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สาขาวิทยาศาสตร์สุขภาพ

Title :	Water Proton NMR for In Situ Detection of Insulin Aggregates
Author :	Marc B. Taraban, Huy C. Truong, Yue Feng, Elena V. Jouravleva, Mikhail A. Anisimov and Yihua Bruce Yu
Journal :	Journal of Pharmaceutical Sciences: Article first published online: 7 SEP 2015 | DOI: 10.1002/jps.24633
Abstract :	The need for quality control during the manufacturing and distribution of biopharmaceuticals is becoming increasingly necessary. At present, detecting drug degradation through the monitoring of active factor aggregation is accomplished through “invasive” techniques, such as size-exclusion chromatography (SEC), analytical ultracentrifugation (AUC), and so on. Unfortunately, these analytical methods require sampling the drug by opening the drug container that renders the remaining drug unusable regardless of the outcome of the test. Visual inspection, the current non-invasive quality control method is qualitative and can only detect visible particulates. Thus, it will miss sub-visible protein aggregates. In this paper, human insulin preparations were used to demonstrate that the transverse relaxation rate of water protons R2(1H2O) can serve as a sensitive and reliable indicator to detect and quantify both visible and sub-visible protein aggregates. R2(1H2O) is measured using a wide-bore low-field bench-top NMR instrument with permanent magnets. Such analysis could be carried out without opening the drug container, thus saving a drug for further use. The results suggest a novel, economical, non-destructive in situ analytical technique that allows for on-the-site quantification of protein aggregation in biopharmaceutical products. © 2015 Wiley Periodicals,
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Title :	Modeling of an Active Tablet Coating Process

Author :	Gregor Toschkoff, Sarah Just, Klaus Knop, Peter Kleinebudde, Adrian Funke, Dejan Djuric, Georg Scharrer and Johannes G. Khinast
Journal :	Journal of Pharmaceutical Sciences: Article first published online: 7 SEP 2015 | DOI: 10.1002/jps.24621
Abstract :	ablet coating is a common unit operation in the pharmaceutical industry, during which a coating layer is applied to tablet cores. The coating uniformity of tablets in a batch is especially critical for active coating, that is, coating that contains an active pharmaceutical ingredient. In recent years, discrete element method (DEM) simulations became increasingly common for investigating tablet coating. In this work, DEM was applied to model an active coating process as closely as possible, using measured model parameters and non-spherical particles. We studied how operational conditions (rotation speed, fill level, number of nozzles, and spray rate) influence the coating uniformity. To this end, simulation runs were planned and interpreted according to a statistical design of (simulation) experiments. Our general goal was to achieve a deeper understanding of the process in terms of residence times and dimensionless scaling laws. With that regard, the results were interpreted in light of analytical models. The results were presented at various detail levels, ranging from an overview of all variations to in-depth considerations. It was determined that the biggest uniformity improvement in a realistic setting was achieved by increasing the number of spray nozzles, followed by increasing the rotation speed and decreasing the fill level. © 2015 Wiley Periodicals,
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Title :	Solidarity in the Moral Imagination of Bioethics
Author :	Bruce Jennings and Angus Dawson
Journal :	Hastings Center Report: Article first published online: 1 SEP 2015 | DOI: 10.1002/hast.490
Abstract :	How important is the concept of solidarity in our society's calculus of consent as regards the legitimacy and ethical and political support for public health, health policy, and health services? By the term “calculus of consent,” we refer to the answer that people give to rationalize and justify their obedience to laws, rules, and

