polymers. *Int. J. Pharm.* 1983; 15: 25-35.

Krause K.P., Kayser O., Mäder K., Gust R., Müller R.H. Heavy metal contamination of nanosuspension produced by high-pressure homogenization. *International Journal of Pharmaceutics.* 2000; 196: 169-172.

Kumbar, S. G., Kulkarni, A. R. and Aminabhavi, T. M., Crosslinked chitosan microspheres for encapsulation of diclofenac sodium: effect of crosslinking agent. *Journal of Microencapsulation.* 2002; 19 (2): 173-180.

Lamprecht A., Ubrich N., Ombreiro Pérez M., Lehr C.M., Hoffman M., Maincent P. Influences of process parameters on nanoparticle preparation performed by a double emulsion pressure homogenization technique. *International Journal of Pharmaceutics.* 2000; 196: 177-182.

Lee, J., Kim S., Devaraj N., Lahan J., Bawendi M., and Jensen K. Microencapsulation of Quantum Dots and Organization into Spatial Patterns. Thin Film Synthesis and Biological & Chemical Microsystems. Materials research report at MIT. 2003.

Légaré D., Richard D., Mukhopadhyay R., Stierhof YD., Rosen BP., Haimeur A., Papadopoulou B., Ouellette M., The leishmanial ABC protein pgpA is an intracellular metal thiol transporter ATPase. J. Biol. Chem. 2001; 276: 26301–26307.

Lindsay D.S. and Blagburn B.L. Veterinary Pharmacology and Therapeutics. 7th edition. Edited by H.Richard Adams. Iowa, 1995; Section 11. Chemotherapy of Parasitic Diseases. Chapter 47: Antiprotozoan drugs: 955-983.

Lira R, Sundar S., Makharia A., Kenney R., Gam A., Saraiva E. and Sacks D.. Evidence that the high incidence of treatment failures in Indian Kala-Azar is due to the emergence of antimony-resistant strains of *Leishmania donovani*. The Journal of Infectious Diseases. 1999. 180:564-567.

Liu X.D., Furuta T., Yoshi H., Linko P., and Coumans J.W. Cyclodextrin encapsulation to prevent the loss of l-menthol and its retention during drying. Biosci.Biotechnol.Biochem. 2000; 64(8): 1608-1613.

Luzardo-Alvarez A., Blarer N., Peter K., Romero J.F., Reymond C., Corradin G., Gander B. Biodegradable microspheres alone do not stimulate murine macrophages *in vitro*, but prolong antigen presentation by macrophages *in vitro* and stimulate a solid immune response in mice. Journal of Controlled Release. 2005; 109: 62-76.

Luzardo-Alvarez A., Merkle H.P., Gander B. Responses of cultured macrophages to microspheres. Journal of Controlled Release. 2005. 101(1-3): 347- 349.

Maa Y.F., Nguyen P.A., Sweeney T., Shire S.J. and Hsu C.C. Protein Inhalation powders: spray drying vs spray freeze drying. Pharmaceutical Research. 1999; 16(2): 249-54.

Machado-Pinto J., Pinto J., da Costa C.A., Genaro O., Marques M.J., Modabber F., and Mayrink W. Immunochemotherapy for cutaneous leishmaniasis: a controlled trial using killed *Leishmania (Leishmania) amazonensis* vaccine plus antimonial. International Journal of Dermatology. 2002; 41: 73-78.

Makino K., Nakajima T., Shikamura M., Ito F., Ando S., Kochi C., Inagawa H., Soma G.I., 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 and Surfaces B: Biointerfaces. 2004; 36: 35-42.

Maren T. H. Colorimetric microdetermination of antimony with rhodamine B. Analytical chemistry. 1947; 19(7): 487-491.

Marquis N., Gourbal B., Rosen BP., Mukhopadhyay R., Ouellette M. Modulation in aquaglyceroporin AQP1 gene transcript levels in drug-resistant *Leishmania*. Mol. Microbiol. 2005; 57: 1690–1699.

Martinac A., Filipovic-Grcic J., Perissutti B., Voinovich D. and Pavelic Z. Spray-dried chitosan/ethylcellulose microspheres for nasal drug delivery: Swelling study and evaluation of *in vitro* drug release properties. *Journal of Microencapsulation*. 2005; 22(5): 549-561.

