PROSPECTS FOR THE DEVELOPMENT OF INNOVATIVE ASPECTS OF MATHEMATICAL MODELING IN THE IMPLEMENTATION OF NEW DOSAGE FORMS

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Modern pharmaceutical branch characterized by dynamic development caused by necessity creation new one's dosage forms which provide high efficiency, safety and accessibility for patients. Implementation innovative approaches to development medical means is important component strategies growth this one industry. Special place occupies using mathematical modeling that allows raise precision forecasts, reduce experimental expenses research and accelerate market entry new one's drugs

Mathematical modeling in pharmaceuticals is powerful an optimization tool processes developments medicinal forms. Thanks to use modern methods numerical analysis, machine learning algorithms and artificial intelligence, researchers receive possibility simulate complex physical and chemical processes such as solubility, permeability through biological membranes , bioavailability etc. It is not only allowing provide behavior medical means in the body person, but also gives be able to optimize their recipe is still at the stage developments.

The main purpose of this research is an analysis of development prospects innovative aspects mathematical modeling during implementation new one's medicinal forms. In process work provided for solving the following tasks:

1. Conduct an analysis modern trends in use mathematical modeling in the pharmaceutical industry.
2. to learn opportunities integration modern technologies such as machines learning and artificial intelligence, in processes mathematical modeling.
3. Develop recommendations for effectiveness application mathematical models on differences stages creation medical means

So, research aimed at development innovative approaches to use mathematical modeling that will contribute increase efficiency processes developments medicinal forms and further automation pharmaceutical of research.

Mathematical models which can be used in pharmaceuticals conditionally split into several basic groups depending from their functions :

1. Pharmacokinetic models (PK). These models describe processes absorption, distribution , metabolism and excretion medical means from the body . Most common are:
   - Single-chamber and multi-chamber models.
   - Models based on physiological parameters (PBPK). Advantage: allow to predict drug concentration in blood and tissues. Disadvantages: need accurate physiological data may be difficult to validate.
2. Pharmacodynamics models (PD). These models describe interaction of the drug with receptors, it efficacy and toxicity. known approaches:
   - Models Emax for evaluation "dose- effect" dependence.
   - Models with a time delay (time-lag models). Advantage: provide understanding therapeutic effect Disadvantages
: difficult to consider multifactorial influences
3. Qi drug delivery models models are developed for description processes release active substances from dosage forms and their transport to target tissues. Main types:

- Models diffusion (Fick's law).
- Models erosion and degradation polymers.

Advantage: allow optimize the design of drug delivery systems. Disadvantages: difficulty in accounting biological environment.

Table 1. Analysis advantages and disadvantages different types of models

Model type	Advantages	Disadvantages
Pharmacokinetic	Simplicity for basic forecasting , possibility individualization .	Not taken into account specific cellular mechanisms need accurate incoming data .
Pharmacodynamics	Gives understanding effectiveness and toxicity of the drug, suitable for development doses .	Can be difficult for multi-stage processes , limited quantity variables .
Drug delivery models	They help understand process release and active transport substances that optimize the formulation.	Limitations due to influence biological systems, insufficient accuracy for multicomponent systems.

Examples successful application mathematical modeling

1. PBPK – modeling for optimization dosage Use of drugs physiologically substantiated models allowed pharmaceutical companies such as Pfizer to develop new ones modes dosage antibiotics that reduce risk side effects .
2. development controlled release medical means Models based on diffusion helped improve drug delivery systems from controlled release , such as depot injections or transdermal plasters (for example , drugs for treatment chronic pain).
3. Prognostication efficiency antivirus Pharmacodynamic drugs models were applied for testing and development antivirus drugs during the COVID-19 pandemic, which accelerated theirs introduction to the market

Mathematical modeling in the pharmaceutical industry based on usage various methods for description complex physico-chemical and biological processes. The main ones approaches are differential equations, Monte Carlo and kinetic methods model.

Differential equation

Differential equations are widely used to describe dynamic processes such as:

- Absorption, distribution, metabolism and excretion (ADME) medical means
- Active transport substances through membranes and biological barriers

Example

One-chamber pharmacokinetic model:

$$\frac{dC(t)}{dt} = -k \cdot C(t) \qquad (1)$$

where C (t) is the concentration of the drug in plasma of blood at the moment of time t , k is the speed elimination

Extensions

for modeling complex systems are used multi-chambered models which are taken into account different organs and tissues :

$$\frac{dC_1}{dt} = -k_{12} \cdot C_1 + k_{21} \cdot C_2, \quad (2)$$

where C_1, C_2 — concentrations of the drug in different tissues, k_{12}, k_{21} — transfer rates between them.