	policies that benefit others. The calculus of consent answers questions such as, Why should I care? Why should I help? Why should I contribute to the public provision of others? Consent here does not have to be a deliberate, explicit act of informed agreement. And a calculus does not have to be a quantifiable, quasimathematical operation; more often, such a calculus takes narrative form in stories that a society tells about itself and that individuals tell about their place in it. One vital function of bioethics is to inform and shape those stories. Bioethics has the potential to offer society a keener insight and perception of what is ethically at stake in controversies concerning health, science, and society. This insight is what we shall refer to as a "moral imagination," by which we do not mean make-believe or fantasy but, rather, the capacity to take a critical distance from the given, to think reality otherwise. The moral imagination enables one to see connections between factors at work in history, in large social and communal structures, and in the shape of one's own life, thoughts, and feelings. Here we are especially concerned with the contribution that the concept of solidarity can make to the moral imagination of bioethics. We contend that solidarity must become more widely active and explicit in bioethics analysis and argumentation as it endeavors to shape reasons for obeying norms and rules of common benefit in an open, diverse society.
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Title :	Mechanical Loading Stimulates Expression of Collagen Cross-Linking Associated Enzymes in Periodontal Ligament
Author :	Masaru Kaku, Juan Marcelo Rosales Rocabado, Megumi Kitami, Takako Ida, Yosuke Akiba, Mitsuo Yamauchi and Katsumi Uoshima
Journal :	Journal of Cellular Physiology: Accepted manuscript online: 7 SEP 2015 05:44AM EST | DOI: 10.1002/jcp.25184
Abstract :	Type I collagen, a major extracellular component of the periodontal ligament (PDL), is post-translationally modified by a series of specific enzymes. Among the collagen-modifying enzymes, lysyl oxidase (LOX) is essential to initiate collagen cross-linking and lysyl hydroxylases (LHs) to regulate the cross-linking pathways that are important for tissue specific mechanical properties. The purpose of this

	study was to investigate the effects of mechanical loading on the expression of collagen-modifying enzymes and subsequent tissue changes in PDL. Primary human PDL cells were subjected to mechanical loading in a 3D collagen gel, and gene expression and collagen component were analyzed. Wistar rats were subjected to excessive occlusal loading with or without intraperitoneal injection of a LOX inhibitor, β-aminopropionitrile (BAPN). Upon mechanical loading, gene expression of LH2 and LOX was significantly elevated, while that of COL1A2 was not affected on hPDL-derived cells. The mechanical loading also elevated formation of collagen α-chain dimers in 3D culture. The numbers of LH2 and LOX positive cells in PDL were significantly increased in an excessive occlusal loading model. Notably, an increase of LH2-positive cells was observed only at the bone-side of PDL. Intensity of picrosirius red staining was increased by excessive occlusal loading, but significantly diminished by BAPN treatment. These results demonstrated that mechanical loading induced collagen maturation in PDL by up-regulating collagen-modifying enzymes and subsequent collagen cross-linking which are important for PDL tissue maintenance.
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Journal :	Journal of Pharmaceutical Sciences: Article first published online: 7 SEP 2015 | DOI: 10.1002/jps.24621
Abstract :	Tablet coating is a common unit operation in the pharmaceutical industry, during which a coating layer is applied to tablet cores. The coating uniformity of tablets in a batch is especially critical for active coating, that is, coating that contains an active pharmaceutical ingredient. In recent years, discrete element method (DEM) simulations became increasingly common for investigating tablet coating. In this work, DEM was applied to model an active coating process as closely as possible, using measured model parameters and non-spherical particles. We studied how operational conditions (rotation speed, fill level, number of nozzles, and spray rate) influence the coating uniformity. To this end, simulation runs were planned and