Martins P.S., Ochoa R., Pimenta A.M.C., Ferreira L.A.M., Melo A.L., da Silva J.B.B., inisterra R.D., Demicheli C., Frézard F. Mode of action of β -cyclodextrin as an absorption enhancer of the water-soluble drug meglumine antimoniate. *Int J Pharm*. 2006; 325(1-2): 39-47.

Mathew S. T., Gayathri Devi S., and Sandhya KV. Formulation and evaluation of Ketorolac Tromethamine-loaded albumin microspheres for potential intramuscular administration. *AAPS PharmSciTech* 2007; 8 (1): Article 14.

Medda S., Jaisankar P., Manna R.K., Pal B., Giri V.S., Basu M.K. Phospholipid microspheres: a novel delivery mode for targeting antileishmanial agent in experimental leishmaniasis. *J Drug Target*. 2003; 11(2):123-8.

Medintz I.L., Uyeda H.T., Goldman E.R. and Mattoussi H. Quantum dot bioconjugates for imaging, labeling and sensing. *Nature materials*. 2005; 4: 435-446.

Miguel D.C., Yokoyama-Yasunaka J.K., Andreoli W.K., Mortara R.A., Uliana S.R. Tamoxifen is effective against *Leishmania* and induces a rapid alkalization of parasitophorous vacuoles harbouring *Leishmania (Leishmania) amazonensis* amastigotes. *J Antimicrob Chemother*. 2007; 60(3):526-34

Minemoto Y., Fang X., Hakamata K., Watanabe Y., Adachi S., Kometani T., and Matsuno R. Oxidation of Linoleic acid encapsulated with soluble soybean polysaccharide by spray-drying. *Biosci.Biotechnol.Biochem*. 2002; 66(9): 1829-1834.

Mittal M.K., Rai S., Ravinder A., Gupta S., Sundar S. and Goyal N., Characterization of natural antimony resistance in *Leishmania donovani* isolates. *Am.J.Trop.Med.Hyg*. 2007; 76(4), 681-688.

Monteiro O.A.C. Jr., Airoidi C. Jr. Some studies of crosslinking chitosan-glutaraldehyde interaction in a homogeneous system. *International Journal of Biological Macromolecules*. 1999; 624: 119-128.

Mori T., Murakami M., Okumura M., Kadosawa T., Uede T. and Fujinaga T. Mechanism of macrophage activation by chitin derivatives. *J.Vet.Med.Sci*. 2005; 67(1): 51-56.

Müller C.R., Bassani V.L., Pohlmann A.R., Michalowski C.B., Petrovick P.R., and Guterres S.S. Preparation and characterization of spray-dried polymeric nanocapsules. *Drug development and industrial pharmacy*. 2000; 26(3): 343- 347.

Murray C. B. and Kagan C.R. Synthesis and characterization of monodisperse nanocrystals and close-packed nanocrystal assemblies. *Annu. Rev. Mater. Sci*. 2000; 30: 545–610.

Nan A., Croft S. L., Yardley V., Ghandehari H. Targetable water-soluble polymer-drug conjugates for the treatment of visceral leishmaniasis. *Journal of Controlled Release*. 2004; 94: 115-127.

Nègre É., Chance M. L., Hanboula S.Y., Monsigny M., Roche A.C., Mayer R.M., and Hommel M. Antileishmanial Drug targeting through Glycosylated Polymers Specifically internalized by Macrophage membrane lectins. *Antimicrobial Agents and Chemotherapy*. 1992; 36 (10): 2228-2232.

Nielloud F. and Mart-Mestres G. Pharmaceutical emulsions and suspensions. *Drugs and pharmaceutical sciences*. CRC press. London. 2000; 105: 325.

Oliveira B.F., Santana M.H.A. and Ré M.I. Spray-dried chitosan microspheres cross-linked with D,L-Glyceraldehyde as a potential drug delivery system: preparation and characterization. *Brazilian Journal of Chemical Engineering*. 2005; 22(3): 353-360.

