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In Silico Evaluation of the Physicochemical, Pharmacokinetic and Drug-Likeness Properties of Gabapentin Using SwissADME

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Abstract: ***Gabapentin is a structurally distinctive γ-aminobutyric acid (GABA) analogue widely used in the management of neuropathic pain and as an anticonvulsant agent. The present study focuses on the in silico evaluation of the physicochemical, pharmacokinetic, drug-likeness, and medicinal-chemistry properties of gabapentin using the SwissADME web-based platform. The molecular structure of gabapentin was subjected to computational analysis to determine key parameters including molecular weight, hydrogen-bonding characteristics, topological polar surface area (TPSA), lipophilicity, aqueous solubility, gastrointestinal (GI) absorption, blood–brain barrier (BBB) permeability, cytochrome P450 (CYP) enzyme inhibition, and compliance with established drug-likeness rules. The predicted results provide an integrated assessment of the relationship between the molecular structure of gabapentin and its absorption, distribution, metabolism, and excretion (ADME) characteristics. The analysis indicates that gabapentin possesses favorable physicochemical properties and satisfies major drug-likeness criteria, while its polar and ionizable structural features influence its permeability and distribution characteristics. The SwissADME profile also provides useful insights into the absence or presence of significant metabolic interactions predicted through major CYP isoenzymes. Overall, the study demonstrates the usefulness of SwissADME as a rapid computational tool for preliminary characterization of gabapentin and provides a structural basis for understanding its pharmacokinetic behavior. Such in silico approaches can complement experimental investigations and support the rational evaluation of drug molecules in pharmaceutical and medicinal chemistry research.***

Keywords: Gabapentin; SwissADME; ADME; Drug-likeness; Pharmacokinetics; Lipophilicity; GI absorption; Blood–brain barrier; CYP inhibition; In silico analysis

1. Introduction

Gabapentin is a structurally distinctive analogue of **γ-aminobutyric acid (GABA)** and is an important therapeutic agent used primarily in the management of neuropathic pain and as an anticonvulsant drug. Although structurally related to GABA, gabapentin does not act simply by mimicking the classical inhibitory action of GABA. Its pharmacological activity is associated with interaction with specific molecular targets involved in neuronal excitability, making it an important compound in the treatment of neurological disorders. [7–9]

The physicochemical characteristics of a drug molecule play an important role in determining its absorption, distribution, metabolism and excretion (ADME) properties. Parameters such as **molecular weight, lipophilicity, hydrogen-bonding capacity, topological polar surface area (TPSA), aqueous solubility and molecular flexibility** influence the interaction of a drug with biological membranes and aqueous physiological environments. Evaluation of these properties at an early stage of drug research can provide valuable information about the potential pharmacokinetic behavior of a compound. [1,2]

In silico drug-design and computational ADME approaches have become valuable complementary methods in pharmaceutical and medicinal chemistry research. Computational prediction can provide rapid information about molecular properties without requiring extensive experimental investigations at the initial screening stage. Among the available computational resources, **SwissADME** is a widely used web-based platform for estimating physicochemical properties, lipophilicity, water solubility, pharmacokinetic characteristics and drug-likeness of small molecules. [1]

SwissADME provides predictions of important parameters including gastrointestinal absorption, blood–brain barrier (BBB) permeability, P-glycoprotein (P-gp) substrate status, cytochrome P450 (CYP) enzyme interactions, skin permeation and commonly used drug-likeness filters such as **Lipinski, Ghose, Veber and Muegge rules**. These parameters provide an integrated computational assessment of the molecular features that may influence the pharmacokinetic behavior of a candidate drug. [1]

Gabapentin is particularly interesting for computational ADME evaluation because its molecular structure contains **polar and ionizable functional groups**, which strongly influence its solubility, lipophilicity and membrane permeability. Therefore, analysis of its molecular descriptors provides an opportunity to establish a relationship between its structural characteristics and predicted ADME behavior.

In the present study, **SwissADME was employed to investigate the physicochemical, lipophilicity, aqueous-solubility, pharmacokinetic and drug-likeness properties of gabapentin**. The study evaluates molecular descriptors including molecular weight, hydrogen-bond donors and acceptors, TPSA, fraction of sp^3-hybridized atoms and rotatable bonds, together with different predicted lipophilicity and solubility parameters. Pharmacokinetic characteristics including gastrointestinal absorption, BBB

permeability, P-gp substrate status and skin permeation were also examined. In addition, the available drug-likeness predictions were evaluated using established computational filters. The objective of this work is to provide a comprehensive **in silico structure–property and ADME profile of gabapentin** and to demonstrate the usefulness of SwissADME as a rapid preliminary tool for pharmaceutical and medicinal-chemistry investigations.

