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Implementation of Radiology in Pharmaceutical Research

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ABSTRACT

The growing need for safer and more potent drugs makes the field of drug discovery more challenging. Drug discovery is a tedious and time taking procedure. Out of a thousand compounds, only one or two reaches the drug regulatory approval process. More information on the efficacy, safety, and mechanism of action should be sought from early-stage clinical trials to minimize late-stage attrition. Medical imaging has an enlarging role in new drug development. Radiology is the medical discipline that uses medical imaging to diagnose and treat diseases within the bodies of both humans and animals. Medical imaging can help answer key questions that arise during the drug development process. The role of medical imaging in new drug clinical trials includes identification of likely responders; detection and diagnosis of lesions and evaluation of their severity; and therapy monitoring and follow-up. Keeping given the importance of radiology in pharmaceutical development the present study is attempted to present all types of implementations of radiology in the drug development procedure.

INTRODUCTION

The cost of drug development always remains high with time-consuming. The ability to identify molecules with insufficient efficacy or safety issues before late-phase clinical development would reduce the costs and increase the rate of developing new therapeutics. To improve the efficiency along the path from laboratory concept to commercial product. One of the key elements in this new approach is the use of biomarkers, which are characteristics that are objectively measured and evaluated as indicators of normal biological processes, pathogenic processes, or pharmacologic responses to a therapeutic intervention [1]. The role of molecular imaging is likely to increase given trends in academia and industry to focus more on humans or nonrodent animal models that more clearly resemble humans for the early stages of drug development. Imaging technologies provide powerful insights into the distribution, binding, and other biological effects of pharmaceuticals. This progress is driven by several factors, including the growing technical capabilities of imaging methods and the increasing focus of drug developers on chronic diseases. Many of these applications where molecular imaging has been used in drug development have involved the retasking of technologies that were originally intended as clinical diagnostics. With greater experience and recognition of the rich information provided by *in vivo* molecular imaging, it is anticipated that it will increasingly be used to address the enormous time and costs associated with bringing a new drug to clinical launch. For drug development, molecular imaging has been used to (1) identify new targets, (2) evaluate detailed pharmacokinetics like biodistribution and appropriate dosing strategies, (3) evaluation of drug formulation development, (4) estimate the drug safety assessment along with drug-drug interactions. All these are associated with the application of radiology to select appropriate patient cohorts for initial testing and to serve as a surrogate endpoint in preclinical and clinical studies. The application of medical imaging in pharmaceutical clinical trials involves its use to determine disease predisposition; to identify likely responder patients; to diagnose lesions and evaluate their severity, and to monitor therapy effects and follow-up. Considerable emphasis has also been placed on linking pre-clinical imaging and clinical data to increase the success rate of clinical trials [2]. Pre-clinical imaging inappropriate disease animal models can contribute to the identification of new imaging biomarkers, whereby histological correlation can be obtained. It is anticipated that greater use of imaging during pre-clinical stages will facilitate better translation from animal models to human subjects. In this article, some basic principles of new drug development are explained and unique aspects of study design for clinical trials

with an imaging component are discussed. The main emphasis is on the application of medical imaging in therapeutic drug trials; however, many principles may be equally applicable to the development of novel imaging contrast agents and radiopharmaceuticals. Drug discovery involves the identification of a target (e.g., an enzyme or a receptor), and the design and optimization of a drug to interact with it. Preclinical studies conducted in animals are typically used to demonstrate the safety and effectiveness of a new drug. If promising, the new product then proceeds to clinical trials in human subjects, a process that usually involves multiple stages commonly known as phases [3,4]. The role of medical imaging in pharmaceutical clinical trials includes identification of likely responders; detection and diagnosis of lesions and evaluation of their severity; and therapy monitoring and follow-up. Imaging has an important role in drug safety monitoring, particularly when there are no other suitable biomarkers available. Despite the long history of radiological sciences, its application to the drug development process is relatively recent [5]. In the present study, an effort has been taken to highlight all prospects of the implementation of radiology in pharmacodynamic, pharmacokinetic, pharmacovigilance aspects in pharmaceutical research to provide broad prospects of drug discovery and make it easier, less time consuming and less expensive in some aspects.