Ordóñez-Gutiérrez L., Espada-Fernández R., Dea-Ayuela M.A., Torrado J.J., Bolás-Fernandez F., Alunda J.M. *In vitro* effect of new formulations of amphotericin B on amastigote and promastigote forms of *Leishmania infantum*. *Int. J. Antimicrob. Agents*. 2007; 30(4):325-9.

Osorio E.J., Robledo S.M., Arango J.M., Muskus C.E. *Leishmania*: papel de la glicoproteína P en la mediación de Resistencia a medicamentos y estrategias de reversión. *Biomédica*. 2005; 25: 242-60.

Ouellette M., Drummelsmith J., Papadopoulou B. Leishmaniasis: drugs in the clinic, resistance and new developments. *Drug resistance updates*. 2004; 7: 257-266.

Papadopoulou V., Kosmidis K., Vlachou M., Macheras P. On the use of the Weibull function for the discernment of drug release mechanisms. *International Journal of Pharmaceutics*. 2006; 309: 44–50.

Patravale V.B., Date A.A. and Kulkarni R.M. Nanosuspensions: a promising drug delivery strategy. *Journal of Pharmacy and pharmacology*. 2004; 56: 827-840.

Paul W. and Sharma C.P. Chitosan, a drug carrier for the 21st century: a review, *STP Pharm. Sci*. 2000; 10: 5–22.

Peppas N.A. Analysis of Fickian and non-Fickian drug release from polymers. *Pharm. Acta.Helv*. 1985;60:110-111.

Pintado V. y López-Vélez R. Leishmaniasis visceral asociada a la infección por el virus de la inmunodeficiencia humana. *Enfermedades infecciosas y microbiología clínica*. 2001; 19 (7): 353 – 357.

Piñero J.E., Martínez S., del Castillo A., Portús M., Valladares B. In vitro susceptibility of *Leishmania infantum* strains isolated from Spanish HIV-positive patients to Abelcet and Fungizone. *J. Antimicrob. Chemother*. 2002; 50(2):304-6.

Piñero J., Temporal R.M., Silva-Gonçalves A.J., Jiménez I.A., Bazzocchi I.L., Oliva A., Perera A., Leon L.L., Valladares B. New administration model of trans-chalcone biodegradable polymers for the treatment of experimental leishmaniasis. *Acta Trop.* 2006; 98 (1): 59-65.

Porporatto C., Bianco I. D., Riera C.M., and Correa S.G. Chitosan induces different L-arginine metabolic pathways in resting and inflammatory macrophages. *Biochemical and Biophysical Research Communications.* 2003; 304: 266-272.

Porporatto C., Bianco I.D. and Correa S. G. Local and systemic of the polysaccharide chitosan at lymphoid tissues after oral administration. *Journal of Leukocyte Biology.* 2005; 78: 62-69.

Porter, C.J.H., Moghimi, S.M., Illum, L., Davis, S.S. The polyoxyethylene polyoxypropylene block copolymer Poloxamer-407 selectively redirects intravenously injected microspheres to sinusoidal endothelial-cells of rabbit bone-marrow. 1992; *FEBS Lett.* 305, 62–66.

Pouton C.W. Lipid formulation for oral administration of drugs: non-emulsifying, self-emulsifying and 'self-microemulsifying' drug delivery systems. *European Journal of Pharmaceutical Sciences.* 2000; 11. Suppl.2: S93-S98.

Prasad V., Semwogerere D. and Weeks E. R. Confocal microscopy of colloids. *Journal of physics: condensed matter.* 2007; 19: 113102 (25pp).

Prego C., García M., Torres D., Alonso M.J. Transmucosal macromolecular drug delivery. *Journal of Controlled Release.* 2005; 101: 151-162.

Prior S., Gander B., Blarer N., Merkle H. P., Subirá M.L., Irache J.M., Gamazo C. *In vitro* phagocytosis and monocyte-macrophage activation with poly(lactide) and poly(lactide-co-glycolide) microspheres. *European Journal of Pharmaceutical Sciences.* 2002; 15: 197-207.

Privitera N., Naon R., Vierling P., Riess J.G. Phagocytic uptake by mouse peritoneal macrophages of microspheres coated with phosphocoline or polyethylene glycol phosphate-derived perfluoroalkylated surfactants. *International Journal of Pharmaceutics.* 1995; 120: 73-82.

