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DRUG DESIGN AS AN IMPORTANT APPROACH IN THE DRUG DISCOVERY: AN OVERVIEW

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ABSTRACT

Designing of drugs have major role in the drug discovery and development of bioactive compounds over last three decades. Novel software-based methods such as molecular modelling, structure-based drug design, structure-based virtual screening, ligand interaction and molecular dynamics are considered to be powerful tool for investigation of pharmacokinetic and pharmacodynamic properties of drug, and structural activity relationship between ligand and its target. Computational approaches such as docking confer interaction of small molecules with structural macromolecules and thereby hit identification and lead optimization. These methods are faster, and accurately provide valuable insights of experimental findings and mechanisms of action. In addition, appropriate implementation of these techniques could lead to a reduction in cost of drug designing and development. Currently in biomedicine sciences this software is exhibiting imperative role in the different phases of drug discovery. The review discusses working principle and successful applications of most commonly used software for drug designing and development. A non-systematic review of the current literature was undertaken to enumerate the various strategies employed in drug design to improve the success rates in the pharmaceutical research and development. The review covers the exploitation of genomics and proteomics, complementarity of target-based and phenotypic efficacy screening platforms, drug repurposing and repositioning, collaborative research, focusing on underserved therapeutic fields, outsourcing strategy and pharmaceutical modelling and artificial intelligence.

KEYWORD: DDDPlus, GastroPlus, MapCheck, Ligand interactions and molecular dynamic using Auto Dock, Schrodinger, GOLD, BioSuite, QSARPro, GeneSpring, Imaging software Scge-Pro, AMIDE, Discovery Studio Visualizer.

1. INTRODUCTION

Drug design is an creative process of finding new drugs based on knowledge of biological targets. In the simplest sense, drug design includes the design of molecules whose shape and charge are complementary to their interacting and binding molecular targets. Drug design is often, but not always, based on computer modelling techniques and bioinformatics approaches in the age of big data. In addition to small molecules, bio pharmacy, especially therapeutic antibodies, are an increasingly important class of active ingredients, as well as computer-assisted methods to improve the affinity, selectivity, and stability of these protein-based therapeutics.[1]

Drug development and research includes preclinical studies on cell-based and animal models, as well as clinical studies in humans, eventually advancing to the regulatory approval stage of to market the drug. increase. Modern drug discovery identifies screening hits, and optimizes those hits for affinity, selectivity (to reduce the possibility of side effects), efficacy of, metabolic stability and oral bioavailability. If drugs that meet all of these requirements are identified, the drug development process begins prior to clinical trials.[2-3]

Drug discovery is a long process that takes about 10-15 years[4] and costs up to US $ 2,558 million before the drug hits the market.[5] It is a multi-step process that begins with preclinical and clinical research in the process of identifying suitable drug discovery targets, validating drug discovery targets, discovering lead generation, optimizing lead molecules and then discovery of new drug.[6]

High cost, high risk, uncertainties in results, longer time span and highly complex procedures are the biggest challenges in new drug development. To overcome these problems, new and more cost-effective drug discovery and design methods (Figure 1) must be adopted, including Software and computational drug design, molecular docking, etc.[7,8] This review highlights the most commonly used programs and potential applications used in drug discovery.

1.1 Drug Designing: A drug is defined as a substance used to treat, alleviate, diagnose, treat, or prevent disease. The development of potential drugs begins with the study of the biochemical and physiology of diseases for which pharmaceutical intervention is possible. Drug design, also known as rational drug design or simply rational design, is the ingenious process of finding new drugs based on knowledge of biological targets. A drug is a term pioneered by Albert to denote a pharmacologically inactive chemical moiety that can be used to temporarily alter the physicochemical properties of a drug to increase its usefulness and reduce its associated toxicity.[10]

Converting a protein, from a primary sequence to a three-dimensional structure gives structural biologists some ideas in drug design. Conservative protein sequences can provide similar structures, and placing protein structures in a database helps computer structure definition, build algorithms and predict three-dimensional structures based on primary sequences. Pharmaceuticals are defined as substances used to treat, alleviate, diagnose, treat, or prevent disease. The development of any potential drug begins with the study of the biochemical and physiology of diseases for which drug intervention is possible.[9]

The drug design can be used as tool to

a) Improve permeability and absorption as membrane permeability significantly affects drug efficacy.
b) Increase the dissolution of the drug molecule from the dosage form as absorption is a limiting step.
c) Study distribution profile, before a drug reaches its physiological goal and has the desired effect.[11,12]