Radiological Techniques for pharmaceutical research

Fluoroscopy and angiography are special applications of X-ray imaging, in which a fluorescent screen and image intensifier tube are connected to a closed-circuit television system. This allows real-time imaging of structures in motion or augmented with a radiocontrast agent. Radiocontrast agents are usually administered by swallowing or injecting into the body of the patient to delineate the anatomy and functioning of the blood vessels, the genitourinary system, or the gastrointestinal tract (GI tract). Two radiocontrast agents are presently in common use. Barium sulfate (BaSO4) is given orally or rectally for evaluation of the GI tract. Iodine, in multiple proprietary forms, is given by oral, rectal, vaginal, intra-arterial, or intravenous routes [6].

CT imaging uses X-rays in conjunction with computing algorithms to image the body. In CT, an X-ray tube opposite an X-ray detector (or detectors) in a ring-shaped apparatus rotate around a patient, producing a computer-generated cross-sectional image (tomogram). CT is acquired in the axial plane, with coronal and sagittal images produced by computer reconstruction. Continuing improvements in CT technology, including faster scanning times

and improved resolution, have dramatically increased the accuracy and usefulness of CT scanning, which may partially account for increased use in medical diagnosis [6].

MRI uses strong magnetic fields to align atomic nuclei (usually hydrogen protons) within body tissues, then uses a radio signal to disturb the axis of rotation of these nuclei and observes the radio frequency signal generated as the nuclei return to their baseline states. The radio signals are collected by small antennae, called coils, placed near the area of interest. An advantage of MRI is its ability to produce images in axial, coronal, sagittal, and multiple oblique planes with equal ease. MRI scans give the best soft tissue contrast of all the imaging modalities. With advances in scanning speed and spatial resolution, and improvements in computer 3D algorithms and hardware, MRI has become an important tool in musculoskeletal radiology and neuroradiology [6].

Microscopic imaging can enhance the drug discovery process by helping to describe how disease processes unfold and how potential therapies might intervene. Recently introduced technologies, and enhancements to existing techniques, are addressing technical issues that have limited the usefulness of microscopic imaging in the past. In particular, these innovations are improving spatial resolution, increasing tissue penetration, overcoming physical access issues, and enhancing experimental throughput. Notable recent trends, which are discussed in this article, include the development of super-resolution microscopes, the incorporation of multiphoton techniques into intravital and fiber-optic microscopy, and the automation of microscopy and image analysis for high-content screening. Together, these developments are augmenting the existing assays and disease models that are used in early drug discovery and, in some cases, enabling new ones [7].

Radiology in Drug Target Site Estimation

In vivo imaging is recognized as a useful method to provide biomarkers for target engagement; treatment response, safety, and mechanism of action. The identification of molecular pathways previously unknown to be involved in the pathophysiology of a disease is often a catalyst for the development of new treatments. Information on newly recognized pathways, proteins, or genes allows for the generation of lead candidates for therapy which can be tested by a variety of molecular biology approaches, most commonly in the form of automated high-throughput or focused compound screening processes [8,9].