Proulx M.E., Desormeaux A., marquis J.F., Olivier M., Bergeron M.G. Treatment of visceral leishmaniasis with sterically stabilized liposomes containing camptothecin. *Antimicrob. Agents Chemother.* 2001; 45: 2623-2627.

Qi L., Xu Z., Chen M. *In vitro* and *in vivo* suppression of hepatocellular carcinoma growth by chitosan nanoparticles. *Eur. J. Cancer.* 2007; 43(1): 184-93.

Rath S., Trivelin L.A., Imbrunito T.R., Tomazela D.M., Nunes de Jesús M. e Calvo Marzal P. Antimonials impregnados o tratamento da leishmaniose: estado da arte. *Quim.Nova.* 2003; 26: 550-555.

Ritger P.L. and Peppas N.A. A simple equation for description of solute release. I. Fickian and non-Fickian release from non-swellable devices in the form of slabs, spheres, cylinders or discs. *J. Controlled Release*. 1987a; 5: 23–36.

Ritger P.L. and Peppas N.A. A simple equation for description of solute release II. Fickian and anomalous release from swellable devices. *J. Controlled Release*. 1987b; 5: 37–42.

Roberts W.L., McMurray W.J., Rainey P.M. Characterization of the Antimonial Antileishmanial Agent Meglumine Antimoniate (Glucantime). *Antimicrobial Agents and Chemotherapy*. 1998; Vol.42, No.5: 1076-1082.

Roberts W.L., Hariprashad J., Rainey P.M., Murray H.W. Pentavalent antimony-mannan conjugate therapy of experimental visceral leishmaniasis. *Am.J.Trop.Med.Hyg.* 1996; 55(4): 444-446.

Roberts W.L., Berman J.D., Rainey P.M. *In vitro* antileishmanial properties of tri- and pentavalent antimonial preparations. *Antimicrobial Agents and Chemotherapy*. 1995; 39(6): 1234-1239.

Rodrigues J.M. Jr, Croft S.L., Fessi H., Bories C., Devissaguet J.P. The activity and ultrastructural localization of primaquine-loaded poly (d,l-lactide) nanoparticles in *Leishmania donovani* infected mice. *Trop. Med. Parasitol.* 1994; 45(3): 223-8.

Rodriguez-Cabezas M.N., Mesa-Valle C.M., Azzouz S., Moraleda-Líndez V., Craciunescu D., Gutiérrez-Rios M.T., de Frutos M.I., Osuna A. *In Vitro* and *in vivo* activity of new rhodium (III) complexes against *Leishmania donovani*. 2001; *Pharmacol.* 63: 112-119.

Rome R.C., Sheskey P.J., Owen S.C. *Handbook of Pharmaceutical excipients*. 5th edition. Pharmaceutical Press. London, 2006.

Roser M., Fischer D., Kissel T. Surface-modified biodegradable albumin nano- and microspheres. II: effect of surface charges on *in vitro* phagocytosis and biodistribution in rats. *European Journal of Pharmaceutics and Biopharmaceutics*. 1998; 48: 255-263.

Rybczynska M., Liu R., Lu P., Sharom F.J., Steinfelds E., Pietro A.D., Spitaler M., Grunicke H., Hofmann J. MDR1 causes resistance to the antitumour drug miltefosine. *Br.J.Cancer*. 2001; 84(10): 1405-11.

Sánchez-Brunete J. A., Dea M. A., Rama S., Bolás F., Alunda J. M., Raposo R., Méndez M. T., Torrado-Santiago S., and Torrado J. J. Treatment of Experimental Visceral Leishmaniasis with Amphotericin B in Stable Albumin Microspheres. *Antimicrob. Agents Chemother.* 2004; 48(9): 3246–3252.

Sandri G., Poggi P., Bonferoni M.C., Rossi S., Ferrari F., Caramella C. Histological evaluation of buccal penetration enhancement properties of chitosan and trimethyl chitosan. *J. Pharm Pharmacol.* 2006; 58(10): 1327-36.

Santivarangkna C., Kulozik U., Foerst P. Alternative drying processes for the industrial preservation of lactic acid starter cultures. *Biotechnol Prog.* 2007; 23(2): 302-15.

