Transport of nanomaterials in complex media

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ABSTRACT

Potential benefits of nanotechnology are immense, also its dangers. Nanomaterials are developed for their new radical properties involving to completely new and amazing results. Although exists a wide consensus about the advances of nanotechnology in fields like materials, medicine and energy, there is also huge doubts about biological, environmental and security implications. Some studies had identified knowledge gaps that must be addressed immediately, some of the recommendations are: to determine the kinetics and transport mechanism of nanoparticles in human body, and their characterization. The main objective of this paper is to describe the progress made in the design of equipment and protocols for future study of nanomaterials transport in biological media.

Keywords: Nanomaterials, Franz Diffusion Cell, Difussion

1 INTRODUCTION

Nanotechnology shows rapid advances that promise to change and impact radically, many areas of science and technology.

Also, It offers lots of possibilities for human progress, creating many types of nanomaterials applicable in different areas that include but are not limited to; novel medical treatments [1,2,3,4], agricultural research [5], diagnostic methods for food safety [5,6,7,8], environmental recovery procedures [9, 10], energy applications such as solar cells [11, 12], even in daily high-volume products like cosmetics [13, 14], clothes and / or dirt repellent surfaces [15] and self-cleaning paint [15]. However, it is essential and urgent to evaluate not only the benefits but also the potential risks of nanoparticles and propose effective actions by appropriate regulatory criteria.

For this reason in recent years, many researchers [6, 13, 16-33] have analyzed the cytotoxicity and genotoxicity of micro and nanoparticles in biological systems, finding significant effects on most organs of the body. Such wide spread effects in the body are due in part to: i) the fourth different mechanisms (inhalation, ingestion, dermal contact and iatrogenic method) by which nanoparticles can be transported in to the body, ii) its reactivity, iii) size, iv) novel properties different from their macroscopic counterparts, v) ease of transport to the whole human body by circulatory and lymphatic systems [34-38].

Fig. 1 illustrates the potential lifecycle of nanoparticles in the human body. This figure shows an overview of ADME (Absorption, Distribution, Metabolism and Excretion) processes in the body [35]. This schematic indicates that nanoparticles are distributed to the same organ through various exposure routes. For example nanoparticles that are in the gastrointestinal tract could enter through ingested products but also they can reach the gastrointestinal tract through an indirect route, such as entry by the respiratory tract or the skin, where they are subsequently absorbed by the circulatory system. From there, the particles can be distributed in the liver, taken by the hepatocytes and excreted in the bile to the gastrointestinal tract.

Some recent studies [16-33] regarding the effect of nanoparticles in the body, show effects that include among others: oxidative stress, generation of reactive oxygen species, increase of Ca + concentration into the cell, lipid peroxidation, mitochondrial damage, cell membrane damage and DNA damage that causes cell death. All these studies have been carried out experimentally by in vitro and in vivo tests.

Recent studies sponsored by the Scientific Committee on Emerging and Newly Identified Health Risks (SCENIHR) with the purpose of assessing the potential risks of nanomaterial's to human health, have identified knowledge gaps that must be addressed immediately, some of the recommendations are: to determine the kinetics and transport mechanism of nanoparticles, their characterization, standardization of synthesis process of the nanoparticles, standardization of transport test protocols and evaluation of how can we extrapolate toxicology data from in vitro to in vivo.

Given these observations, the main objective of this paper is to describe the progress made in the design of equipment and protocols for future study of the transport of nanomaterials in complex media. We present the design of a modified diffusion cell for testing transdermal penetration of nanomaterials as well as the protocol for testing in such device, also the design of a decellularization system of organs (tissues) and its protocol, in order to obtain extracellular organ matrices in which the transport studies of nanoparticles can be conducted by infusion. Analysis and transport assays will be presented for nanoparticles (SiO_2) in these prototype systems.