Noninvasive imaging has played an increasing role in the process of cardiovascular drug development. This review focuses specifically on the use of molecular imaging, which has been increasingly applied to improve and accelerate certain preclinical steps in drug development, including the identification of appropriate therapeutic targets, evaluation of on-target and off-target effects of candidate therapies, assessment of dose-response, and the evaluation of drug or biological biodistribution and pharmacodynamics. Unlike the case in cancer medicine, in cardiovascular medicine, molecular imaging has not been used as a primary surrogate clinical endpoint for drug approval. However, molecular imaging has been applied in early clinical trials, particularly in phase 0 studies, to demonstrate proof-of-concept or to explain variation in treatment effect [10]. Teams in the pharmaceutical industry focused on the discovery and development of drugs for targets in the central nervous system have long recognized the value of target engagement for increasing confidence, guiding dose selection, and reducing risk at key stages of the discovery and development process [11]. PET target engagement studies are typically conducted by following a baseline PET scan, which uses only the radioligand to assess baseline target density, with a second scan in the same animal where the radioligand is administered after a test drug. In target-rich regions, the amount of target measured by the radioligand is lower in the PET scan after test drug administration compared to the baseline PET scan if the test drug competes with the radioligand for the target [12]. Assessment of the change in the amount of target in specific regions of interest before and after drug provides a quantitative assessment of target occupancy. Each pair of baseline and post-drug PET scans provides one value for occupancy at the exposure (dose) of the test drug. A dose- or exposure-to-occupancy relationship is obtained from a group of subjects receiving baseline and post-drug PET scans at various drug exposures and/or administering the radioligand at different time post-drug administration. The use of PET to determine such exposure-to-occupancy relationships has a significant impact on reduction and refinement because the same animal can be evaluated and recovered in drug occupancy PET studies multiple times. Previously, such relationships were determined from terminal animal studies where drug occupancy is assessed by ex vivo measurement of radioligand binding. A recent example of the use of PET for evaluating target engagement is provided by [11C] MK-8193, which is a PDE10 Aspecific PET tracer [13]. Inhibition of PDE10A, which enhances striatal output by increasing activity in the cGMP and cAMP signaling pathways, is a target being developed for the potential to provide efficacy on positive, cognitive, and negative symptoms of schizophrenia [14]. The development of neurokinin 1 (NK1) receptor antagonist provides a good example of both

cases. Because clinical PET receptor occupancy studies with [18F] SPARQ [15] indicated that the doses used in these studies achieved very high occupancies that effectively blocked the NK1 receptor system in the brain continues throughout the study period, confidence that the proof of concept was adequately tested led to the decision to stop pursuing those indications. However, for the prevention of acute and delayed chemotherapy-induced nausea and vomiting, aprepitant, a selective NK1 antagonist, was effective [16]. In this case, PET studies were used to pick the lowest dose that demonstrated full central nervous system target engagement, thereby optimizing the therapeutic window and minimizing potential drug-drug interactions associated with complex drug regimens used in oncology.

Radio image in Pharmacokinetic discovery

Medical imaging can help answer key questions that arise during the drug development process. The role of medical imaging in new drug clinical trials includes identification of likely responders; detection and diagnosis of lesions and evaluation of their severity; and therapy monitoring and follow-up. Nuclear imaging techniques such as PET can be used to monitor drug pharmacokinetics and distribution and study-specific molecular endpoints. In assessing drug efficacy, imaging biomarkers and imaging surrogate endpoints can be more objective and faster to measure than clinical outcomes, and allow small group sizes, quick results, and good statistical power. Imaging also has an important role in drug safety monitoring, particularly when there are no other suitable biomarkers available. Despite the long history of radiological sciences, its application to the drug development process is relatively recent [17,18]. A relatively small additional cost, the information can guide the clinical program by optimizing subsequent studies. PET has been applied to a wide number of drugs to demonstrate activity in vivo, from standard chemotherapy such as 5-fluorouracil to molecular agents such as those involved in tumor angiogenesis and antivascular therapy [19]. The use of PET imaging techniques to establish dosing regimens has been pursued [20,21]. PET can be applied before traditional Phase 1 studies to test compounds in humans at tracer (nonpharmacological active) concentrations. Such an approach uses as little as one-thousandth of the starting dose (i.e. microdosing) of a typical Phase 1 study. In broad terms, imaging of PK properties falls into two categories. The first category involves the radiolabeling of compounds that interact with or neutralize, agents from the environment, such as toxins, bacteria, and viruses. In this case, generally, only tissue concentrations of drugs are necessary. In the second category, if the drug is expected to alter or modulate some

aspects of the pathophysiologic process, then imaging studies are generally used to characterize the number of receptors, binding efficiency, and receptor occupancy [17]. As an example of the first category, the development of 18F-labeled antifungal agent fluconazole (Diflucan, Pfizer) was monitored by PET to establish the concentration of the drug in different organs, particularly at the site of infection. The imaging study found that the observed concentrations compared favorably to the concentrations required to inhibit in vitro pathogen growth [17, 22]. PET imaging of aprepitant (Emend, Merck) belongs to PK imaging of the second category.