Schettini D.A., Costa Val A.P., Souza L.F., Demicheli C., Rocha O.G.F., Melo M.N., Michalick M.S.M. and Frézard F. Distribution of liposome-encapsulated antimony in dogs. *Brazilian Journal of Medical and Biological Research*. 2003; 36: 269-272.

Schipper N.G.M., Varum K. M., and Artusson P. Chitosans as Absorption Enhancers for poorly absorbable drugs.1: Influence of molecular weight and degree of acetylation on drug transport across human intestinal epithelial (Caco-2) cells. *Pharmaceutical research*. 1996; 13 (11): 1686-1692.

Schmelz O., Mews A., Basché T., Herrmann A. and Müllen K. Supramolecular complexes from CdSe Nanocrystals and Organic Fluorophors. *Langmuir*. 2001; 17: 2861-2865.

Segura I., García-Bolao I. Meglumine antimoniate, amiodarone and torsades de pointes: a case report. *Resuscitation*. 1999; 42(1): 65-8.

Sereno D., Holzmüller P. & Lemesre J.L. Efficacy of second line drugs on antimony-resistant amastigotes of *Leishmania infantum*. *Acta Trop*. 2000; 74: 25-31.

Sereno D., Roy G., Lemesre J.L., Papadopoulou B., Ouellette M. DNA transformation of *Leishmania infantum* axenic amastigotes and their use in drug screening. *Antimicrob. Agents Chemother*. 2001; 45: 1168-1173.

Shaked-Mishan P., Ulrich N., Ephros M., Zilberstein D. Novel intracellular Sb V reducing activity correlates with antimony susceptibility in intracellular *Leishmania donovani*. *J.Biol. Chem*. 2001; 276: 3971–3976.

Sharma, A. and Schulman, S. G. Introduction to Fluorescence Spectroscopy. Wiley interscience. 1999.

Sheng W., Kim S., Lee J., Kim S.W., Jensen K. and Bawendi M. G. In-situ encapsulation of quantum dots into polymer microspheres. *Langmuir*. 2006; 22: 3782-3790.

Sierra Romero G. A., de Moraes Flores É.M., Ferreira Noronha E., de Oliveira Macêdo V. High frequency of skin reactions in patients with leishmaniasis treated with meglumine antimoniate contaminated with heavy metals. A comparative approach using historical controls. *Mem. Inst. Oswaldo Cruz, Rio Janeiro*. 2003; 98(1): 145-149.

Silva O.A., Silva P.B., Silva O.V., Braga G.M., Albuquerque Junior A., Queiros Neto V., Rocha M.E., Silva E.F. Canine visceral leishmaniasis in northeast Brazil: epidemiological aspects. *Bull. Soc. Pathol. Exot*. 2007; 100(1): 49-50.

Singla A.K. and Chawla M. Chitosan: some pharmaceutical and biological aspects-update. *Journal of Pharmacy and Pharmacology*. 2001; 53: 1047-1067.

Srinivasan C., Lee J., Papadimitrakopoulos F., Silbart L.K., Zhao M., Burgess D.J. Labeling and Intracellular Tracking of Functionally Active Plasmid DNA with Semiconductor Quantum Dots. *Molecular Therapy*. 2006; 14(2): 192-201.

Stouch T.R., Gudmundsson O. Progress in understanding the structure-activity relationships of P-glycoprotein. *Advanced Drug Delivery Reviews*. 2002; 54: 315-328.

Suzuki H., Sugiyama Y. Role of metabolic enzymes and efflux transporters in the absorption of drugs from the small intestine. *European Journal of Pharmaceutical Sciences*. 2000; 12: 3-12.

Suzuki K., Okawa Y., Hashimoto K., Suzuki S., Suzuki M. Protecting effect of chitin and chitosan on experimentally induced murine candidiasis. *Microbiol. Immunol.* 1984; 28(8): 903-12.

Tabata Y., Ikada Y. Effect of the size and surface charge of polymer microspheres on their phagocytosis by macrophage. *Biomaterials*. 1988; 9(4): 356-62.