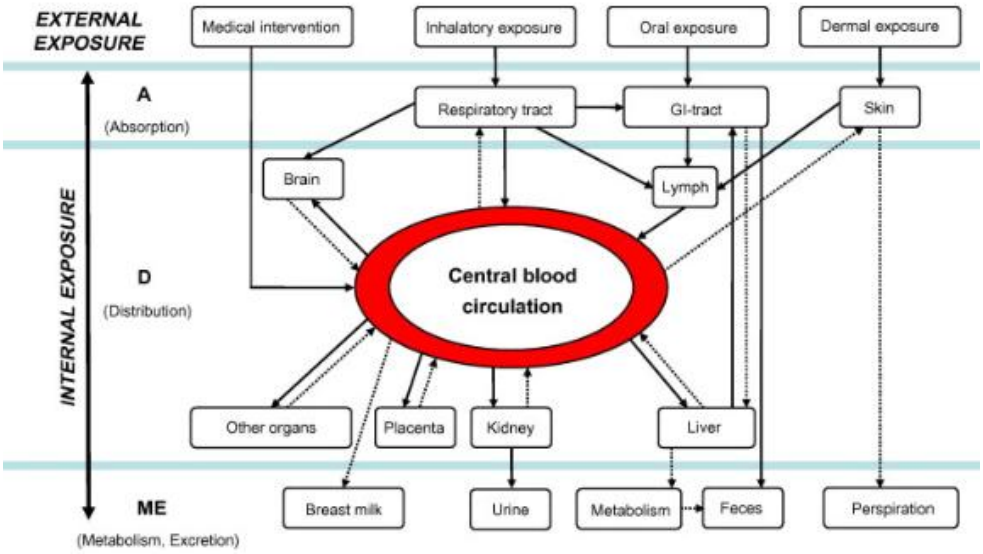

Figure 1: ADME Processes. Werner I. Hagens, et al. [35]

2 MATERIALS AND METHODS

2.1 Design of a Franz Diffusion Cell

For the nanomaterial´s transport study in biological media, some researchers have used the so called Franz diffusion cell [29, 32, 39-42], which consists of a two vessels – a donor and a receptor- which are separated by a synthetic membrane, skin or tissue to be evaluated. In the donor compartment a representative sample of the formulation under consideration is placed (in case a solution containing nanoparticles) and the receptor uses a solution that solubilizes the substance that diffuses across the complex media. At predetermined times; small aliquots from the receptor chamber are taken and analyzed for the active using a suitable analytical method.

To carry out the design of the diffusion cell different prototypes were considered such as those used in previous studies for example Gamer [29], Sonavane [32] an Estevez [48]. These studies used the static Franz diffusion cell, this implies that such cells don´t have entry and exit ports for flow circulation through the receptor and/or donor compartments. Thinking in future requirements the diffusion cell was designed with flow ports in both compartments, for that reason the proposed cell prototype has two functionalities as a flow and/or static cell.

The experimental diffusion cell prototype is made of borosilicate glass, the receptor compartment has a volume of approximately 32.7 ml and the surface area exposed for diffusion is currently of 3,8 cm2 (Figure 2).

The receptor compartment is jacketed with a second chamber for maintain the receptor medium at a fixed temperature by means of a water thermostated bath. The receptor solution is constantly stirred with a magnetic bar at fixed rpms to keep the solution homogeneous.

The two cell compartments are held together with a clamp and screws as illustrated in Figure 2. The membrane is mounted between the cell compartments using an o-ring placed in the mouth of the receptor container to position the membrane.