	interpreted according to a statistical design of (simulation) experiments. Our general goal was to achieve a deeper understanding of the process in terms of residence times and dimensionless scaling laws. With that regard, the results were interpreted in light of analytical models. The results were presented at various detail levels, ranging from an overview of all variations to in-depth considerations. It was determined that the biggest uniformity improvement in a realistic setting was achieved by increasing the number of spray nozzles, followed by increasing the rotation speed and decreasing the fill level.
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Title :	The Effect of Sex and Age on Small Intestinal Transit Times in Humans
Author :	Monika Fischer and Hala M. Fadda
Journal :	Journal of Pharmaceutical Sciences: Article first published online: 26 AUG 2015 DOI: 10.1002/jps.24619
Abstract :	This study utilizes a novel approach of small bowel video capsule endoscopy for investigating the influence of sex and age on small intestinal transit times (SITT) in humans. A total of 81 outpatients undergoing investigations with the small bowel video capsule endoscope (SB-VCE) and meeting inclusion criteria were included in this study. Following an overnight fast, patients swallowed the SB-VCE with a glass of water. SITT were calculated from the first duodenal image to the first cecal image. This study showed that the SB-VCE provides accurate and reliable measurements of SITT under real-life conditions. A large inter-individual variability in SITT was observed, with times ranging from 50 to 460 min. This variability can have implications on drug absorption and bioavailability. The median SITT were 219 min for females and 191 min for males. Although SITT were 28 min longer in females than males, this difference was not found to be statistically significant ($p = 0.66$). No correlation was found between age and SITT (Pearson's correlation coefficient 0.19). Therefore, any drug bioavailability differences of modified release dosage preparations that are observed between adult patient groups of different age or sex are unlikely to be attributable to SITT.
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Title :	Comparison of Ensemble and Single Molecule Methods for Particle Characterization and Binding Analysis of a PEGylated Single-Domain Antibody
Author :	Lumelle A. Schneeweis, Linda Obenauer-Kutner, Parminder Kaur, Aaron P. Yamniuk, James Tamura, Neil Jaffe, Brian W. O'Mara, Stuart Lindsay, Michael Doyle and James Bryson
Journal :	Journal of Pharmaceutical Sciences: Article first published online: 7 SEP 2015 | DOI: 10.1002/jps.24624
Abstract :	Domain antibodies (dAbs) are single immunoglobulin domains that form the smallest functional unit of an antibody. This study investigates the behavior of these small proteins when covalently attached to the polyethylene glycol (PEG) moiety that is necessary for extending the half-life of a dAb. The effect of the 40 kDa PEG on hydrodynamic properties, particle behavior, and receptor binding of the dAb has been compared by both ensemble solution and surface methods [light scattering, isothermal titration calorimetry (ITC), surface Plasmon resonance (SPR)] and single-molecule atomic force microscopy (AFM) methods (topography, recognition imaging, and force microscopy). The large PEG dominates the properties of the dAb–PEG conjugate such as a hydrodynamic radius that corresponds to a globular protein over four times its size and a much reduced association rate. We have used AFM single-molecule studies to determine the mechanism of PEG-dependent reductions in the effectiveness of the dAb observed by SPR kinetic studies. Recognition imaging showed that all of the PEGylated dAb molecules are active, suggesting that some may transiently become inactive if PEG sterically blocks binding. This helps explain the disconnect between the SPR, determined kinetically, and the force microscopy and ITC results that demonstrated that PEG does not change the binding energy.
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Title :	Stress-Induced Activation of Apoptosis Signal-Regulating Kinase 1 Promotes Osteoarthritis
Author :	Qian-Shi Zhang, Gregory J. Eaton, Carol Diallo and Theresa A. Freeman

Journal :	Journal of Cellular Physiology: Accepted manuscript online: 7 SEP 2015 05:44AM EST | DOI: 10.1002/jcp.25186
Abstract :	Apoptosis signal-regulated kinase 1 (ASK1) has been shown to affect a wide range of cellular processes including stress-related responses, cytokine and growth factor signaling, cell cycle and cell death. Recently, we reported that lack of ASK1 slowed chondrocyte hypertrophy, terminal differentiation and apoptosis resulting in an increase in trabecular bone formation. Herein, we investigated the role of ASK1 in the pathogenesis of osteoarthritis (OA). Immunohistochemistry performed on articular cartilage samples from patients with OA showed ASK1 expression increased with OA severity. In vitro analysis of chondrocyte hypertrophy, maturation and ASK1 signaling in embryonic fibroblasts from ASK1 knockout (KO) and wild type (WT) mice was examined. Western analysis demonstrated an increase in ASK1 signaling commensurate with chondrogenic maturation during differentiation or in response to stress by the cytokines, tumor necrosis factor alpha or interleukin 1 beta in WT, but not in ASK1 KO embryonic fibroblasts. Surgically induced moderate or severe OA or OA due to natural aging in WT and ASK1 KO mice was assessed by microCT of subchondral bone, immunohistochemistry, histology and OARSI scoring. Immunohistochemistry, microCT and OARSI scoring all indicated that the lack of ASK1 protected against OA joint degeneration, both in surgically induced OA and in aging mice. We propose that the ASK1 MAP kinase signaling cascade is an important regulator of chondrocyte terminal differentiation and inhibitors of this pathway could be useful for slowing chondrocyte maturation and cell death observed with OA progression.
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Title :	Taking Science Seriously in the Debate on Death and Organ Transplantation
Author :	Michael Nair-Collins
Journal :	Hastings Center Report: Article first published online: 17 JUN 2015 | DOI: 10.1002/hast.459
Abstract :	The concept of death and its relationship to organ transplantation continue to be a source of debate and confusion among academics, clinicians, and the public. Recently, an international group of scholars and clinicians, in collaboration with the