Tan W.B., Zhang Y. Surface modification of gold and quantum dot nanoparticles with chitosan for bioapplications. *Journal of biomedical materials research*. 2005; 75(1): 56-62.

Tasdemir D., Kaiser M., Brun R., Yardley V., Schmidt T.J., Tosun F., and Rüedi P. Antitrypanosomal and antileishmanial activities of flavonoids and their analogues: *in vitro*, *in vivo*, structure-activity relationship, and quantitative structure-activity relationship studies. *Antimicrobial agents and chemotherapy*. 2006; 50(4): 1352-1364.

Tayrouz Y., Ding R., Burhenne J., Riedel K.D., Weiss J., Hoppe-Tichy T., haefili W.E., Mikus G. Pharmacokinetic and pharmaceutic interaction between digoxin and Cremophor RH40. *Clin. Pharmacol. Ther.* 2003; 73: 397-405.

Tempone A.G., Perez D., Rath S., Vilarinho A.L., Mortara R.A. and de Andrade H.F. Jr. Targeting Leishmania (L.) Chagasi amastigotes through macrophage scavenger receptors: the use of drugs entrapped in liposomes containing phosphatidylserine. *Journal of Antimicrobial Chemotherapy*. 2004; 54: 60-68.

The Merck Index. Thirteen edition. Merck & Co; inc. NJ, 2001; 1084-1085.

Thomasin C., Hô N.T., Merkle H.P., Gander B. Drug microencapsulation by PLA/PLGA coacervation in the light of thermodynamics. Overview and theoretical considerations. *J. Pharm Sci.* 1998; 87(3): 259-68.

Usami Y., Okamoto Y., Minami S., Matsushashi A., Kumazawa N.H., Tanioka S., Shigemasa Y. Migration of canine neutrophils to chitin and chitosan. *J. Vet. Med. Sci.* 1994;56(6): 1215-6.

Usami Y., Okamoto Y., Takayama T., Shigemasa Y., Minami S. Chitin and chitosan stimulate canine polymorphonuclear cells to release leukotriene B4 and prostaglandin E2. *J. Biomed. Mater. Res.* 1998; 42: 517- 522.

U.S. Geological Survey. <http://pubs.usgs.gov/of/2001/of01-041/html/docs/xrpd.htm>. Revised: October, 1th, 2007.

Valiathan R., Dubey M.L., Mahajan R.C., Malla N. Leishmania donovani: effect of verapamil on *in vitro* susceptibility of promastigote and amastigote stages of Indian clinical isolates to sodium stibogluconate. *Experimental Parasitology*, 2006; October, 114(2): 103-8.

Valladares J.E., Alberola J., Esteban M., Arboix M. Disposition of antimony after the administration of N-methylglucamine antimoniate to dogs. *Vet. Rec.* 1996; 138 (8):181-183.

Valladares J.E., Riera C., Alberola J., Gállego M., Portús M., Cristòfol C., Franquelo C., Arboix M. Pharmacokinetics of meglumine antimoniate after administration of a multiple dose in dogs experimentally infected with *Leishmania infantum*. *Veterinary Parasitology.* 1998; 75: 33-40.

Vasir J.K., Tambwekar K., Garg S. Bioadhesive microspheres as a controlled drug delivery system. *International Journal of Pharmaceutics.* 2003; 255:13–32.

Vila Jato J.L. *Tecnología Farmacéutica. I: Aspectos fundamentales de los sistemas farmacéuticos y operaciones básicas. Síntesis.* Madrid, 1997; 577-608.

Vogelson C. T. Advances in drug delivery systems. *Modern drug discovery. Nanotechnology.* 2001; 4(4):49–50, 52.

Wallance R. B., Wilson M. E. *Public Health & Preventive Medicine. Diseases Transmitted Primarily by Arthropod Vectors.* 14th edition. Appleton&Lange. 1998; Stamford, Connecticut. Chapter 13: 334-335.

Watanabe Y., Fang X., Minemoto Y., Adachi S., Matsuno R. Suppressive effect of saturated acyl L-ascorbate on the oxidation of linoleic acid encapsulated with maltodextrin or gum arabic by spray-drying. *J. Agric Food Chem.* 2002 Jul 3;50(14):3984-7.