2.2 Protocol for using the Franz Diffusion Cell.

The protocol defined for the study in the diffusion cell is as follows:

i) The receptor solution is composed of a phosphate buffer (PBS) 1X with a pH of 7.4, also a group of antibiotics including Gentamicin and Penicilin as well as an antimycotic agent (Fluconazole) added to prevent the growth of microorganism on the membrane and in the receptor solution.

ii) The heating jacket of the diffusion cell must be set at a temperature of 37°C which is the average body temperature of humans.

iii) The receptor medium solution should be homogenized with a magnetic stirrer at a constant velocity of 600rpm.

iv) The receptor sampling arm of the cell must be covered with a foil cap.

v) Tissue discs are mounted in the diffusion cell with the appropriate direction facing the receptor solution.

vi) The two compartments are assembled with a stainless steel clamp and four screws.

vii) An stabilization time equivalent to 30 minutes has to be provided.

viii) In order to perform a test, 2 ml of the nanoparticles solution should be placed in the donor compartment.

ix) Aliquots of the receptor medium (2 ml) are taken every 0.5 h, 1h, 2h, 3h, 6h, 9h, 12h, 18h and 24h, respectively.

x) Immediately after the collection of each aliquot 2 ml of buffer solution has to be added in the receptor medium.

xi) The concentration of nanoparticles in the samples are determined sprectrophotometrically or using any other appropriate technique.

The protocol design was based on different procedures established by researches who previously have worked on Franz diffusion cells to determine the distribution of nanomaterials in tissues. [39-47]

Section headings should be 12-point boldface capital letters, centered in the column. Sub-section headings require initial capitals using boldface and left justification. Headings should appear on separate lines, using the Arabic numbering scheme. The abstract and reference section headings are not numbered.

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References should be collected at the end of your paper. They should be prepared according to a recognized style, e.g. the Harvard or sequential numeric system making sure that your accumulated list corresponds to the citations made in the main text and that all material mentioned is generally available to the readers. When referring to them in the text, type the corresponding reference number in square brackets as in this example [1].

3 RESULTS

Equations must be placed flush-left with the text margin and preceded and followed by a line of white space.

$$\frac{ih}{2p}\frac{\partial y}{\partial t} = -\frac{h^2}{8p^2 m}\nabla y + U(x,y,z,t)y \qquad (1)$$

Numbered equations should be numbered consecutively, with numbers in parentheses, flush right, and level with the last line of the equation.

4 CONCLUSIONS

Tables and illustrations can appear within columns or span both columns. If two column figures or tables are required, place them at the top or at the bottom a page. They should have a self-contained caption and be center justified. Figures must be 600 dpi resolution or equivalent. All lettering should be 10-point type or larger. Figures must not extend into the margins.

	Style	Size	Justified
Title	**Bold**	**14**	**Center**
Authors	Normal	12	Center
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Subsection	**Bold**	**12**	**Left**
Main Text	Normal	10	Left/Right
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Table 1: Formatting summary for Nanotech manuscripts.

Figures and Tables should be sequentially numbered. Captions should be centered and use the same type and size font as regular text.

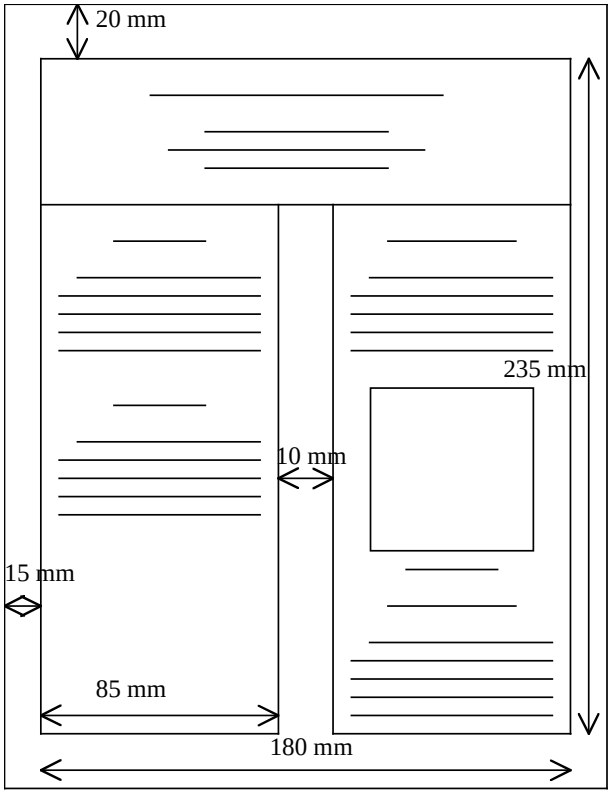

Figure 1: Formatting dimensions for manuscripts.