Summary of SwissADME Findings of gabapentin.

Parameter	SwissADME result	Interpretation
Molecular formula	$C_9H_{17}NO_2$	Small molecular structure
Molecular weight	171.24 g/mol	Low molecular weight
Heavy atoms	12	Relatively small molecule
Fraction Csp^3	0.89	Highly aliphatic/3D character
Rotatable bonds	3	Moderate flexibility
H-bond acceptors	3	Good H-bond accepting capacity
H-bond donors	2	Good H-bond donating capacity
TPSA	63.32 Å²	Moderately polar molecule
XLOGP3	−1.10	Low predicted lipophilicity
WLOGP	1.37	Moderate lipophilicity
MLOGP	1	Moderate lipophilicity
SILICOS-IT LogP	1.24	Moderate lipophilicity
Consensus LogP	0.63	Low-to-moderate lipophilicity
ESOL LogS	−0.01	Very soluble
ESOL solubility	1.67 × 10² mg/mL	Very soluble
Ali LogS	0.26	Highly soluble
Ali solubility	3.12 × 10² mg/mL	Highly soluble
SILICOS-IT LogS	−1.35	Soluble
SILICOS-IT solubility	7.56 mg/mL	Soluble
GI absorption	High	Favorable predicted GI absorption
BBB permeant	Yes	Predicted BBB permeability
P-gp substrate	No	P-gp substrate not predicted
CYP1A2 inhibition	Temporarily unavailable	Cannot be interpreted
CYP2C19 inhibition	Temporarily unavailable	Cannot be interpreted
CYP2C9 inhibition	Temporarily unavailable	Cannot be interpreted
CYP2D6 inhibition	Temporarily unavailable	Cannot be interpreted
CYP3A4 inhibition	Temporarily unavailable	Cannot be interpreted
Log Kp	−8.13 cm/s	Very low predicted skin permeation
Lipinski	Yes; 0 violation	Favorable
Ghose	Yes	Favorable

2. Results and Discussion

SwissADME Analysis of Gabapentin

The SwissADME analysis was performed to evaluate the physicochemical, lipophilicity, aqueous-solubility, pharmacokinetic, and drug-likeness characteristics of gabapentin. The calculated molecular formula of gabapentin was **$C_9H_{17}NO_2$**, with a molecular weight of **171.24 g/mol**. The molecule contains **12 heavy atoms**, a fraction of sp^3-hybridized atoms of **0.89**, and **3 rotatable bonds**, indicating a relatively small and structurally flexible aliphatic molecule. The calculated **topological polar surface area (TPSA) was 63.32 Å²**, while the molecule possesses **3 hydrogen-bond acceptors and 2 hydrogen-bond donors**. These characteristics indicate an appreciable polar character and a strong capacity for hydrogen-bonding interactions with the aqueous biological environment.

Lipophilicity

The calculated lipophilicity values showed some variation among the different computational models. The **XLOGP3 value was −1.10**, whereas WLOGP, MLOGP, and SILICOS-IT gave values of **1.37, 1.00, and 1.24**, respectively. The resulting **consensus LogP was 0.63**. The consensus value indicates that gabapentin has **low-to-moderate lipophilicity**, rather than a strongly lipophilic character. The relatively low lipophilicity is consistent with the presence of the amino and carboxylic acid functionalities in the molecule. Such polarity is expected to favor aqueous interactions while potentially limiting simple passive diffusion through highly lipophilic biological membranes. [1]

The variation among the individual LogP models is noteworthy and demonstrates the model-dependent nature of computational lipophilicity prediction. Therefore, the **consensus LogP (0.63)** is the most appropriate value for the overall interpretation of gabapentin's lipophilic character.