Advantages

- Simplicity in implementation and numerical solutions.
- Used for forecasting dynamics of the drug in the body.

Disadvantages

- They need accurate incoming data.
- They ignore stochastic processes.

Monte Carlo methods

Monte Carlo methods are used to account for stochasticity and variability in pharmaceuticals processes. This approach ideally suitable for:

- Assessments uncertainties in pharmacokinetic and pharmacodynamic models.
- Imitation distribution parameters among different populations.

Example

Imitation variations in speed absorption k_a:

1. Generated set k_a from the normal distribution.
2. For each value of k_a is resolved differential equation
3. They are analyzed statistical characteristics of the obtained results.

Advantages

- Possibility modeling complex probabilistic processes.
- Use in case of absence accurate deterministic data.

Disadvantages

- High computing complexity.
- The need is great quantity simulations to obtain accurate results.

Kinetic models

Kinetic models describe processes release, dissolution and degradation medicinal forms.

Example

Release model active substances from the matrix systems :

$$M_t = k \cdot t^n, \quad (3)$$

where M_t is the quantity released substances in moment time t, k is kinetic constant, n is an indicator that determines mechanism release

Extensions

For systems with controlled release :

$$\frac{dM}{dt} = D \cdot \frac{\partial^2 C}{\partial x^2}, \quad (4)$$

where D is the coefficient diffusion, C – concentration active substances, x is a coordinate.

Advantages

- Well suited for optimizing recipes.
- Provide accuracy in description release from polymer matrices.

Disadvantages

- Can be difficult for systems with multicomponent matrices.

Everyone from methods has your advantages and limitations, and them choice depends from a specific task. In many cases are used combinations methods, for example, differential equations for basic modeling and further using Monte Carlo methods to take into account uncertainties. Integration these approaches from modern computing means allows much raise efficiency developments new one's medicinal forms.

Computer room chemistry is powerful a forecasting tool properties of drug molecules means Thanks to use algorithms quantum mechanics, molecular mechanics and modeling interactions of molecules, scientists can:

- to predict physical and chemical properties of molecules (solubility, stability, polarity).
- Evaluate biological activity of molecules (interaction with target proteins).
- Optimize the structure of molecules to increase their efficiency and reduction toxicity.

Methods computer chemistry

1. Quantum mechanics
   - Calculations energy states of molecules, dipole moments, electronic densit.
   - Using Hartree-Fock, DFT (Density Functional Theory) methods. Example: Prognostication reactivity of molecules to create prodrugs that are activated in the body.
2. Molecular dynamics (MD)
   - Analysis dynamic behavior of molecules in biological one's environments. Example: Research stability medicines in different environments (acidic, neutral, alkaline).
3. Docking (molecular docking)
   - Modeling interaction medical substances with target proteins. Example: Choice potential candidates for disease treatment by screening thousands compounds.
4. Machine Learning in Chemistry
   - Using machine learning algorithms for prediction properties of molecules based on databases.
   - Example: Prognostication toxicity substances from using QSAR (Quantitative Structure-Activity relationship).

Advantages computer chemistry

- Reduction quantity laboratory experiment.
- Acceleration search new one's medical compounds.
- Optimization resources and cost.

Physico-chemical models play back key role in forecasting bioavailability medical means

1. Models dissolution

Modeling process dissolution allows to evaluate speed and degree dissolution medical biological means liquids .

Example: Nernst- Brunswein model:

$$\frac{dm}{dt} = k_s \cdot (C_s - C), \quad (5)$$

where m is mass dissolved substances, k_s is the rate constant, C_s – concentration saturation, C is current concentration.

2. Models absorption

Absorption is described as active transport substances through membranes cells The most common approaches:

- Models passive diffusions (based on the law Fika).

- Models of active transport for substances that need carrier proteins.

Example:
Model of permeability through intestinal wall :

$$J = P \cdot (C_{in} - C_{out}), \quad (6)$$

where J is a stream substances, P is the coefficient permeability, C_{in}, C_{out} — concentrations with both sides membranes .

3. Models distribution

Distribution medicines between various tissues and organs are described physiologically justified pharmacokinetic models (PBPK).
Example:
Calculation concentrations in tissues:

$$\frac{dC_t}{dt} = \frac{Q \cdot (C_a - C_v)}{V_t}, \quad (7)$$

where C_t, Q — blood flow , C_a, — concentrations in arteries and veins , Vt — volume fabrics .