REFERENCES

[1] Roszek, B., de Jong, W.H., Geertsma, R.E. Nanotechnology in medical applications: state-of-the-art in materials and devices. RIVM report 265001001/2005.

[2] Kumar, Challa. Nanomaterials for cancer therapy. ed wiley vch. mörlenbunch, germany. 2006.

[3] Vera, Jerry., Bayazitoglu, Yildiz. Gold nanoshell density variation with laser power for induced hyperthermia. International Journal of Heat and Mass Transfer 52 (2009) 564–573.

[4] V.R. Singh. Ultrasound hyperthermia control system for deep-seated tumours: Ex vivo study of excised tumours, modeling of thermal profile and future nanoengineering aspects. IRBM 29 (2008) 326–336.

[5] Bouwmeester, et al. Review of health safety aspects of nanotechnologies in food production. Regulatory Toxicology and Pharmacology 53 (2009) 52–62

[6] Lomer, M.C., Thompson, R.P., Powell, J.J., 2002. Fine and ultrafine particles of the diet: influence on the mucosal immune response and association with Crohn's disease. Proc. Nutr. Soc. 61 (1), 123–130.

[7] Chaudhry Q, Scotter M, Blackburn J, Ross B, Boxall A, Castle L, et al. Applications and implications of nanotechnologies for the food sector. Food Addit Contam Part A Chem Anal Control Expo Risk Assess 2008;25(3):241-58.

[8] Powell, P., Faria, N., Thomas-McKay, E., Pele, L. Origin and fate of dietary nanoparticles and microparticles in the gastrointestinal tract. Journal of Autoimmunity 34 (2010) J226-J233.

[9] Shen, Y., Tang, J, Nie, Z., Wang, Y., Ren, Y., Zuo, L. Tailoring size and structural distortion of Fe3O4 nanoparticles for the purification of contaminated water. Toxicology Letters 176 (2008) 1–12

[10] Pradeep, T. Noble metal nanoparticles for water purification: A critical review. Thin Solid Films 517 (2009) 6441–6478

[11] Puetz, A., et al. Organic solar cells incorporating buffer layers from indiumdoped zinc oxide nanoparticles. (2010), doi:10.1016/j.solmat.2010.09.020.

[12] Günes, S., et al. Hybrid solar cells using PbS nanoparticles. Solar Energy Materials & Solar Cells 91 (2007) 420–423

[13] Tan, M.H., Commens, C.A., Burnett, L., Snitch, P.J., 1996. A pilot study on the percutaneous absorption of microfine titanium dioxide from sunscreens. Australas. J. Dermatol. 37 (4), 185–187.

[14] Serpone, N., Dondi D., Albini A. Inorganic and organic UV filters: Their role and efficacy in sunscreens and suncare products. Inorganica Chimica Acta 360 (2007) 794–802.

[15] Molins, Ricardo. Oportunidades y amenazas de la nanotecnología para la salud, los alimentos, la agricultura y el ambiente. Revista COMUN//CA. Año 4 Segunda etapa, Enero - Abril 2008.

[16] Preining, O. The physical nature of very small particles and its impact on their behaviour. J. Aerosol Sci. 5 (6), 481–495 (1998).

[17] Oberdorster, G., Oberdorster, E., Oberdorster, J. Nanotoxicology: an emerging discipline evolving from studies of ultrafine particles. Environ. Health Perspect. 2005. 113 (7), 823–839.

[18] Hillyer, J.F., Albrecht, R.M. Gastrointestinal persorption and tissue distribution of differently sized colloidal gold nanoparticles. J. Pharm. Sci 2001. 90 (12), 1927–1936.