Watts P.J., Davies M.C., Melia C.D. Microencapsulation using emulsification/solvent evaporation: an overview of techniques and applications. *Crit. Rev. Ther. Drug Carrier Syst.* 1990; 7(3): 235-59.

Westesen K., Bunjes H., Koch M.H.J. Physicochemical characterization of lipid nanoparticles and evaluation of their drug loading capacity and sustained release potential. *Journal of Controlled Release.* 1997; 48: 223-236.

WHO. Special focus on the First WHO Global Partners' Meeting on NTD, 19–20 April 2007.

Woodard J.T., Musolf M.C., Miller P.J. Process for forming a coated active agent-containing article. 1994; U.S. Patent 5310572.

www.buchi.com. Revised: October, 7th, 2007.

www.dpd.cdc.gov/dpdx/HTML/Leishmaniasis.htm. Revised: October, 16th, 2004.

www.emdchemicals.com/analytics/literature/KF_Titration_Basics.pdf. Revised: October, 1th, 2007.

www.evidenttech.com. Revised: Desember, 5th, 2006.

www.gate2tech.com. Revised: October, 7th, 2007.

www.mh-hannover.de/3548.html. Revised: October, 11th, 2007.

www.micromedex.com. Revised: October, 16th, 2004.

www.paho.org/English/AD/DPC/CD/leish-2007.pdf. Revised: September, 27th, 2007

www.who.int/leishmaniasis/home_leishnet/en/. Revised: September, 27th, 2007.

www.who.int/tdr/diseases/default.htm. Revised: September, 27th, 2007

Wyllie S., Cunningham M. L., and Fairlamb A. H. Dual Action of antimonial drugs on thiol redox metabolism in the human pathogen *Leishmania donovani*. *The Journal of biological chemistry*, 2004; 279 (38): 39925-39932.

Yamoaka K., Nakagawa T. and Uno T., Application of the Akaike Information Criterion (AIC) in the evaluation of linear pharmacokinetics equations. *J. Pharmacokinet. Biopharm.* 1978; 6: 165–175.

Yang M. , Velaga S. , Yamamoto H. , Takeuchi H. , Kawashima Y. , Hovgaard L., van de Weert M. , Frokjaer S. Characterisation of salmon calcitonin in spray-dried powder for inhalation. Effect of chitosan. 2007; 331(2):176-81.

Yardley V. and Croft S.L. A comparison of the activities of three amphotericin B lipid formulations against experimental visceral and cutaneous leishmaniasis. *Int.J.Antimicrobial Agents.* 2000; 13: 243-248.

Yardley V., Croft S.L., De Doncker S., Dujardin J.C., Koirala S., Rijal S., Miranda C., Llanos-Cuentas A., Chappuis F. The sensitivity of clinical isolates of *Leishmania* from Peru and Nepal to miltefosine. *Am. J. Trop. Med. Hyg.* 2005; 73(2): 272-5.

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.I. 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 and Infection.* 2006; 8(9-10): 2484-2491.

Yu L. Amorphous pharmaceutical solids: preparation, characterization and stabilization. *Adv. Drug Deliv. Rev.* 2001; 16; 48(1):27-42.

Yu W.W., Chang E., Drezek R., Colvin V.L. Water-soluble quantum dots for biomedical applications. *Biochemical and Biophysical Research Communications.* 2006; 348: 781-786.

Yu W.W., Qu L., Guo W. and Peng X. Experimental Determination of the Extinction Coefficient of CdTe, CdSe, and CdS nanocrystals. *Chem.mater.* 2003; 15: 2854-2860.

Zahr A.S., Davis C.A., Pishko M.V. Macrophage uptake of core-shell nanoparticles surface modified with poly(ethylene glycol). *Langmuir*. 2006; 22: 8178-8185.

Zhang H., Yao M., Morrison RA., Chong S. Commonly used surfactant, Tween 80, improves absorption P-glycoprotein substrate, digoxin, in rats. *Arch. Pharm. Res.* 2003; 26(9): 768-772.

Zolnik B.S., Raton J.L., Burgess D.J. Application of USP Apparatus 4 and in situ fiber optic analysis to microsphere release testing. *Dissolution Technologies*. 2005; 11-14.