1.2. Drug Discovery: Drug discovery is a long-term, interdisciplinary effort. It is a sequential process that starts with target and lead discovery, followed by in vitro and in vivo lead optimization and preclinical studies to evaluate if a compound meets a predetermined set of criteria to begin clinical development.[13,14] Efficient technologies including innovative genomics, proteomics, bioinformatics and combinatorial chemistry, high-throughput screening (HTS), virtual screening, de novo, in vitro design, in silico ADME screening and structure-based design.[15]

2. Approaches to Drug Discovery

2.1. Strategies for Improving the Success of Drug Discovery and Development

2**.1.1. Key Approaches:** Several strategic approaches to improving the effectiveness of drug discovery has been used. These include the use of genomic and proteomics, complementarity of phenotypic and target screening platforms, expansion of use of existing drug molecules through repurposing and relocation, use of collaborative research, research into underserved therapeutic areas, outsourcing and pharmaceutical modelling, and artificial maintenance of intelligence etc. Therapeutic domains, outsourcing, pharmaceutical modelling and artificial intelligence are important part of drug discovery.

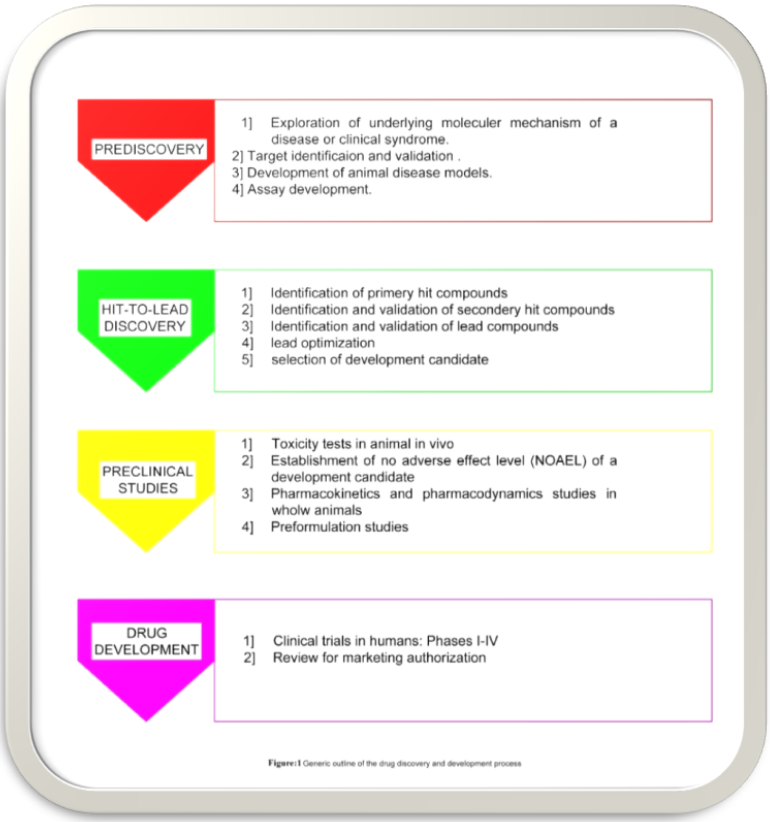

Figure: 1 General overview of drug discovery and development processes.

2.2 Exploitation of genomics and proteomics: It is an established fact that majority of diseases have a molecular or genetic ethology.[16,17] Some condition including sickle cell disease, cystic fibrosis, muscular dystrophy and Huntington disease are caused by single gene mutations.[16] Syndromic conditions such as diabetes and cardiovascular diseases have multifactorial causes including multiple gene mutations confounded by and lifestyle factors.[16] In the concept of drug discovery, genes have therefore been classified as disease genes, disease-modifying genes, and druggable genes.[18] Disease genes are those whose mutations cause or predispose a person to the development of a given disease.[19] Disease-modifying genes encode functional proteins whose altered expression is directly linked to the etiologicand progression of a given disease. Druggable genes encode proteins that possess recognition domains capable of interacting with drug molecules eliciting a pharmacological response.[20]

In the current era of target-based drug discovery, it is imperative that the target is scrupulously identified and validated to establish its essentiality in the disease phenotype. This prevents downstream attrition with available data indicating that a significant proportion (52%) of drug failure in clinical trials is due to poor efficacy.[21,22]

Exploitation of genomics is not restricted to target identification and validation. Rather, recent trends in pharma R&D show that genomics may be employed in the recruitment of study participants for clinical trials with the selection favoring those subjects more likely to benefit from the intervention being trialed. This ensures that the effect of the drug will be evident if the drug is indeed effective against the target disease and absent if ineffective. The outcome so observed would therefore be attributable to the therapeutic intervention and shielded from other confounders. Genomics can also be used as a predictive tool to forecast potential toxicities emanating from a specific molecule.[23]

