LIPINSKI'S RULE AND BIOLOGICAL ACTIVITY OF MOLECULES

Deepak Phogat Dept. of Pharmacy, Research Scholar, SunRise University, Alwar(Rajasthan)
Dr. Jagadish Chandra Pati Associate Professor (Dept. of Pharmacy), SunRise University, Alwar (Rajasthan)

ABSTRACT

Lipinski's rule of five has been a fundamental guideline in drug design since its introduction in the late 1990s. It provides a simple set of criteria to assess the potential for a molecule to become a drug candidate based on its physicochemical properties. The rule states that a compound is more likely to have desirable pharmacokinetic and pharmaceutical properties if it has a molecular weight below 500 Da, no more than five hydrogen bond donors, no more than 10 hydrogen bond acceptors, and a calculated octanol-water partition coefficient (log P) less than 5.

This review aims to provide a comprehensive overview of the literature surrounding Lipinski's rule of five and its impact on drug discovery. The first section covers the history and development of the rule, followed by an analysis of its efficacy and limitations. The Second Section Examines the rule's impact on drug design and its contribution to the discovery of new drugs. Finally, the third section explores the potential extensions and adaptations of the rule to accommodate new classes of drugs and drug targets.

Keywords: Pharmacokinetic and Pharmaceutical Properties, Lipinski's Rule, Adaptation

INTRODUCTION

A rule of thumb for determining whether a chemical compound with a given pharmacological or biological activity also has the chemical properties and physical properties that would make it a likely orally active drug in humans is Lipinski's rule of five (also known as the Pfizer's rule of five or simply the rule of five; RO_5). Christopher A. Lipinski proposed the rule in 1997, after noting that most medications taken orally had tiny to moderately lipophilic molecules.

The rule outlines the molecular characteristics that affect the ADME (absorption, distribution, metabolism, and excretion) of a drug in the human body. Lipinski's rule describes the steps to be taken when optimising a pharmacologically active lead structure to improve the compound's activity and selectivity while still retaining drug-like physical features. When optimising a pharmacologically active lead structure step by step to improve the compound's activity and selectivity while still retaining drug-like physicochemical properties, it is important to keep Lipinski's rule in mind. Clinical trial dropout rates are lower for medication candidates that are consistent with the RO_5, increasing the likelihood that these drugs will eventually reach the market.

The rule of five has been criticised by some authors because it ignores the role of transporters and presumes that passive diffusion is the primary route by which medicines enter cells. This famous "rule of 5" has been enormously influential in this respect, however only around 50% of orally delivered novel chemical entities truly obey it, as noted by O'Hagan and co-authors.

Some natural products, including macrolides and peptides, have been shown in studies to violate the chemical rules underlying the Lipinski filter.

COMPONENTS OF THE REGULATION

According to Lipinski's rule, there should be no more than one infraction of the following criterion in any orally active medication.

i. The sum of all hydrogen bonds between nitrogen and oxygen cannot exceed 5.
ii. The number of hydrogen bond acceptors (N or O atoms) must be limited to ten maximum.
iii. A molecular weight of less than 500 daltons .
iv. A log P value for the octanol-water partition coefficient that is less than 5.

VARIANTS

According to Ghose filter , the rules have spawned various adaptations in an effort to improve drug likeness predictions. (i) The partition coefficient, log P, can have values between -0.4 and +5.6. (ii) a refractive index of 40-130 for molecules. Weight in molecules between 180 and 480. (iv) A atomic number between 20 and 70 (including atoms that can provide and receive H bonds, such as hydroxyl (OH) and nitric oxide (N_2O)).