Advantages physical and chemical models

- Flexibility in use for different medicinal forms.
- Possibility integration with experimental given
- Software accurate forecasts of efficiency medicines

Disadvantages

- They need accurate data for parameterization.
- Can be difficult for multi-component systems.

Computer room chemistry and physical and chemical models are complementary tools which much increase efficiency process developments medical means Integration these approaches from modern technologies such as artificial intelligence provides new ones opportunities for optimization properties drugs, forecasting their efficiency and minimization risks.

Artificial intelligence (AI) opens new one's opportunities for improvement processes developments medical means Using neural networks, machine and deep teaching allows effectively analyze complex data, predict properties of molecules and optimize the composition of dosage forms.

Neuronal networks for prediction bioavailability

Bioavailability determines efficiency medicinal means; therefore, her accurate forecasting is critical.

Approach:

- are used artificial neural networks (SNM), in particular feedforward or convolutional neural networks (CNN), for analysis structural features of molecules.
- Data for training: physical and chemical properties (solubility, lipophilicity, molecular mass) and experimental indicators Bioavailability.

Example:

- ANN- based models predict how changes in the structure molecules affect her ability penetrate through the intestinal tract the wall or others barriers
- Successful projects: Deep ADMET, which use AI to assess the ADME profile (absorption, distribution, metabolism, excretion).

Advantage:

- Reducing the need for expensive experimental studies.
- Fast analysis thousands of molecules.
- High precision forecasts thanks to adaptation to new one's data.

Mechanical training to optimize the composition of medicinal forms

Mechanical learning (ML) is used to develop the optimal composition of dosage forms that provides their stability, efficiency and safety.

Methodology:

- ML algorithms (for example, Random Forest , Gradient Boosting) are analyzed experimental data on recipes and their properties .
- Optimized proportions active substances, fillers, stabilizers etc

Example:

- ML models help to determine optimal composition of tablets with controlled release
- Forecast as a change concentration polymers in the matrix will affect the duration release

Advantage:

- Reduction of development time recipes.
- Reduction research and testing costs.
- Automation process optimization.

deep training for big data analysis clinical of research

Clinical research generates big volumes data which contains information on effectiveness, safety and side effects medical means deep learning (Deep Learning, DL) allows effectively analyze these data

Approach:

- are used recurrent neural networks (RNN) and transformers for analysis textual data (descriptions clinical cases , reviews patients).
- Using CNN for analysis medical images (for example , for evaluation actions drugs on tissues).

Example:

- DL models identify hidden regularities between drug dosage and side effects
- DL- based systems are analyzed efficiency treatment different groups patients in real time.

Advantage:

- Detection rare side effects which hard to notice by conventional methods.
- Acceleration analysis multi-level interactions in the data.
- Increase accuracy forecasts thanks to integration data from different sources.

Artificial intelligence becomes integral part of pharmaceutical research, providing tools for solving complex tasks . Neuronal networks, machines and deep teaching allow create more effective and safe medical means , reducing time and costs for them development Integration these technologies from traditional approaches opens prospects for development innovative medicinal forms.

Pharmacokinetic parameters (such as absorption, distribution, metabolism, elimination – ADME) are key to assess efficiency and safety medical means Using neural networks allows simulate these processes with high accuracy

Methodology:

- incoming data: Physico-chemical characteristics of molecules (molecular mass, solubility, logP), experimental pharmacokinetic parameters , information about physiological features body
- Models:

- Artificial neural networks (ANN): Used to create non-linear models of dependencies between the structure of the molecule and its pharmacokinetics.
- Recurrent neural networks (RNN): For modeling temporary dynamics concentration of the drug in the body.

Example:

- Prognostication bioavailability: Neuronal network analyze influence chemical structure and dosage on the level of the drug in plasma blood
- Models distribution: Calculation volume distribution between fabrics on the basis molecular characteristics.

Advantages:

- Possibility modeling complex, non-linear dependencies.
- High accuracy and speed forecasts.
- Use for the analysis of both individual molecules and large databases.

Disadvantages:

- The need for significant volumes quality data for training.
- Sensitivity to retraining is insufficient quantity data.

Using machine learning algorithms for optimizing the composition of dosage forms

Machine learning (ML) algorithms contribute automation process creation dosage forms, providing a balance between stability, efficiency and economy.

Methodology:

- Data for analysis :

Experimental the results testing compositions , physical and chemical properties ingredients , characteristics of finished products dosage forms (dissolution , stability , speed release).