2.3 Repurposing and repositioning of existing drug molecules: Drugs that have been developed for a specific therapeutic application may in the course of their clinical use potentially reveal beneficial effects in other therapeutic areas outside the scope of their original indications. These molecules may, therefore, be evaluated for use in the new diseases areas without requiring structural modifications (drug repurposing).[24] The two approaches have the potential to resuscitate/rescue previously abandoned molecules as well asexpanding the therapeutic applications of drugs in current use. Examples of successful applications of drug repurposing and repositioning are given in following Table 1. Theyinclude the drug miltefosine which was developed in the1980s as an antitumor agent but abandoned due todose-limiting gastrointestinal side effects. The drug was refocused as an antileishmanial drug with significant success.[25]

Table 1: Examples of successfully repurposed drugs.

Drug	Original indication	Repurposed indication
Zidovudine	Anticancer	Antiretroviral
Miltefosine	Anticancer	Leishmaniasis
Sildenafil	Pulmonaryarterial hypertension	Erectile dysfunction
Thalidomide	Immunosuppressant	Lymphoproliferative syndrome
Bupropion	Antidepressant	Smoking cessation aid
Rituximab	Anticancer	Rheumatoid arthritis

3. Drug Design: The development of a new drug starts with the design of suitable candidate compounds, so-called “Ligands,” which are selected on the basis of how these compounds are recognized by the target protein and binds to it. “Ligbuild” is a powerful tool to build a legend just based on a protein structure in Brookheaven format. Performing experiments to know protein dynamics is expensive as well as time-consuming. The only alternative to computer simulation of the dynamics of molecule (MD simulation)becoming increasingly important to identify which molecular properties are important and what are the molecular interactions responsible for binding. Evaluation of binding agent is done by scoring approach. “Score” is a tool to evaluate the binding affinity of protein-ligand complex with known 3D structure. Candidate molecules are further screened out on several criteria. Permeability across the bio membrane is an important characteristic.

The activity prediction studies on the basis of shape of the molecule include

i) Fast and efficient clustering of molecules based on molecular shape.

ii) Field-based similarity computation of molecular structure.

iii) Flexible Quantitative Structure Activity Relationships (QSAR) analysis of molecules based on shape cluster.

A Comparative Molecular Field Analysis (CoMFA) has been widely used as a type of 3D QSAR method during the last 10 years[26] and plays important role in the drug design.

4. Software's Used in Drug Design

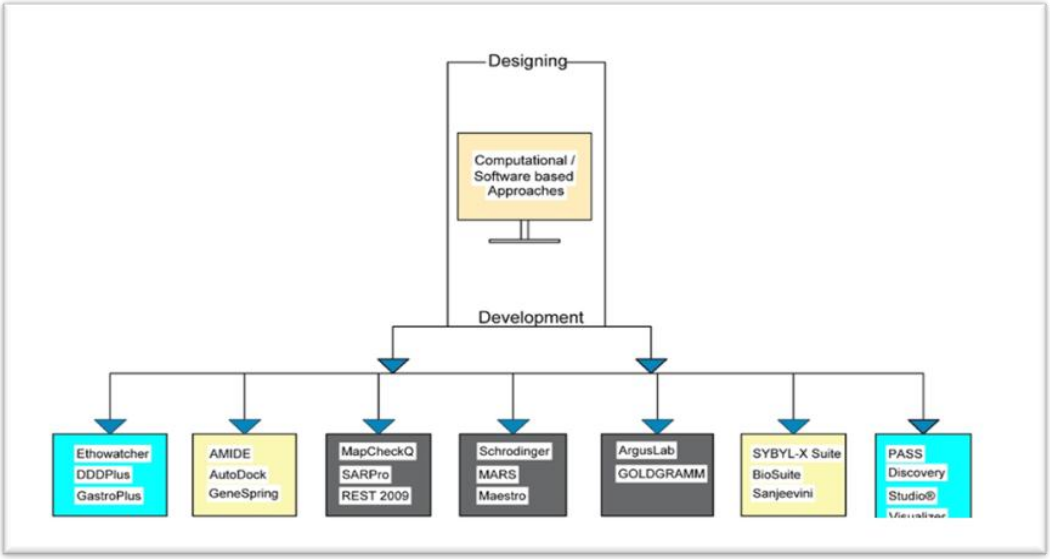

Figure: 2 Software based approaches for drug designing and development.