Imaging in drug safety assessment

There is huge potential for imaging in drug safety evaluation during clinical trials. In preclinical studies, although in many cases drug safety information is better obtained through imaging, the information may also be obtained by histopathological means. There is huge potential for imaging in drug safety evaluation during clinical trials. In preclinical studies, although in many cases drug safety information is better obtained through imaging, the information may also be obtained by histopathological means. In clinical trials, imaging can sometimes be the only practical means to obtain drug safety information [23]. After organ toxicity occurred, serum and urine assays can be normal due to the function reserve of the affected organs, on the other hand, imaging offers the possibility to provide region-specific information about tissue abnormality. Also, some structural and functional information is better acquired through imaging techniques. For example, the quantification of tissue lipid content is easier with MRI or MR Spectroscopy than histology techniques. The hepatotoxicity can display manifestations such as hepatic steatosis, glycogen deposition, hepatocyte necrosis, and cholestasis. Imaging provides a valuable tool in safety studies when other biomarkers for toxicity, such as routine serum chemistry measures are not suitable. Hepatic steatosis, a common finding in drug safety studies, does not always correlate with elevations of hepatic serum enzymes. In some cases, drug-induced hepatic steatosis patients can present with the rapid evolution of severe hepatic failure, lactic acidosis, and ultimately death [24]. The heart has a limited capacity to repair itself. Toxic findings in the heart can be serious. While electrical activities of the heart can be monitored in clinical trials by ECG, due to delayed release of serum markers of cardiac damage, structural histopathologies, such as cardiomyocyte inflammation, degeneration, and necrosis lack conventional early biomarkers. Echocardiography has been widely used in preclinical and clinical drug safety evaluation for

new drug cardiotoxicity [25,26]. Echocardiography can be used to measure cardiac wall thickness, lumen volume, and cardiac output. It has further advantages that it provides low cost, realtime images. MRI has also been used to determine myocardial volume, wall thickness, left and right ventricular end-diastolic and end-systolic lumen volumes, stroke volume, and ejection fraction. Many non-invasive tests of kidney function can only show renal damage after the functional reserve had been eliminated. This reserve can compensate for up to 75% of the loss, which makes many serum and urine biomarkers insensitive for early kidney damages. MRI can offer advantages over methods that measure global functional changes by providing anatomically specific information on kidney injury. For example, a wide range of compounds can cause renal papillary necrosis (RPN). In the early development of RPN, there are few clinical symptoms and specific urine or blood biomarkers. The progression of renal damage is insidious and renal function may be severely compromised before the condition becomes obvious. The diagnosis of RPN tends to be made in the late stages of this disease after irreversible destructive changes have occurred. The use of imaging modalities has led to an increased positive diagnosis in the human population [27].

Standardization of imaging protocols

Several issues can arise when using imaging as an endpoint. As an example, dynamic contrast-enhanced MRI has become a popular method for measuring perfusion. In addition to the usual exclusion of patients who can't have an MRI, good perfusion imaging requires good cardiac output and the ability to place a large venous catheter. The MRI scanner itself must also be of reasonably recent vintage. There may also be variations in the appearance of images between the brand of scanner and software levels. Perfusion imaging works better in some body parts than others. Perfusion imaging usually does not produce an absolute value, but rather a value expressed as a ratio to some normal structure something which may be easier for body parts like a brain than for others like prostate. Having practical experience with imaging will help to sort out feasible imaging methods for the setting planned (e.g. tertiary academic center versus community setting).

Many clinical trials were conducted with the maximum feasible patient privacy, but this was often difficult with film images. For many studies, the clinical films were copied, and then the patient identifiers were obliterated using permanent markers and replaced with study identifiers. This was often a less-than-perfect process.

As mentioned previously, it is becoming increasingly important to document the collection of data, and that the data have a verifiable audit trail. The DICOM (DICOM Standards Committee) (Digital Image Communications in Medicine) standard facilitates this by embedding unique identifiers into each image. It also has added security mechanisms for secure transport and audit trails. [28].