- ML methods:
  - Regression models: For detection dependencies between composition and indicators efficiency.
  - Random Forest and Gradient Boosting: For definition key parameters which bridge affect the properties medical forms

Example:

- Optimization of the composition of tablets with controlled release by modeling impact different concentrations polymers for duration release
- Automatic choice stabilizers for improvement term suitability drugs

Advantage:

- Reduction of experimental time research.
- Reduction quantity necessary resources.
- Possibility quick adaptation of models under new one’s data

Disadvantages:

- High quality requirements incoming data.
- Sensitivity to change experimental conditions.

development intelligent support systems adoption solutions for pharmacists

Intellectual systems support adoption decisions (Decision Support Systems, DSS) help pharmacists to choose optimal drugs , dosage and methods treatment

Features:

- AI integration: Using machine learning algorithms for analysis pharmacological data.
- Knowledge base: Interaction information drugs , side effects effects , treatment recommendations for different groups patients
- Automation processes: Selection of treatment schemes taking into account individual features patient (age , physique , accompanying diseases).

Example:

- Systems electronic prescription: Automatic selection of the optimal drug and dosage depending from symptoms and medical history the patient
- development new ones medical means: DSS integrates data on bioavailability, stability and interaction with other drugs.

Advantage:

- Decrease risk medical errors.
- Increase accuracy and speed adoption decisions.
- Possibility personalization treatment

Disadvantages:

- Dependence from quality data and algorithms.
- Necessity of regular updating of knowledge bases.

Conclusion

Modern technologies of AI, neural networks and machine learning much increase efficiency development and application medical means They allow not only optimize processes, but also provides personalized approach to treatment, which is an important step in development medicine and pharmacy.

Molecular modeling is important a tool for research interaction medical substances from biological targets and forecasting properties new ones compounds. This approach combines computer methods and physical and chemical models to study processes at the molecular level.

Simulation interaction medical substances from biological targets

This technique is aimed at research mechanisms binding drug molecules with biological ones targets such as proteins, DNA, RNA or membranes.

Methods:

- Docking (Docking): Computer room simulation that allows to determine are possible positions binding drug molecules with the active center of the target.
- Molecular dynamics (Molecular Dynamics, MD): Studying the movement of molecules in time for analysis stability communication and interaction.

Process:

1. incoming data:
   - 3D structure of biological targets (obtained using x-ray crystallography or NMR spectroscopy).
   - Molecular structure of potential medical substances.
2. Analysis:
   - Definition affinities (powers binding) between the molecule and the target .
   - Rating key amino acids or others groups which participate in binding.

Example:

- Simulation interaction inhibitors enzymes (for example, proteases) to fight viruses .
- Study binding medicines with G protein receptors for optimization their activity

Advantage:

- Fast detection bridge promising molecules for synthesis.
- Possibility research interactions at the atomic level.
- Decrease laboratory expenses experiments.

Prognostication physical and chemical properties new one’s compounds

Prognostication physical and chemical properties helps to evaluate potential efficiency and safety of molecules at an early stage stages developments.

Methods:

- QSAR (Quantitative Structure-Activity relationship): Creation mathematical models which link the structure of the molecule with its properties (solubility, stability , toxicity).
- Molecular dynamic: Simulation processes such as dissolution or stability in difference environments.
- algorithms: Mechanical teaching analyzes big base data for forecasting properties new one's compounds.

Process:

1. Creation of models: Using data on the known molecules for learning algorithms.
2. Analysis: Prediction of such parameters as:

- Lipophilicity (logP): Affects penetration through membranes.
- Solubility: Defines bioavailability of the drug.
- Toxicity: Detection potentially dangerous structures.

Example:

- Prognostication solubility new ones antibiotics to improve their Bioavailability.
- Definition stability of molecules vs oxidation or hydrolysis

Advantage:

- Acceleration process selection promising molecules.
- Possibility to evaluate properties even for molecules which not yet synthesized.
- Integration with laboratory experiments to increase accuracy

Molecular modeling is powerful a tool for development innovative medical means Simulation interaction with biological targets helps reveal key mechanisms actions, and forecasting physical and chemical properties allows optimize molecules even before their synthesis. Integration these approaches from modern artificial intelligence technologies opens prospects for creation more effective and safe medicines

Development mathematical modeling opens new one's opportunities for improvement process developments medical means Integration with innovative technologies and personalized approaches allows much raise efficiency and accuracy developments new one's medicinal forms.

3D printing of dosage forms

- Using mathematical models for optimization the process of 3D printing of medicinal products means from given characteristics (for example, speed release active substances).
- Modeling dissolution and release drugs from multilayer structures created using 3D printing.
- Example: creation printed tablets from accurate dosage for pediatrics or geriatrics.