4.1 DDDPlus (Dose Dissolution and Disintegration software): DDDPlus (Dose Disintegration and Dissolution Plus) is used to study disintegration and dissolution pattern of dosage form and active ingredients. It is an advanced computer program employed by formulation scientists to simulate in vitro disintegration and dissolution of active pharmaceutical ingredients (API) and excipients under different experimental conditions. In the formulation of new API, a single calibration experiment is generally required, after which DDDPlus predicts how changes in formulation or experimental parameters will affect the dissolution rate. This software provides precise information of dissolution and disintegration rate so it is not necessary to rely on conventional 'cut and try' methods to finalize a formulation design.

- Physicochemical properties of the formulation ingredients under study: pKa's, solubility, diffusion coefficient, and density.
- Manufacturing properties for immediate release dosage forms.
- Particle size distribution for each of the formulation ingredients.
- Different flow patterns and fluid velocities for each experimental apparatus.
- Interactions between the active ingredient and formulation excipients.
- Microclimate pH-dependence of solubility and dissolution/precipitation.
- Micelle-facilitated dissolution through the incorporation of surfactants in the media.

Uses

1. Calculates the fluid velocity automatically based on the instrument speed and apparatus type.
2. DDDPlus has an optimization module that calibrates drugs dissolution rate using a single experimental data set.

4.2. GastroPlus (simulation software for drug discovery and development): GastroPlus is a mechanistically based simulation software package that simulates intravenous, oral, oral cavity, ocular, intranasal and pulmonary absorption, pharmacokinetics, and pharmacodynamics in human and animals. Model parameters can be fitted to data for a single recordor across multiple records simultaneously. The program will run one simulation for each record each time and it changes the values of one or more model parameters. Typically, hundreds of iterations will be performed, each with N simulations, where N is the number of records whose observations are being used to compare predicted and observed values.

Objective function weighting is user-defined, and includes the most common weighting schemes.[27,28]

Uses

1. To study Transporter-based drug-drug interactions.
2. To study Metabolic and/or transporter induction.
3. Can be linked with the industry's 1-ranked dissolution/absorption (ACAT) model.
4. Can be used with either compartmental or physiologically based pharmacokinetics (PBPKPlus).
5. To apply competitive and/or time-dependent inhibition kinetics by parent and/or metabolite.
6. Simulate DDIs for any species (human, beagle, rat, mouse, rhesus monkey, cynomolgous monkey, rabbit, or cat).
7. Account for enzyme expression level differences in various populations.
8. Built-in tool to easily calculate the fraction metabolized from in vitro assays.

4.3: MapCheck: The MapCheck compare absolute dose measurements of both systems with ion chamber results.

It compares IMRT QA process of Sunnuclear's MapCheck and Varian's Portal Dosimetry. The MapCheck system create verification plan for each field, export calculated dose map (Frontal) to MapCheck for each field, calibrated diode array prior to collecting data. Standard deviation increases with plan complexity. The average measured dose is independent of plan complexity. It is user friendly software for data analysis, easier commissioning process and generates comprehensive report.

Use

1. MapCheck used for IMRT verification.
2. Small detectors identify MLC.
3. Dose based EPID IMRT QA done by using MapCheck.[29,30]

4.4. Ligand interactions and molecular dynamic using AutoDock: AutoDock is an automated program employed to predict ligand and protein (bio-macromolecular targets) interactions. Continuous advancement in bimolecular X-ray crystallography helps to provide structural information of complex biomolecules such as protein and nucleic acids. These structures could be employed as targets for new drug molecules in controlling human, animal and plant diseases and disorders, and understanding of fundamental aspects of biology.

Multiple steps are employed for AutoDock calculations:

• Preparation of coordinate files using AutoDock tools.
• Precalculation of atomic affinities using AutoGrid.
• Docking of ligands using AutoDock.
• Analysis of results using AutoDock Tools.

Uses

1. Identification of aromatic rings.
2. Used to explore the conformational states of a flexible ligand, using the maps generated by AutoGrid to evaluate the ligand-protein interaction at each point in the docking simulation.[31,32]

4.5 Schrodinger: Schrodinger software has wide range of applications that can solve most of the challenges these bio-molecules will bring. It highlightsparticular advances in molecular modeling, molecular dynamics, ligand-receptor docking, and biologics that were designed to handlethese challenges. Structure based properties of molecule such as understanding of conformational changes and hydrophobicity of structures can be analysed by this software. Confirmation of macrocycles is performed by utilizing a high-performance molecular dynamics simulation engine for bimolecular systems that combines speed and accuracy. This intern provides information atomic movements of macrocycles that further used to understandshape, stability, and energetics. Schrodinger provides powerful andintuitive graphical interfaces for system setup, running simulations, and analysing trajectories.