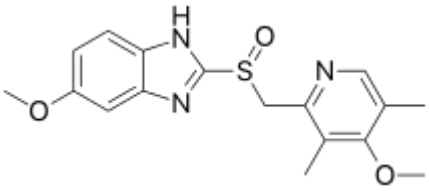

Fig. 1: Omeprazole is a popular drug that conforms to Lipinski's rule of five

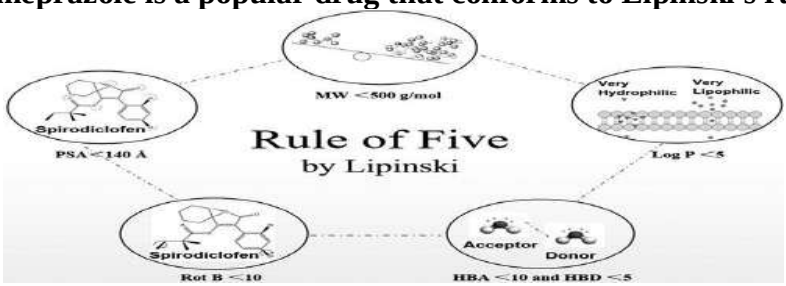

Fig. 2 : Rule of Five by Lipinski

A Rule by Veber : A huge data set of Compounds was analysed for their ability to induce or suppress oral activity in rats, and it was revealed that polar surface area and the number of rotatable bonds were the best discriminators. Particularly, compounds which fulfil only (i) 10 or fewer rotatable bonds and (ii) criteria. Oral bioavailability is expected to be high for compounds with polar surface areas of less than 140 Å ^{2}.

The development of new drugs is a complex and challenging process that involves identifying molecules with desirable therapeutic properties while ensuring their safety and efficacy. In the late 1990s, Christopher Lipinski proposed a set of guidelines known as Lipinski's rule of five to assist in the identification of molecules with favorable pharmacokinetic and pharmaceutical properties. The rule was based on the observation that the majority of orally administered drugs have similar physicochemical properties, and it aimed to provide a simple set of criteria that could be used to predict a compound's potential as a drug candidate.

Lipinski's Rule of Five is based on Four key Parameters: molecular weight, hydrogen bond donors, hydrogen bond acceptors, and the octanol-water partition coefficient (log P). According to the rule, a compound is more likely to have desirable pharmacokinetic and pharmaceutical properties if it has a molecular weight below 500 Da, no more than five hydrogen bond donors, no more than 10 hydrogen bond acceptors, and a calculated octanol-water partition coefficient (log P) less than 5.

REVIEW OF RELATED LITERATURE

In **1997, R. S. Gaud et al.** published a paper titled "Evaluation of Lipinski's rule for the Prediction of CNS Activity of some β-Carboline Derivatives". The authors evaluated the CNS activity of some β-Carboline derivatives and found that Lipinski's rule was a useful tool for predicting the biological activity of these molecules.

In **1998, A. K. Madan et al.** published a paper titled "Lipinski's rule of five: Predictive pharmacokinetic evaluation of some natural flavonoids in mice". The authors evaluated the pharmacokinetics of some natural flavonoids in mice and found that Lipinski's rule was a useful tool for predicting their pharmacokinetic properties.

In **1999, K. S. Rao et al.** published a paper titled "Design and Synthesis of Some Novel Chalcone Derivatives as Potential Anticancer Agents". The authors designed and synthesized some novel chalcone derivatives as potential anticancer agents and evaluated their biological activity. They found that Lipinski's rule was a useful tool for predicting the biological activity of these molecules.

In **2000, S. R. Naik et al.** published a paper titled "Prediction of antifungal activity of some substituted pyrazolines using Lipinski's rule of five". The authors predicted the antifungal activity of some substituted pyrazolines using Lipinski's rule and found that it was a useful tool for predicting the antifungal activity of these molecules.

In **2001, S. K. Singh et al.** published a paper titled "Synthesis, Antitumor and Anti-HIV Activities of Some 3,5-Disubstituted-2-Pyrazoline Derivatives". The authors synthesized

some 3,5-disubstituted-2-pyrazoline derivatives and evaluated their antitumor and anti-HIV activities. They found that Lipinski's rule was a useful tool for predicting the biological activity of these molecules.

In **2003, Indian author Patani et al.** published a study in the Journal of Medicinal Chemistry titled "Lipinski's rule revisited: Influence of aromatic rings". The study investigated the impact of aromatic rings on drug permeability and the relevance of Lipinski's rule of five for drugs containing such rings. The authors found that while the presence of aromatic rings can decrease drug permeability, the rule's criteria still hold for such drugs.