Water Solubility

The three SwissADME solubility models predicted favorable aqueous solubility. The **ESOL model gave a LogS of −0.01**, corresponding to a predicted solubility of approximately **1.67 × 10² mg/mL (0.976 mol/L)** and classified the compound as **"Very soluble."** The Ali model predicted a **LogS of 0.26**, corresponding to approximately **3.12 × 10² mg/mL (1.82 mol/L)** and classified gabapentin as **"Highly soluble."** The SILICOS-IT model gave a comparatively lower **LogS of −1.35**, corresponding to approximately **7.56 mg/mL (4.42 × 10^{-2} mol/L)**, while still classifying the compound as **"Soluble."** [1,6]

Although the absolute solubility values differ between prediction models, all three models indicate that gabapentin possesses **favorable aqueous-solubility characteristics**. This behavior can be related to its relatively small molecular size, polar functional groups, hydrogen-bonding capacity, and ionizable nature. The agreement in the qualitative classification- ranging from soluble to very/highly soluble- provides supportive evidence for good interaction with an aqueous environment.

Pharmacokinetic Properties

The SwissADME pharmacokinetic prediction indicated **high gastrointestinal (GI) absorption** for gabapentin. This suggests a favorable predicted capacity for gastrointestinal uptake. The high GI absorption prediction, together with the favorable aqueous-solubility profile, indicates that the physicochemical characteristics of the molecule are compatible with oral administration. [1]

Interestingly, the SwissADME output also predicted **BBB permeability ("Yes")**. This result indicates that, according

to the computational model used in the analysis, gabapentin has the potential to cross the blood–brain barrier. This finding is particularly relevant because gabapentin is pharmacologically associated with activity in the central nervous system. Nevertheless, the BBB prediction should be regarded as a **computational prediction rather than direct experimental evidence of brain penetration**. [1]

The analysis further indicated that gabapentin is **not predicted to be a P-glycoprotein (P-gp) substrate**. A "No" prediction suggests that P-gp-mediated efflux is not predicted to be a major determinant of the compound's disposition according to this model. This may be relevant when considering the potential influence of transporter-mediated efflux on intestinal or BBB distribution. [1]

CYP Enzyme Inhibition

The SwissADME output reports the predicted inhibition status for **CYP1A2, CYP2C19, CYP2C9, CYP2D6, and CYP3A4 as "Temporarily unavailable."** Consequently, no scientifically justified conclusion regarding gabapentin's CYP-inhibitory potential can be drawn from the supplied SwissADME results. [1]. For publication, it is preferable to report this explicitly rather than describing gabapentin as a CYP inhibitor or non-inhibitor based on the present output. Additional experimental or validated computational evidence would be required to characterize its interaction with individual CYP isoenzymes.

Skin Permeation

The predicted **Log Kp value was −8.13 cm/s**, indicating very low predicted skin permeability. Thus, based on the SwissADME calculation, gabapentin is not expected to readily permeate the skin. This finding is consistent with the molecule's relatively polar character and modest lipophilicity. [1]

Drug-Likeness

Gabapentin showed favorable drug-likeness characteristics in the parameters visible in the supplied SwissADME output. In particular, it **passed Lipinski's rule with zero violations**, indicating that the molecule falls within the specified physicochemical limits of the Lipinski filter. The compound also received a **"Yes" classification under the Ghose filter** in the displayed results.

The absence of Lipinski violations is supported by gabapentin's relatively low molecular weight, moderate hydrogen-bonding characteristics, and relatively low consensus lipophilicity. However, drug-likeness filters should be regarded as screening tools rather than definitive predictors of pharmacological activity, bioavailability, or clinical efficacy. [2]

3. Conclusion

Overall, the SwissADME analysis demonstrates that gabapentin possesses a favorable physicochemical and drug-likeness profile characterized by low molecular weight (171.24 g/mol), moderate polarity (TPSA 63.32 Å²), a consensus LogP of 0.63, and favorable predicted aqueous solubility. The ESOL, Ali, and SILICOS-IT models consistently classified gabapentin as soluble, although the predicted absolute solubility values varied among the models. The compound was predicted to exhibit high gastrointestinal absorption and BBB permeability, while it was not predicted to be a P-glycoprotein substrate. The very low predicted skin-permeation coefficient (Log Kp = −8.13 cm/s) suggests limited transdermal permeability. Gabapentin satisfied Lipinski's rule with zero violations and also passed the Ghose filter, supporting its favorable drug-like physicochemical characteristics. However, predictions for inhibition of CYP1A2, CYP2C19, CYP2C9, CYP2D6, and CYP3A4 were reported as temporarily unavailable and therefore cannot be interpreted from the present analysis. Collectively, these computational findings provide a useful structural and physicochemical basis for understanding the ADME characteristics of gabapentin and demonstrate the applicability of SwissADME as a preliminary in silico tool for drug-property evaluation. [1–6]

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