The molecular dynamics simulations software is employed to studya series of stabilized stapled α-helical peptides at different temperatures. The predicted α-helical propensities derived from the simulationswere in good agreement with the experimentally observed circular dichroism melting curves. The local flexibility of key residues could berelated to differences in affinity of the stapled peptides binding to MDM2. These simulations explore new approaches for the α-helicalstapled peptides designing and development of potent inhibitors of α-helical protein–protein interfaces.[33,34]

Use

1. To study molecular dynamics simulation studies.
2. To study quantum mechanics.
3. To study prediction of binding affinity.

4.6 GOLD (Genetic Optimization for Ligand Docking): GOLD (Genetic Optimization for Ligand Docking) is a genetic algorithm to provide docking of flexible ligand and a protein with flexible hydroxyl groups. This software uses a scoring function which is based on favourable conformations found in Cambridge Structural Database and on empirical results on weak chemical interactions. Different values of the genetic algorithm parameters are used to control the balance between the speed of GOLD and the reliability of its predictions. It gives reliable results and correct atom typing for both protein and ligand. GOLD is a part of GOLD Suite software that also includes two additional software components, Hermes and GoldMine. GOLD provides all the functionality required for docking ligands into protein binding sites from prepared input files. The Hermes visualize is used for the preparation of input files for docking with GOLD, visualization of docking results and calculation of descriptors. The input files like the addition of hydrogen atoms, including those necessary for defining the correct ionization and tautomeric states of protein residues are obtained from Hermes. The Hermes visualizer is also employed for interactivedocking setup such as for defining the binding site and the setting ofconstraints. Gold Mine is a tool for the analysis and post-processing ofdocking results. GOLD will likely be used in conjunction with a modeling program to create and edit starting models.[35,36]

Use

1. It is used for Protein-Ligand Docking by using Genetic Algorithm.
2. Forbinding mode predictions.

4.7 BioSuite: BioSuite together utilize the functions of macromolecular sequenceand structural analysis, chemo informatics and algorithms for aiding drug discovery. It is organized into four major modules containing 79different programs making it one of the few comprehensive suites thatcater to a major part of the spectrum of bioinformatics applications. Thefour major

modules Genome and Proteome Sequence Analysis, 3DModeling and Structural Analysis, Molecular Dynamics Simulations and Drug design, are made available through a convenient graphics-userinterface along with adequate documentation and tutorials.

The Genome and Proteome Sequence Analysis module of Bio Suite deals with the applications relating to the analysis of the nucleic acid and protein sequences, not only of individual molecules, but also of complete genome and proteome sequences. This module would enable to annotate genomes, predict protein secondary structures, derive a phylogenetic relationship among organisms and compare two genomes for similarities at the gene or protein level. The 3D modeling and analysis module has capabilities to build, analyse and predict three dimensional structures of macromolecules and macromolecular complexes. The 'Simulations' module essentially simulates the behaviour of a molecule, in terms of its three dimensional structure.[37,38]

Uses

1. To study Genome analyzing and sequence analyzing.
2. To study 3D modeling, simulation, structural changes, drug design, pathway modeling, SNP analysis and comparative genomics.

4.8 QSARPro: This software identifies of relationship of a molecular activity or property with the structural parameters, analysis of such relationships and rapid predictions using reliable statistical modeling. It is employed to evaluate more than 1000 molecular descriptors including physicochemical, topological and electro-topological, information theory based, quantum mechanical, electrostatic and hydrophobic, alignment independent, MMFF atom types and so on. QSAR modeling typically involve activities such as descriptor choice and calculation, statistical evaluation of the calculated descriptors, training and test set assignment, regression and results analysis. It evaluates multiple options for classes of descriptors, test set, choice of linear or nonlinear regression and choice of regression technique to determine the option that is most suitable to a particular project.[39,40]

Use

1. To explore and exercise various combinations of variable selection methods and regression methods.
2. To Alignngiven set of molecules in the protein active site with respect to the co-crystal ligand to develop a basis for the placement of ligand.
3. Protein-protein interaction studies.

4.9 GeneSpring: This software represents a collection of samples for which arrays have been run in order to answer a specific scientific question. In this, anew experiment is created from selected project. New experiment byloading samples of a particular technology and performing a set ofcustomary pre-processing steps like, normalization, summarization, andbaseline transform etc. which will convert the raw data to a state whereit is ready for analysis. Multiple samples are involved in the experiment with which it was created, multiple interpretations, which group thesesamples by user-defined experimental parameters, and all other objectscreated as a result of various analysis steps in the experiment. The software consists of three parts, a UI layer, a database and a filesystem. The file system is where all objects are stored physically. Theseare stored in the app/data subfolder in the installation folder. A SQLdatabase carries all annotations associated with the various objects inthe file system properties like notes, names etc.[41]

Use

1. Batch effect correction.
2. Circular binary Segmentation.
3. Filters to identify copy-neutral LOH events and regions of allelicimbalance.
4. Identify common variations across a set of samples.