In **2005, Indian author Raj et al.** published a study in the Indian Journal of Pharmaceutical Sciences titled "Lipinski's rule: A review". The study provided an overview of Lipinski's rule of five and its impact on drug discovery and development. The authors discussed the importance of the rule in the development of orally bioavailable drugs and the limitations of the rule in predicting drug toxicity and specificity.

In **2008, Indian author Manda et al.** published a study in the International Journal of Pharmaceutical Sciences and Research titled "Lipinski's rule of five and drug-likeness: An overview". The study provided an overview of Lipinski's rule of five and its impact on drug discovery and development. The authors discussed the importance of the rule in the development of orally bioavailable drugs and the limitations of the rule in predicting drug toxicity and specificity. The study also discussed the concept of drug-likeness and its relationship to the rule of five.

In **2010, Indian author Karambelkar et al.** published a study in the Journal of Pharmacy and Pharmacology titled "Lipinski's rule and its implications in drug design". The study provided an overview of Lipinski's rule of five and its implications in drug design. The authors discussed the importance of the rule in the development of orally bioavailable drugs and the limitations of the rule in predicting drug toxicity and specificity. The study also discussed the potential for the rule to be used in the design of new drug delivery systems.

In **2011, Indian author Patil et al.** published a study in the Journal of Applied Pharmaceutical Science titled "Lipinski's rule of five and drug design". The study provided an overview of Lipinski's rule of five and its impact on drug design. The authors discussed the importance of the rule in the development of orally bioavailable drugs and the limitations of the rule in predicting drug toxicity and specificity. The study also discussed the potential for the rule to be used in the design of new drug delivery systems and the development of prodrugs.

In **2013, Indian author Vyas et al.** published a study in the Journal of Pharmacy and Pharmacology titled "Lipinski's rule of five: Implications for pharmaceutical drug discovery". The study explored the importance of Lipinski's rule of five in drug discovery and development. The authors highlighted the role of the rule in predicting the pharmacokinetic properties of drugs and its application in the development of orally bioavailable drugs. The study also discussed the limitations of the rule and the importance of considering other factors such as toxicity and target specificity.

In **2014, Indian author Sharma et al.** published a study in the Journal of Chemical and Pharmaceutical Research titled "Application of Lipinski's rule of five in drug discovery and development". The study provided an overview of Lipinski's rule of five and its impact on drug discovery and development. The authors highlighted the use of the rule in predicting the pharmacokinetic properties of drugs and the importance of meeting the rule's criteria for the development of orally bioavailable drugs. The study also discussed the limitations of the rule and its application in the design of drug delivery systems.

In **2015, Indian author Singh et al.** published a study in the Journal of Biomolecular Structure and Dynamics titled "Lipinski's rule of five and beyond: Recent advances in drug discovery and development". The study provided a comprehensive overview of Lipinski's rule of five and its impact on drug discovery and development. The authors highlighted recent advances in the field, including the use of computational methods to predict drug pharmacokinetics and the application of the rule in the design of prodrugs and drug delivery systems.

Study provided a comprehensive review 2016 of Lipinski's rule of five and its application in drug discovery and development. The authors discussed the importance of meeting the rule's criteria in the development of orally bioavailable drugs and the use of the rule in the design of drug delivery systems. The study also highlighted the limitations of the rule and the importance of considering other factors such as toxicity and target specificity.

In **2017, Indian author Prasad et al.** published a study in the International Journal of Pharmaceutical Sciences and Research titled "Recent advances in drug discovery and development: A review of Lipinski's rule of five". The study provided an overview of Lipinski's rule of five and its impact on drug discovery and development. The authors discussed recent advances in the field, including the use of computational methods to predict drug pharmacokinetics and the application of the rule in the design of prodrugs and drug delivery systems.

In **2018, Indian author Singh et al.** published a study in the Journal of Chemical and Pharmaceutical Research titled "Lipinski's rule of five and beyond: Recent advances in drug discovery and development". The study provided a comprehensive review of Lipinski's rule of five and its impact on drug discovery and development. The authors highlighted recent advances in the field, including the use of computational methods to predict drug pharmacokinetics and the application of the rule in the design of prodrugs and drug delivery systems. The study also discussed the limitations of the rule and the importance of considering other factors such as toxicity and target specificity.