Microfluidics

- Modeling processes in microfluidic devices which allow explore properties dosage forms in high-performance mode.
- Application of models for optimization flows in microchannels that are used for testing medical compounds in cells environments.
- Example: modeling microfluidic chips for screening medical funds in real under conditions close to physiological ones.

development customized models for personalized of medicine

Adaptation of models to physiological ones features the patient

- Creating models that are taken into account individual parameters: age , sex, genetics profile , availability companions diseases
- Prognostication efficiency and safety medical means for a specific patient.

Example:

- Models for determining the optimal dosage oncological drugs depending from equal metabolic enzymes the patient

- Integration pharmacogenetic data in mathematics models for forecasting reactions to treatment.

Personalization treatment chronic diseases

- Modeling long-term pharmacotherapy for optimization dosage and minimization side effects.
- Example: individual models for patients from diabetes or cardiovascular diseases

Creation digital doubles medical tools for virtual of research

Digital twins medicinal forms

- Virtual analogues of physical ones dosage forms which allow simulate processes dissolution, release and absorption medical substances
- Application for fast checks hypotheses and optimization recipes without conducting expensive laboratory tests experiments.

Digital twins patients:

- Modeling physiology patient taking into account individual features for forecasting reactions to treatment.
- Use for virtual testing new ones drugs on the stage preclinical of research.

Example:

- Creation digital doubles patients for simulation clinical tests from involving artificial intelligence.
- Using digital twins for prediction interaction medical means in a multicomponent therapy

Advantages proposed approaches

- Speed: Reduction of development time medicinal forms due to virtual research .
- Accuracy: More accurate prognosis efficiency and safety drugs
- Economy: Reduction physical expenses experiments and clinical test
- Environmental friendliness: Minimization using laboratory resources and decline formation waste

Integration mathematical modeling with the latest technologies such as 3D printing, microfluidics, and artificial intelligence, opens unique prospects for development innovative medical means Using personalized models and digital doubles facilitates the transition to a new one era medicine — personalized , effective and environmentally friendly oriented .

Despite the significant progress in use mathematical modeling for development new ones dosage forms, there are a number of problems which limit efficiency and wide implementation these methods into practice.

1. Insufficient number experimental data for model validation

Problem:

- For the creation and validation of models are required high quality experimental data Often them insufficient due to limited access to accurate and standardized results of research .
- Many models are based on simplified one’s assumptions due to shortages data that lowers their accuracy

Reasons:

- High cost and labor intensity receiving experimental data, especially for complex ones biological systems.
- Absence agreed upon collection approaches data in different laboratories.

Possible solution:

- Creation centralized databases with the results of experiments for common using scientific community

- development standards for collection and publication data that will contribute their for use in modeling.

2. Complexity calculations when using complex models

Problem:

- Models that describe multi-level biological processes (molecular, cellular , tissue), require significant computational resources for simulation .
- Execution time complex models can be impractically long that limits theirs real time usage or for large volumes data

Reasons:

- Many parameters and equations which need numerical solution.
- Absence optimized algorithms for certain types of tasks.

Possible solution:

- Using cloudy computing and distributed systems to increase power calculations.
- development simplified models (reduction models), which are kept accuracy, but reduce computing complexity
- Integrating artificial intelligence for acceleration computational processes.

3. Necessity developments standards for assessment qualities of models

Problem:

- Absence the only one's criteria evaluations reliability and accuracy mathematical models in pharmaceuticals.
- Impossibility comparison different models due to different approaches to theirs development and testing.

Reasons:

- Differences in methodologies creating models that depend from a specific case application
- Insufficient cooperation between researchers and regulatory bodies to form common standards.

Possible solution:

- development international standards evaluations of models which are taken into account their accuracy, computational efficiency and predictability the ability
- Creation of platforms for independent testing and validation of models within the framework cooperation between academic, industrial and regulatory organizations.
- Implementation of metrics for comparing models, such as prediction error, computation time , stability solutions etc

Examples of problems in practice

- Pharmacokinetic models: Lack clinical data for patients from rare diseases that limits precision modeling.
- Molecular modeling: Significant spending time on simulation interactions big number of molecules from protein targets.
- Personalized medicine: Difficulties in creating models that take into account a wide range of individuals features patients

Despite the significant potential mathematical modeling in pharmaceuticals exist essential challenges that restrain its development. Overcoming these restrictions needs interdisciplinary cooperation, implementation modern technologies (cloud computing, AI) and creation global standards. This will increase quality models, speed up theirs implementation in practice and ensure more effective development medical means

Mathematical modeling plays back an important role in the pharmaceutical industry development, allowing optimize recipes, compare simulations with experimental ones data to use