4.10. Imaging software Scge-Pro: SCGE-Pro is widely used for single cell gel electrophoresis or Comet assay. It is a collaborative project with Computer Division on development of imaging software for cytogenetic and DNA damage analysis. Genotoxicity of environmental factors such as low and high LET radiations, drugs, chemical mutagens and carcinogens is investigated byemploying Comet assay. In this imaging method fluorescence in-situ hybridization (FISH)technique is used to measure gene specific repair in relation to total DNA or loss of heterozygosity (LOH) for single gene. An intracellularDNA damage in different cell as well as repair kinetics of eukaryotic cellis investigated through these assays. Studies such as effect of 3.3 MeVproton beams on DNA damage of mouse peripheral blood leukocytes iscarried out using Neutral Comet assay.[42,43]

Uses

1. Clinical application such as prenatal diagnosis, DNA repair deficiency syndrome, diabetes, cancer susceptibility, genomic instability.
2. Human bio-monitoring: Aging and nutrition.
3. Environmental bio-monitoring: Aquatic or terrestrial conditions.
4. Genotoxicity evaluation of radiation and chemicals in human and animal models.
5. Clinical and molecular epidemiology, agricultural sciences, radiation biology

4.11 AMIDE (A Medical Image Data Examiner): AMIDE is developed in such a way that; it should provide multimodality volumetric medical image analysis. Data sets (e.g., PET, CT, MRI) and regions of interest (ROI's) are logically organized within atree structure so that an unlimited number of these items can be displayed, modified, and analysed simultaneously.

The data hierarchy within AMIDE is built around a tree abstractioncomposed of a succession of objects such as data sets and ROI's eachobject in AMIDE is assigned its own Euclidean space, and the location ofthis local coordinate frame is defined with respect to the global coordinate frame.

The following object types have been implemented in AMIDE:
• Study the root object in AMIDE, this object is used for grouping a setof related medical images and ROIs into a logical unit, and keepstrack of parameters that affect the whole study.
• Data set used for encapsulating volumetric medical images, thisobject contains the raw image data along with information neededfor interpreting that data (voxel sizes, colour table, thresholds, patient weight, injected dose, calibration factors, etc.).
• ROI region of interest objects specify a volume of space over whichstatistics are to be calculated. Currently implemented ROIs are ellipsoids, boxes, cylinders, and is contours (2D or 3D).
• Fiducial Marker Fiducial reference markers encode only a locationin space and are used forrigid body registration of data sets.

Uses
1. Provides multi-modality medical image analysis to the molecular imaging research community.
2. Gives interactive "wizard" interfaces for making advanced medical imaging algorithms (e.g., factor analysis and cardiac polar maps).[42,43]

4.12 Discovery Studio Visualizer: Discovery Studio Visualizer (DS Visualizer) is used for viewing, sharing and analysing protein and small molecule data. It is a free andemployed for both small molecule and macromolecule applications. It allows data to be transferred and analyze data in several formatslike graphics, 3D structures, SMILES and sequences. The requiredstructures and sequence can be downloaded from PDB or NCBI. Molecular properties can be explored by editing structures and performing calculations.

Uses. Visualization
1. It is used to Study advanced molecular visualizations.
2. It is used to study publication quality graphics.[44,45]

5. Factors Affecting the drug discovery and development process: There are a number of factors that affect the drug discovery and development process. Important ones are as follows:

a) Medicinal objective: In general, more precise the medicinal objective, the less likely it is to develop a new drug; for example, it is easy to develop an antacid but much more difficult is to develop specific proton-pump inhibitor. Thus, the medicinal requirements affect the likelihood of success or failure in new drug discovery.

b) Ability of Medicinal chemist: The attributes of the chemist will influence the outcome of evolving new drugs on the basis of knowledge of chemistry of lead molecule and biology of diseased state.

c) Screening facilities: A successful and rapid mass screening mainly depends on the capacity to evaluate a large number of compounds and detect potentially clinically useful drugs in a very short span of time.

d) Drug development facility: Good facilities with interdisciplinary efforts by chemistry, biology, pharmacy and medical groups are necessary for drug development.