[19] G. Oberdörster Z. Sharp, V. Atudorei, A. Elder, R. Gelein ans W. Kreyling, C. Cox. Translocation of inhaled ultrafine particles to the Brain. Inhalation Toxicology., 16 (6/7), 437-445 (2004).

[20] A. Nemmar, M.F Hoylaerts, P.H.M Hoet, D. Dinsdale, T. Smith and H. Xu, J. Vermylen, B. Nemery: Am. J. Respir. Crit. Care Med, 166, 998-1004 (2002).

[21] A. Nemmar, M.F Hoylaerts, P.H.M Hoet, D, J. Vermylen, B. Nemery: Toxicol. Appl. Pharmacol., 186, 38-45 (2003)

[22] D.B. Warheit, B.R. Laurence, K.L. Reed, D.H. Roach, G.A.M. Reynolds, T.R. Webb. Comparative pulmonary toxicity assessment of single-wall carbon nanotubes in rats. Toxicological Sciences., 77, 117-125 (2004)

[23] Lam, C. W., James, J.T., McCluskey, R., and Hunter, R.L. Pulmonary toxicity of single-wall carbon nanotubes in mice 7 and 90 days after intratacheal instillation. Toxicological Sciences 77: 126-134.

[24] G. Oberdörster. Manufactured nanomaterials (fullerenes C60) induce oxidative stress in juvenile largemouth bass. Environmental Health Perspectives. 112: 1058-1062 (2004).

[25] Sharma, Vyom. DNA damaging potential of zinc oxide nanoparticles in hµman epidermal cells. Toxicology Letters 185, 211–218 (2009).

[26] Dunford R, Salinaro A, Cai L, Serpone N, Horikoshi S, Hidaka H, Knowland J. Chemical oxidation and DNA damage catalyzed by inorganic sunscreen ingredients. FEBS Lett 1997; 418: 87-90.

[27] Serpone N, Salinaro A, Emeline A. Deleterious effects of sunscreen titanium dioxide nanoparticles on DNA: efforts to limit DNA damage by particle surface modification. Proc SPIE 2001; 4258: 86-98.

[28] Schulz, J., Hohenberg, H., Pflucker, F., Gartner, E., Will, T., Pfeiffer, S., Wepf, R., Wendel, V., Gers-Barlag, H., Wittern, K.P. Distribution of sunscreens on skin. Adv. Drug. Deliv. Rev. 54 (Suppl 1), S157–S163 (2002).

[29] Gamer, A.O., Leibold, E., van Ravenzwaay, B., 2006. The in vitro absorption of microfine zinc oxide and titanium dioxide through porcine skin. Toxicol In Vitro 20 (2006), 301–307.

[30] Maqusood Ahamed, Mohamad S. AlSalhi, M.K.J. Siddiqui. Silver nanoparticle applications and human health. Article in press for Clinica Chimica Acta.

[31] Larese, F, et al. Human skin penetration of silver nanoparticles through intact and damaged skin. Toxicology 255 (2009) 33–37.

[32] Sonavane, G., Tomoda, K., Sano, A., Ohshima, H., Terada, H., Makino, K. In vitro permeation of gold nanoparticles through rat skin and rat intestine: Effect of particle size. Colloids and Surfaces B: Biointerfaces 65 (2008) 1–10.

[33] Carr, K.E., Hazzard, R.A., Reid, S., Hodges, G.M. The effect of size on uptake of orally administered latex microparticles in the small intestine and transport to mesenteric lymph nodes. Pharm. Res. (8), 1205–1209 (1996).

[34] Lin, Patrick; Moor, James. Nanoethics. The ethical and social implication of nanotechnology. Wiley. USA. 2007.

[35] Hagens,W, et al. What do we (need to) know about the kinetic properties of nanoparticles in the body? Regulatory Toxicology and Pharmacology 49 (2007) 217–229.

[36] Hosokawa, M, et al. Nanoparticle Technology Handbook. Ed El Sevier. Primera Edición. Hungary. 2007

[37] Berube, David. Nano-Hype: The truth behind the nanotechnology buzz. Ed Prometheus Books. U.S.A. 2006.