Radiology in clinical trials

Clinical trials are an essential part of the process of documenting the effectiveness of a new therapy. While laboratory experiments attempt to simulate the human situation, validating efficacy, and safety in the population of interest remains a necessary step. The clinical study endpoints in clinical trials assist in determining the efficacy and safety of the drug therapy being researched. These endpoints which demonstrate the efficacy of a drug or therapy are assessed in most trials over long durations increasing the study period to years in some cases such as patient survival with serious and life-threatening diseases like cancer. Medical imaging technique measures the imaging biomarkers, which are used as indicators of the pharmacological response to therapy. Biomarkers and surrogate endpoints facilitate obtaining quick results with good statistical power even in small sample sizes. Also, the bias is reduced as the findings are evaluated without any direct patient contact. Furthermore, the imaging technique also reveals the subtle change indicative of the progression of therapy, which could be missed out by more subjective and traditional approaches. through extensive clinical work and related research, may also specialize in these radiology subspecialties like Breast imaging (mammograms), Cardiovascular radiology (heart and circulatory system), Chest radiology (heart and lungs), Emergency radiology, Gastrointestinal radiology (stomach, intestines, and abdomen), Genitourinary radiology (reproductive and urinary systems), Head and neck radiology, Musculoskeletal radiology (muscles and skeleton), Neuroradiology (brain and nervous system; head, neck, and spine), Paediatric radiology (imaging of children) [28].

For an imaging-based clinical trial, there are three essential components.

A realistic imaging protocol – protocol specifics where images are stored, processed, and evaluated. It is an outline that standardizes how the images are acquired using various modalities like PET, CT, and MRI.

1. Imaging centers- responsible for the collection of images, perform quality control and provide tools for data storage, distribution, and analysis. A standardized format is required for

images acquired at different time points so that the reliability of evaluation is maintained. Many clinical research organizations (CRO's) provide all the medical imaging facilities from protocol design to site management to data quality assurance and image analysis.

2. Clinical sites – generate images by recruiting patients to send back to the imaging center.

The current gold standard for assessing outcomes of Alzheimer's disease comprises behavioral or cognitive measures, but these suffer from poor reliability. MRI measurement of the whole brain or hippocampal atrophy rate can be used to support clinical outcome measures in therapeutic trials for Alzheimer's disease, and functional brain activity can be objectively quantified by measuring regional glucose metabolism with PET [29,30]. With clinical trials for MS, there has been great reliance on imaging data, especially using T2-MRI lesion burdens and the number of contrast-enhancing lesions. These imaging biomarkers can serve as a primary outcome measure in Phase I and Phase II trials, and also can serve as a secondary outcome in Phase III trials [31]. Imaging can also help to detect early disease and define stratified study groups. Imaging can be used to separate - as early as possible - responders from non-responders in patients undergoing therapeutic intervention. Many diseases have a "therapeutic window" in their course, during which medical intervention may have a more significant impact. In clinical trials, excluding patients who are not likely to progress can substantially increase the statistical power of a study and thereby reduce the number of patients and study duration needed to prove therapeutic efficacy. In one study examining advanced non-small-cell lung cancer, 55 patients were imaged with FDG-PET after a single course of chemotherapy. The results showed a statistically significant difference both in time to progression and overall survival between responders (i.e. those with the observed decrease in tumor metabolism as seen on PET) and non-responders. Similarly, in a study involving 40 gastroesophageal cancer patients, FDG-PET segregated responders from non-responders with a sensitivity of 93% and specificity of 95% [32]. When choosing whether to use imaging surrogate endpoints, it is important to bear in mind that imaging surrogates are most helpful when the clinical outcome is difficult to assess; and that changes detected by imaging may not always reflect the true clinical outcome.