Cost of new drug: The following three factors affect the cost of drug development-
(i) Number of compounds synthesized: Of the about 5000-10,000 compounds studied, only one drug reaches the market.
(ii) Nature of the lead molecule: Cost of production will be high if the lead molecule is prepared by an expensive route.
(iii) Standards required for new drugs: The standards required byregulatory authorities prior to release of a drug into the market have increased dramatically. In the discovery phase, each drug cost about $350 million. The Food and Drug Association processes I, II and III cost another $150 million. This brings the total to about $500 million for each drug put on to the market for consumers.[26]

SUMMARY

The software-based drug design is an important aspect and plays a crucial role in the discovery of new drugs. Implementation of software technique provided an opportunity for identification of lead compounds and contributing to major level in drug discovery. This review focusses on various such softwares which are used in drug design and their application in drug design. These softwares includes DDDPlus, GastroPlus, MapCheck, Ligand interactions and molecular dynamic using Auto Dock, Schrodinger, GOLD, BioSuite, QSARPro, GeneSpring, Imaging software Scge-Pro, AMIDE, Discovery Studio Visualizer etc. Use of these software make discovery of drug time saving and cost effective.

REFERENCES

1. Luu KT, Kraynov E, Kuang B, Vicini P, Zhong W-Z. Modeling, Simulation, and Translation Framework for the Preclinical Development of Monoclonal Antibodies. The AAPS Journal, 2013; 15(2): 551–8.
2. Zhou S-F, Zhong W-Z. Drug Design and Discovery: Principles and Applications. Molecules, 201; 22(2): 279.
3. Pammolli F, Magazzini L, Riccaboni M (2011) The productivity crisis in pharmaceutical R&D. Nat Rev Drug Discov, 10: 428–438. https://doi.org/10. 1038/nrd3405.