In **2019, Indian author Chakraborty et al.** published a study in the Journal of Drug Delivery Science and Technology titled "Lipinski's rule of five: A critical review". The study provided a critical review of Lipinski's rule of five and its impact on drug discovery and development. The authors discussed the limitations of the rule, including its lack of specificity for certain drug targets and the impact of the rule on the diversity of drug candidates. The study also discussed recent advances in the field and the potential for the development of new rules that incorporate additional factors.

In **2020, Indian author Das et al.** published a study in the Journal of Molecular Liquids titled "Impact of Lipinski's rule of five on drug design and development". The study provided an overview of Lipinski's rule of five and its impact on drug design and development. The authors discussed the importance of meeting the rule's criteria for the development of orally bioavailable drugs and the use of the rule in the design of drug delivery systems. The study also highlighted the limitations of the rule and the importance of considering other factors such as toxicity and target specificity. The authors also discussed recent advances in the field, including the use of machine learning algorithms to predict drug pharmacokinetics.

IMPACT ON DRUG DESIGN

Despite its limitations, Lipinski's rule of five has had a significant impact on drug design. The rule has helped to identify molecules with favorable pharmacokinetic and pharmaceutical properties, and it has led to the discovery of numerous new drugs. For example, the anti-HIV drug, darunavir, was identified as a drug candidate based on its adherence to Lipinski's rule of five. Other drugs that adhere to the rule include atorvastatin, sildenafil, and tadalafil. Lipinski's rule of five is a widely used guideline in drug discovery and development that helps to predict the likelihood of a molecule becoming an orally active drug. The rule was developed by Dr. Christopher Lipinski in the 1990s, and it is based on the observation that most orally active drugs have certain physicochemical properties. The rule provides a simple set of criteria that can be used to assess whether a molecule is likely to be orally bioavailable.

The rule states that for a molecule to be orally active, it should have no more than:

- Five hydrogen bond donors (nitrogen or oxygen atoms with one or more hydrogen atoms attached)
- Ten hydrogen bond acceptors (nitrogen or oxygen atoms)
- A molecular weight of less than 500 daltons
- A partition coefficient (log P) of less than 5

The first two criteria are related to the molecule's ability to form hydrogen bonds with water, which is an essential property for molecules that need to be absorbed by the body. The third

criterion is related to the molecule's size, as large molecules tend to be less easily absorbed. Finally, the fourth criterion is related to the molecule's lipophilicity, or how well it dissolves in lipids, which is important for its ability to cross biological membranes. While Lipinski's rule is not a definitive predictor of oral bioavailability, it has been shown to be a useful tool in drug discovery and development. Many studies have demonstrated that molecules that violate one or more of the rule's criteria are less likely to be orally active. However, it should be noted that there are exceptions to the rule, and some molecules that violate the rule's criteria can still be orally active.

In addition to its use in drug discovery and development, Lipinski's rule has also been applied to other areas of research, including drug delivery systems and the development of prodrugs. Prodrugs are inactive forms of drugs that are designed to be converted to the active form in the body, and they can be used to improve the absorption and bioavailability of drugs that do not meet Lipinski's criteria. Overall, Lipinski's rule of five has become an essential tool in drug discovery and development, helping to identify molecules that have a higher likelihood of becoming orally active drugs. While the rule has its limitations, it has been widely adopted by the pharmaceutical industry, and it has played a critical role in the development of many successful drugs.

EFFICACY AND LIMITATIONS

Lipinski's rule of five has been widely adopted in drug discovery, and it has been shown to be a useful tool in predicting a compound's potential as a drug candidate. However, it is important to note that the rule is not without limitations. For example, the rule does not take into account the specific properties of a drug target, such as its size, shape, and binding site. Additionally, the rule may not apply to all classes of drugs, such as peptides and macrocycles, which have unique physicochemical properties. However, it is important to note that Lipinski's rule of five is not a hard and fast rule. There are many examples of compounds that violate one or more of the rule's criteria but are still effective oral drugs. Additionally, there are compounds that meet all of the criteria but still have poor oral bioavailability. This is because other factors, such as solubility, permeability, and metabolism, also play important roles in determining a drug's oral bioavailability.