[38] Schmid, G, et al. Nanotecnology: assessment and Perspectives. Ed Springer. Germany. 2006.

[39] Jianhong Wu, Wei Liu, Chenbing Xue, Shunchang Zhou, Fengli Lan, Lei Bi, Huibi Xu, Xiangliang Yang, Fan-Dian Zeng. Toxicity and penetration of TiO2 nanoparticles in hairless mice and porcine skin after subchronic dermal exposure. Toxicology Letters, Volμme 191, Issue 1, 1 December 2009, Pages 1-8.

[40] Karine Padois, Céline Cantiéni, Valérie Bertholle, Claire Bardel, Fabrice Pirot, Françoise Falson. Solid lipid nanoparticles suspension versus commercial solutions for dermal delivery of minoxidil. International Journal of Pharmaceutics, Volume 416, Issue 1, 15 September 2011, Pages 300-304.

[41] Sarah Küchler, Michal R. Radowski, Tobias Blaschke, Margitta Dathe, Johanna Plendl, Rainer Haag, Monika Schäfer-Korting, Klaus D. Kramer. Nanoparticles for skin penetration enhancement – A comparison of a dendritic core-multishell-nanotransporter and solid lipid nanoparticles.
European Journal of Pharmaceutics and Biopharmaceutics, Volume 71, Issue 2, February 2009, Pages 243-250.

[42] Sion A. Coulman, Alexander Anstey, Chris Gateley, Anthony Morrissey, Peter McLoughlin, Chris Allender, James C. Birchall. Microneedle mediated delivery of nanoparticles into human skin. International Journal of Pharmaceutics, Volume 366, Issues 1-2, 21 January 2009, Pages 190-200.

[43] Jongwon Shim, Hyung Seok Kang, Won-Seok Park, Sang-Hun Han, Junoh Kim, Ih-Seop Chang. Transdermal delivery of mixnoxidil with block copolymer nanoparticles. Journal of Controlled Release, Volume 97, Issue 3, 7 July 2004, Pages 477-484.

[44] Clara Luisa Domínguez-Delgado, Isabel Marlen Rodríguez-Cruz, José Juan Escobar-Chávez, Iván Omar Calderón-Lojero, David Quintanar-Guerrero, Adriana Ganem. Preparation and characterization of triclosan nanoparticles intended to be used for the treatment of acne. European Journal of Pharmaceutics and Biopharmaceutics, Volume 79, Issue 1, September 2011, Pages 102-107.

[45] Wei Zhang, Jing Gao, Quangang Zhu, Min Zhang, Xueying Ding, Xiaoyu Wang, Xuemei Hou, Wei Fan, Baoyue Ding, Xin Wu, Xiying Wang, Shen Gao. Penetration and distribution of PLGA nanoparticles in the human skin treated with microneedles. International Journal of Pharmaceutics, Volμme 402, Issues 1-2, 15 December 2010, Pages 205-212.

[46] S. Lombardi Borgia, M. Regehly, R. Sivaramakrishnan, W. Mehnert, H.C. Korting, K. Danker, B. Röder, K.D. Kramer, M. Schäfer-Korting. Lipid nanoparticles for skin penetration enhancement—correlation to drug localization within the particle matrix as determined by fluorescence and parelectric spectroscopy. Journal of Controlled Release, Volume 110, Issue 1, 10 December 2005, Pages 151-163.

[47] L.B. Jensen, K. Petersson, H.M. Nielsen. In vitro penetration properties of solid lipid nanoparticles in intact and barrier-impaired skin. European Journal of Pharmaceutics and Biopharmaceutics, Volume 79, Issue 1, September 2011, Pages 68-75.

[48] Tania Estévez, Ana Aguilera, Amado Sáez, Eugenio Hardy. Diseño y validación de una celda de difusión para estudios de liberación in vitro de biomoléculas. Biotecnología Aplicada 2000;17:187-190.