4. J. A. DiMasi, H. G. Grabowski, and R. W. Hansen, "Innovation in the pharmaceutical industry: New estimates of R&D costs," Journal of Health Economics, 2016; 47: 20–33.
5. D. Vohora and G. Singh, Pharmaceutical Medicine and Translational Clinical Research, Academic Press, 2018.
6. Hassan Baig M, Ahmad K, Roy S, Mohammad Ashraf J, Adil M. Computer Aided Drug Design: Success and Limitations. Current Pharmaceutical Design, 2016; 22(5): 572–81.
7. Hodos RA, Kidd BA, Shameer K, Readhead BP, Dudley JT. In silicomethods for drug repurposing and pharmacology. Wiley Interdisciplinary Reviews: Systems Biology and Medicine, 2016; 8(3): 186–210.
8. Wasko MJ, Pellegrene KA, Madura JD, Surratt CK. A Role for Fragment-Based Drug Design in Developing Novel Lead Compounds for Central Nervous System Targets. Frontiers in Neurology, 2015; 6.
9. Random House Webster's unabridged dictionary. Choice Reviews Online, 1997; 34(09): 34–4839a34–4839a.
10. ALBERT A. Chemical Aspects of Selective Toxicity. Nature, 1958; 182(4633): 4213.
11. Karaman R, Fattash B, Qtait A (2013) The future of prodrugs - design by quantum mechanics methods. Expert Opin Drug Deliv, 10: 713-729.
12. Chan OH, Stewart BH (1996) Physicochemical and drug-delivery considerations for oral drug bioavailability. Drug Discov Today, 1: 461- 473. 23.
13. DiMasi JA, Hansen RW, Grabowski HG. The price of innovation: new estimates of drug development costs. Journal of health economics [Internet], 2003; 22(2): 151–85. Available from: https://www.ncbi.nlm.nih.gov/pubmed/12606142
14. DiMasi JA. The Value of Improving the Productivity of the Drug Development Process. Pharmacoeconomics, 2002; 20(Supplement 3): 1–10.
15. Gatto J. The changing face of bioinformatics. Drug Discovery Today, 2003; 8(9): 375–6.
16. Dean M. From Gene to Therapy: Understanding Human Disease through Genetics. Colloquium Series on The Genetic Basis of Human Disease, 2017; 5(1): i–89.
17. King R, Rotter J, Motulksy A (2002) The genetic basis of common diseases, 2nd ed, 8: 375-376.
18. Hopkins AL, Groom CR (2002) The druggable genome. Nat Rev Drug Discov, 1: 727–730. https://doi.org/10.1038/nrd892.
19. Dixon SJ, Stockwell BR (2009) Identifying druggable disease-modifying gene products. Curr Opin Chem Biol, 13: 549–555. https://doi.org/10.1016/j.cbpa. 2009.08.003.
20. Finan C, Gaulton A, Kruger FA, Lumbers RT, Shah T. The druggable genome and support for target identification and validation in drug development. Science Translational Medicine, 2017; 9(383): eaag1166.
21. Harrison RK (2016) Phase II and phase III failures: 2013–2015. Nat Rev Drug Discov, 15: 817–818. https://doi.org/10.1038/nrd. 2016.184.
22. Hopkins AL. Network pharmacology: the next paradigm in drug discovery. Nature Chemical Biology, 2008; 4(11): 682–90.
23. Garman KS, Nevins JR, Potti A (2007) Genomic strategies for personalized cancer therapy. Hum Mol Genet, 16: R226–R232. https://doi.org/10.1093/hmg/ ddm184.
24. Pushpakom S, Iorio F, Eyers PA et al (2018) Drug repurposing: progress, challenges and recommendations. Nat Rev Drug Discov, 18: 41–58. https://doi.org/10.1038/nrd.2018.168.
25. CHARLTON RL, ROSSI-BERGMANN B, DENNY PW, STEEL PG. Repurposing as a strategy for the discovery of new anti-leishmanial: the-state-of-the-art. Parasitology, 2017; 145(2): 219–36.
26. Baldi A. Computational approaches for drug design and discovery: An overview. Systematic Reviews in Pharmacy, 2010; 1(1): 99.
27. http://www.simulationsus.com/Products. aspx?GastroPlus&grpID=3 &cID=16 & pID=11. (accessed 12.12.16).
28. Honório T da S, Pinto EC, Rocha HVA, Esteves VSD, dos Santos TC. In Vitro–In Vivo Correlation of Efavirenz Tablets Using GastroPlus®. AAPS PharmSciTech., 2013; 14(3): 1244–54.
29. Sun Nuclear - Patient Safety Starts Here [Internet]. www.sunnuclear.com. Available from: http://www.sunnuclear.com
30. Juristic PA, Sharma R, Reuter J. MapCHECK used for rotational IMRT measurements: Step-and-shoot, Tomo therapy, Rapid Arc. Medical Physics, 2010; 37(6Part1): 2837–46.
31. http://www.scripps.edu/olson/forli/autodock _flex_rings.html (accessed 12.12.16).
32. S.M.D. Rizvi, S. Shakil, M. Haneef, A simple click by click protocol to perform docking: Autodock 4.2 made easy for non- Bioinformaticians, Excli. J., 2013; 12: 831–857.
33. http://www.schrodinger.com (accessed 10.12.16).
34. B. Dinesh Kumar, P.V. Kumar, S.P. Bhuvneshwar, A. Mitra, Advanced drug designing software's and their applications in medical research, Int. J. Pharmacy Pharm. Sci., 2010; 2: 16–18.
35. http://www.ccdc.cam.ac.uk/Solutions/GoldSuite/Pages/GOLD.aspx (accessed 20.12.16).
36. E. Yurieva, M. Agostinoa, P.A. Ramsland, Challenges and advances in computational docking: 2009 in review, J. Mol. Recogn, 2011; 24: 149–164.
37. http://www.serc.iisc.ernet.in/facilities/ComputingFacilities/software/biosuite. html (accessed 25.12.16).
38. Uzan J, EswarVee C, Malik Z, Nahum AE. BIOSUITE, NEW SOFTWARE FOR RADIOBIOLOGICAL CUSTOMISATION OF DOSE AND FRACTON SIZE IN EBRT. Radiotherapy and Oncology, 2009; 92: S239.

39. QSAR, QSAR descriptors, 2D QSAR, 3D QSAR, QSAR modeling Software [Internet]. www.vlifesciences.com.Availablefrom: http://www.vlifesciences.com/products/QSARPro/Product_QSARpro.php
40. Hung T-C, Lee W-Y, Chen K-B, Chan Y-C, Chen CY-C. An Investigation of Small GTPases in relation to Liver Tumorigenesis Using Traditional Chinese Medicine. BioMed Research International, 2014; 2014: 1–11.
41. Genomics Applications & Solutions | Agilent [Internet]. www.agilent.com. Available from: http://www.genomics.agilent.com/en/Microarray-Data-Analysis-Software/
42. A.M. Loening, S.S. Gambhir, Amide: a free software tool for multimodality medical image analysis, Mol. Imaging, 2012; 2: 131–137.
43. http://www.scripps.edu/olson/forli/autodock_flex_rings.html (accessed 12.12.16).
44. S.M.D. Rizvi, S. Shakil, M. Haneef, A simple click by click protocol to performdocking: Auto dock 4.2 made easy for non- Bioinformaticians, Excli. J., 2013; 12: 831–857.
45. http://accelrys.com/products/discovery-studio/visualization-download.php (accessed 20.12.16).