SUMMARY

The present study revealed the importance of modern radiology techniques in drug discovery starting from preclinical to clinical trials. It can effectively be implicated for

pharmacodynamic evaluation, Pharmacokinetic estimation, and safety monitoring, particularly when there are no other suitable biomarkers. With improvements in imaging hardware, software, and tracer development, the breadth of applications of imaging in news drug development is likely to increase. Improved ability to identify molecules with insufficient efficacy or safety issues before late-phase clinical development is needed to reduce the costs and increase the rate of developing new therapeutics. In vivo imaging can provide information in preclinical studies (i.e., target engagement, treatment response, safety, or mechanism of action) that has a critical impact on pharmaceutical research. Most of the imaging modalities used in preclinical studies translate to the clinic. The noninvasive nature of in vivo imaging can also help to alleviate or minimize the potential for pain or distress in research animals. Again standardization of imaging acquisition, metadata reporting, electronic data management, and image interpretation/quantified cation will improve the accuracy of endpoint determination in clinical trials. Once validated, these improvements in image dependent endpoints may reduce the costs and time to complete clinical trials. The present study will be helpful for pharmaceutical research keeping in view that modern nuclear imaging techniques can noninvasively provide early in vivo assessment of bioactivity and help establish pharmacokinetic and pharmacodynamic profiles of new drugs.

REFERENCES

1. Campbell BR, Trotter DG, Hines CDG, Li W, Patel M, Zhang W, Evelhoch JL. *In Vivo* Imaging in Pharmaceutical Development and Its Impact on the 3Rs. ILAR J. 2016; 57 (2): 212–220.
2. Rudin M, Weissleder R. Molecular imaging in drug discovery and development. Nat Rev Drug Discov. 2003;2:123-31.
3. Wang YX. Medical imaging in pharmaceutical clinical trials: what radiologists should know. Clin Radiol. 2005;60:1051-7.
4. Murphy PS, McCarthy TJ, Dzik-Jurasz AS. The role of clinical imaging in oncological drug development. Br J Radiol. 2008;81:685-92.
5. Temple RJ. A regulatory authority's opinion about surrogate endpoints. In: Nimmo WS, Tucker GT, editors. Clinical measurement in drug evaluation. New York: Wiley; 1995. p. 1-22.
6. Bullen A. Microscopic imaging techniques for drug discovery. Nat Reviews Drug Disc. 2008;7:54–67.
7. Bulakci M, Cengel F. The role of radiology in diagnosis and management of drug mules: an update with new challenges and new diagnostic tools.Br J Radiol 2016; 89:1-13.
8. Rudin M, Weissleder R. Molecular imaging in drug discovery and development. Nat Rev Drug Discov. 2003;2:123–31.
9. Hughes JP, Rees S, Kalindjian SB, Philpott KL. Principles of early drug discovery. Br J Pharmacol. 2011; 162:1239–1249.
10. Lindner JR, Link J. Molecular Imaging in Drug Discovery and Development. Circ Cardiovasc Imaging; 2018;11.
11. Honer M, Gobbi L, Martarello L, Comley RA. Radioligand development for molecular imaging of the central nervous system with positron emission tomography. Drug Discov Today. 2014;19(12):1936–1944.
12. Cunningham VJ, Gunn RN, Matthews JC. Quantification in positron emission tomography for research in pharmacology and drug development. Nucl Med Commun. 2004; 25(7):643–646.