	World Health Organization, met in the first phase of an effort to develop international guidelines for determination of death. The goal of this first phase was to focus on the biology of death and the dying process while bracketing legal, ethical, cultural, and religious perspectives. The next phase of the project will include a broader group of stakeholders in the development of clinical practice guidelines and will use expert consensus on biomedical criteria for death from the first phase as scientific input into normative deliberation about appropriate policies and practices. Surely, science alone cannot resolve the normative and philosophical questions intertwined in debates about moral status, legal and moral rights, the ethics of killing, and personhood and the nature of the self; however, scientific input is necessary for informed moral deliberation. An objective and unbiased investigation of the biology of death is independent of, and should be undertaken prior to, an analysis of the normative questions engendered by debate about determination of death. This strategy is explicitly endorsed by the International Guidelines for Determination of Death and reflects the prevailing view of these issues in the mainstream medical literature. However, this mainstream literature, exemplified by the IGDD group's recent report, does not exhibit any of the characteristics usually associated with a scientifically rigorous investigation, such as making empirically testable and falsifiable claims, a commitment to evidence and logic over authoritative assertion, or a willingness to revise hypotheses and theories in light of new evidence. Indeed, the core claims and methodologies of the mainstream medical literature on death, both of which are represented by the IGDD report, are not merely scientifically unjustified; they are not science at all. This situation creates a problem for the integrity of science and the academy, and it unjustly obscures and prevents legitimate democratic and moral deliberation about issues that, at bottom, are normative, not scientific.
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Title :	Personalized Screening for Breast Cancer: A Wolf in Sheep's Clothing?	
Author :	Stephen A. Feig |	
Journal :	American Journal of Roentgenology: 1-7. 10.2214/AJR.15.15293 | Sep 8, 2015 :	

Abstract :

Risk-based screening has different meanings to different people. For radiologists, risk-based screening means additional screening beyond the basic American College of Radiology (ACR), Society of Breast Imaging (SBI), and American Cancer Society (ACS) recommendations for annual mammography beginning at 40 years old and continuing as long as a woman is in generally good health and has a remaining life expectancy of at least 5–7 years and no comorbid conditions [1–3]. ACS recommends supplementary annual screening with breast MRI, in addition to mammography, for high-risk women, such as those with a lifetime risk estimate of 20–25% or greater, BRCA1 or BRCA2 mutation (or both), or a first-degree relative of a known BRCA1 or BRCA2 mutation carrier. ACS found insufficient evidence to recommend either for or against annual MRI for women having a 15–20% lifetime risk, such as those with a personal history of breast or ovarian cancer or biopsy-proven atypical ductal hyperplasia (ADH) or atypical lobular hyperplasia (ALH) [4]. Beyond guidelines for average-risk women, ACR and SBI have stipulated ages earlier than 40 years to begin annual mammography for some high-risk women, such as those with a BRCA1 or BRCA2 mutation (or both) or a first-degree relative positive for either mutation, those having a mother or sister with premenopausal breast cancer, or those with a personal history of biopsy-proven ductal carcinoma in situ (DCIS) or ADH [1].

Combined screening with both mammography and ultrasound has been shown to increase cancer detection rates by 30% over those with mammography alone in highrisk women [5, 6]. Some have recommended supplementary screening with ultrasound for women with heterogeneously or extremely dense breasts if they are in the 11–19% lifetime risk group [7]. ACR and SBI do not currently advocate ultrasound screening because of the low biopsy positive predictive value of 8–9%, its operator dependence, the lengthy examination time for handheld ultrasound, and the limited availability of breast ultrasound technologists [1]. However, ACR and SBI guidelines state that adjunctive screening ultrasound may be considered for women having dense breasts [1]. Automated ultrasound systems reduce both examination time and operator dependence and seem to yield detection rates similar to handheld ultrasound; however, recall rates and falsepositive biopsy rates remain high [8].

Database :	American Roentgen Ray Society