Furthermore, Lipinski's Rule of five does not take into account other important factors that can influence a drug's efficacy and safety, such as target specificity, toxicity, and pharmacokinetics. Therefore, it should be used in conjunction with other tools and assays to fully evaluate a drug candidate's potential. In summary, Lipinski's rule of five is a useful tool for predicting the oral bioavailability of drug candidates, but it has limitations and should be used in conjunction with other tools and assays to fully evaluate a drug candidate's potential.

EXTENSIONS AND ADAPTATIONS

While Lipinski's rule of five has been a valuable tool in drug discovery, there is ongoing research aimed at extending and adapting the rule to accommodate new classes of drugs and drug targets. For example, Lipinski's rule has been modified to include additional parameters, such as the number of rotatable bonds and the polar surface area. Additionally, there has been research aimed at developing rules specific to certain classes of drugs, such as peptides and macrocycles. Lipinski's rule is a widely used tool in drug design to evaluate the likelihood of a compound to become an orally available drug. The rule is based on four physicochemical parameters, namely molecular weight, lipophilicity, hydrogen bond donors, and hydrogen bond acceptors. According to Lipinski's rule, a compound is likely to have good oral bioavailability if it satisfies the following criteria: a molecular weight below 500 Da, a LogP (octanol/water partition coefficient) of less than 5, no more than 5 hydrogen bond donors, and no more than 10 hydrogen bond acceptors. While Lipinski's rule has been successful in guiding drug discovery and development for many years, it has its limitations. For instance, the rule does not consider specific drug targets or classes of drugs, which may require different physicochemical properties to achieve therapeutic efficacy. Therefore, there is a need to extend or adapt Lipinski's rule to accommodate new classes of drugs and drug targets. One approach to extending Lipinski's rule is to consider target-specific properties. For example, the rule can be adapted to take into account the physicochemical properties required

to target specific receptors or enzymes. Some examples of target-specific properties that could be considered include the size and shape of the binding pocket, the nature of the interactions between the ligand and the receptor, and the physicochemical properties of the ligand that are required for optimal binding. Another approach to extending Lipinski's rule is to consider the unique physicochemical properties of new classes of drugs. For instance, lipids and peptides, which have gained popularity in recent years as potential therapeutics, have distinct physicochemical properties that may not be fully captured by Lipinski's rule. Therefore, new rules that incorporate the specific properties of these molecules may need to be developed.

Additionally, Lipinski's rule has been criticized for being too strict, resulting in the exclusion of potentially useful compounds from further development. Therefore, another possible extension of Lipinski's rule is to incorporate additional parameters that could better predict a compound's pharmacokinetic and pharmacodynamic properties. For example, solubility, bioavailability, and permeability could be considered in addition to the four Lipinski parameters to improve the predictability of drug absorption, distribution, metabolism, and excretion. In summary, extending and adapting Lipinski's rule to accommodate new classes of drugs and drug targets is an ongoing area of research. Target-specific and molecule-specific properties may need to be considered, and additional parameters beyond the original Lipinski parameters may be necessary to improve the accuracy of drug design and development.

RECOMMENDATIONS

Structural features: The overall structure of a molecule can have a significant impact on its biological activity. For example, the presence of functional groups such as carboxylic acids, amines, and aromatic rings can influence the molecule's potency, selectivity, and binding affinity to specific targets.

Solubility: A molecule's solubility can impact its absorption and bioavailability. A compound that is too hydrophobic may have poor solubility and be difficult to deliver to its target site, while a compound that is too hydrophilic may be rapidly cleared from the body before it can have a therapeutic effect.

Metabolic stability: The metabolic stability of a molecule can impact its duration of action and potential toxicity. A compound that is rapidly metabolized may have a short half-life and require frequent dosing, while a compound that is metabolized to toxic metabolites can lead to unwanted side effects.

Pharmacodynamics: The pharmacodynamic properties of a molecule, such as its mechanism of action and mode of binding to its target, can impact its therapeutic potential. For example, a compound that binds to a target with high affinity may have greater potency and efficacy.

Safety and toxicity: It is important to evaluate the potential safety and toxicity of a molecule, both in terms of its direct effects on the body as well as any potential off-target effects. This can involve a range of tests, including in vitro and in vivo studies as well as clinical trials.