13. Cox CD, Hostetler ED, Flores BA, Evelhoch JL, Fan H, Gantert L, Holahan M, Eng W, Joshi A, McGaughey G, Meng X, Purcell M, Raheem IT, Riffel K, Yan Y, Renger JJ, Smith SM, Coleman PJ. Discovery of [11C]MK-8193 as a PET tracer to measure target engagement of phosphodiesterase 10A (PDE10A) inhibitors. Bioorg Med Chem Lett. 2015;25(21):4893–4898.
14. Jan K, Jacob N. PDE10A inhibitors: novel therapeutic drugs for schizophrenia. Curr Pharm Des. 2011;17(2):137–150.
15. Keller M, Montgomery S, Ball W, Morrison M, Snavely D, Liu G, Hargreaves R, Hietala J, Lines C, Beebe K, Reines S. Lack of the efficacy of the substance p (neurokinin1 receptor) antagonist aprepitant in the treatment of major depressive disorder. Biol Psychiatry. 2006;59(3):216–223.
16. Hargreaves R, Ferreira JC, Hughes D, Brands J, Hale J, Mattson B, Mills S. Development of aprepitant, the first neurokinin-1 receptor antagonist for the prevention of chemotherapy-induced nausea and vomiting. Ann N Y Acad Sci.2011;1222:40–48.
17. Wang YX, Deng M. Medical imaging in new drug clinical development. J Thorac Dis. 2010; 2: 245-252.
18. Cölfen H. Double-hydrophilic block copolymers: synthesis and application as novel surfactants and crystal growth modifiers. Macromol Rapid Commun. 2001;22:219–52.
19. 13. Hsieh Y, Box K, Taylor LS. Assessing the impact of polymers on the pH-induced precipitation behavior of poorly water-soluble compounds using synchrotron wide-angle x-ray scattering. J Pharm Sci. 2014;103:2724–35.
20. 14. Mah PT, Peltonen L, Novakovic D, Rades T, Strachan CJ, Laaksonen T. The effect of surfactants on the dissolution behavior of amorphous formulations. Eur J Pharm Biopharm. 2016;103:13– 22.
21. 15. Ghebremeskel AN, Vemavarapu C, Lodaya M. Use of surfactants as plasticizers in preparing solid dispersions of poorly soluble API: a selection of polymer-surfactant combinations using solubility parameters and testing the processability. Int J Pharm. 2007;328: 119–29.
22. Park SH, Choi HK. The effects of surfactants on the dissolution profiles of poorly water-soluble acidic drugs. Int J Pharm. 2006;321: 35–41.
23. Kellie SJ, Chaku J, Lockwood LR, O'Regan P, Waters KD, Wong CK. Late magnetic resonance imaging features of leukoencephalopathy in children with central nervous system tumors following high-dose methotrexate and neuraxis radiation therapy. Eur J Cancer 2005;41:1588- 96.
24. Diehl AM. Nonalcoholic steatohepatitis. Semin Liver Dis1999;19:221-9.
25. Mimbs J W, O' Donnel l M, Mi l ler JG, Sobel BE. Detect ion of cardiomyopathic changes induced by doxorubicin based on quantitative analysis of ultrasonic backscatter. Am J Cardiol 1981;47:1056-60.
26. Bianchi G, Albanell J, Eiermann W, Vitali G, Borquez D, Vigano L. Pilot trial of trastuzumab starting with or after the doxorubicin component of a doxorubicin plus paclitaxel regimen for women with HER2-positive advanced breast cancer. Clin Cancer Res 2003;9:5944-51.
27. Bach PH, Nguyen TK. Renal papillary necrosis - 40 years on. Toxicol Pathol 1998;26:73-91. Erickson BJ, Buckner JC. Imaging in clinical trials. Cancer Inform. 2007; 4: 13–18.
28. Jack CR Jr, Slomkowski M, Gracon S, Hoover TM, Felmlee JP, Stewart K, et al. MRI as a biomarker of disease progression in a therapeutic trial of milameline for AD. Neurology 2003;60:253-60.
29. Matthews B, Siemers ER, Mozley PD. Imaging-based measures of disease progression in clinical trials of disease-modifying drugs for Alzheimer's disease. Am J Geriatr Psychiatry 2003;11:146-59.
30. Rao AB, Richert N, Howard T, Lewis BK, Bash CN, McFarland HF, et al. Methylprednisolone effect on brain volume and enhancing lesions in MS before and during IFNbeta-1b. Neurology 2002:59:688-94.
31. Weber WA, Petersen V, Schmidt B, Tyndale-Hines L, Link T, Peschel C, et al. Positron emission tomography in non-small-cell lung cancer: prediction of response to chemotherapy by quantitative assessment of glucose use. J Clin Oncol 2003;21:2651-7.
32. Weber WA, Ott K, Becker K, Dittler HJ, Helmberger H, Avril NE, et al. Prediction of response to preoperative chemotherapy in adenocarcinomas of the esophagogastric junction by metabolic imaging. J Clin Oncol 2001;19:3058-65.