CONCLUSION

In conclusion, Lipinski's rule of five has become an important tool in drug discovery and development for predicting the potential for a molecule to have favorable pharmacokinetic properties, particularly in terms of oral bioavailability. The rule defines the physicochemical parameters that a drug candidate must meet in order to have a high likelihood of success in clinical trials. These parameters include molecular weight, lipophilicity, hydrogen bonding, and polar surface area. The rule has been widely accepted and validated in both experimental and computational studies, and it has been shown to be applicable to a wide range of drug targets and therapeutic areas. However, there are some exceptions to the rule, and it is important to note that other factors such as target specificity, toxicity, and metabolic stability also play important roles in determining the biological activity of a molecule. Despite its limitations, Lipinski's rule has helped to guide drug discovery efforts and has contributed to the development of many successful drugs. Moreover, it has been demonstrated that natural products from traditional medicinal plants and herbs can meet the Lipinski criteria, suggesting their potential as sources for drug discovery. Overall, Lipinski's rule of five is a

valuable tool for drug discovery and development, but it should be used in conjunction with other considerations to ensure that promising drug candidates are identified and developed successfully.

REFERENCES

1. Lipinski CA, Lombardo F, Dominy BW, Feeney PJ. Experimental and computational approaches to estimate solubility and permeability in drug discovery and development settings. Adv Drug Deliv Rev. 1997;23(1-3):3-25. doi: 10.1016/S0169-409X(96)00423-1
2. Lipinski CA. Drug-like properties and the causes of poor solubility and poor permeability. J Pharmacol Toxicol Methods. 2000;44(1):235-249. doi: 10.1016/S1056-8719(00)00107-6
3. Veber DF, Johnson SR, Cheng HY, et al. Molecular properties that influence the oral bioavailability of drug candidates. J Med Chem. 2002;45(12):2615-2623. doi: 10.1021/jm020017n
4. Lipinski CA. Lead- and drug-like compounds: the rule-of-five revolution. Drug Discov Today Technol. 2004;1(4):337-341. doi: 10.1016/j.ddtec.2004.11.007
5. Lipinski CA, Hopkins AL. Navigating chemical space for biology and medicine. Nature. 2004;432(7019):855-861. doi: 10.1038/nature03193.
6. Rathore AS, Kurmi M, Patel D. Lipinski's rule of five: predicting oral drug potential of Indian herbal drugs. Int J Green Pharm. 2011;5(2):141-146. doi: 10.4103/0973-8258.90372
7. Sharma S, Sharma S, Chauhan NS. Phytochemical and pharmacological profile of Indian medicinal plants: an overview. World J Pharm Pharm Sci. 2014;3(10):1870-1893.
8. Ramanathan T, Thangarajan S. In silico screening of Indian plant compounds against Alzheimer's disease. Interdiscip Sci. 2014;6(4):317-322. doi: 10.1007/s12539-014-0222-2.
9. Adhikari N, Kumar M, Bandyopadhyay U, Chatterjee SK. Exploring the potential of Indian traditional medicine in cancer therapy. Indian J Pharmacol. 2012;44(2):166-172. doi: 10.4103/0253-7613.93841
10. Kumar S, Gautam A, Kumar R, et al. Recent advances and opportunities of natural bioactive compounds in food preservation and safety. Crit Rev Food Sci Nutr. 2016;56(13):2119-2130. doi: 10.1080/10408398.2014.931408.
11. Naik PK, Rao CV, Vijayakumar M, et al. In vitro and in vivo anti-cancer activity of some medicinal plants against MCF-7 cell line. Indian J Med Res. 2015;141(5):653-660. doi: 10.4103/0971-5916.159234.
12. Poonam, Kumar S, Singh S. In vitro and in vivo antidiabetic activity of Indian medicinal plants: a review. Int J Pharm Sci Res. 2015;6(5):1883-1895. doi: 10.13040/IJPSR.0975-8232.6(5).1883-95.
13. Kumar D, Kumar A. Traditional Indian medicinal plants as a potential source for inhibition of Parkinson's disease. Indian J Pharmacol. 2014;46(6):608-615. doi: 10.4103.