

ADMETPredictor™ and GastroPlus™ Drug Design Activity Manual

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Objectives for ADMET Predictor™

- Identify biopharmaceutical properties on an excel sheet exported from ADMET predictor
- Learn how to use ADMET Predictor™ software to calculate biopharmaceutics properties
- Explain how a modification to a drug structure might alter ADMET properties and bioavailability of a drug.

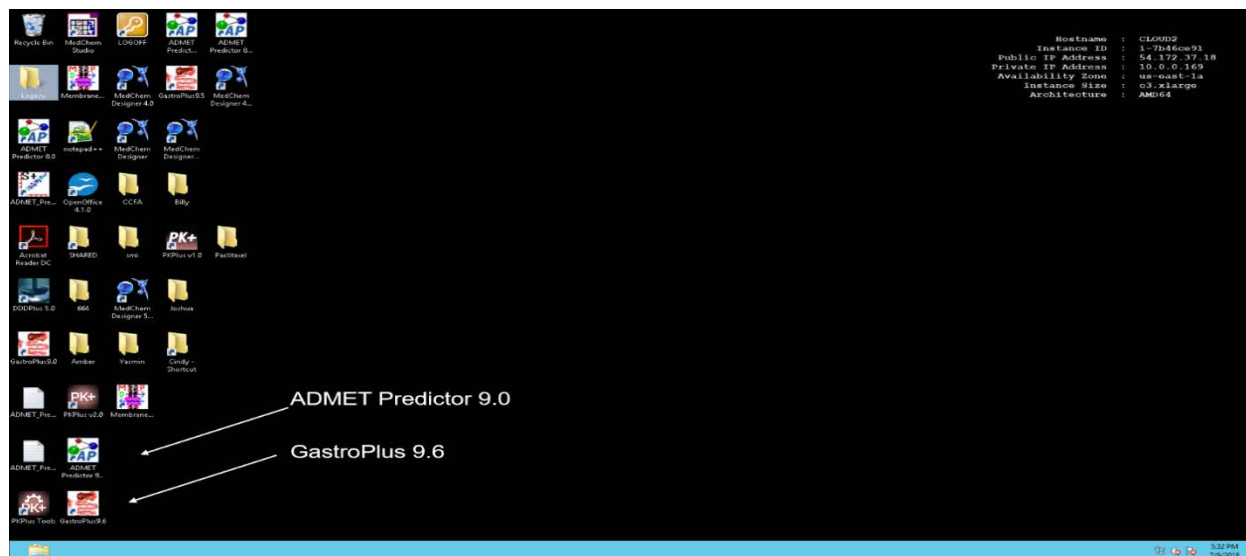
Preparation

- SMILES string: For the ADMET Predictor™ activity, you will need to create a simplified molecular-input line-entry system, or a SMILES string for input of a molecule or drug structures into the program. A SMILES string is a way to represent a drug molecule by text. The following link has examples and information on how to create SMILES strings for drug molecules:
<https://www.daylight.com/dayhtml/doc/theory/theory.smiles.html>. A SMILES string may also be copied from PubChem and pasted into a text editor like Notepad. Other molecular or chemical formats can also be used as input, such as Structure Data Format (sdf extension) files and Molfile (mol extension), and also MedChem Designer™ (freely available program from Simulations Plus).
- Students should have lectures about pKa and how solubility changes with pH; Lipinski's rule of five and other chemical descriptors used to determine oral bioavailability and ADMET biopharmaceutic properties such as the number of hydrogen bond acceptors and donors, rotatable bonds, polar surface area and the partition coefficient or LogP and LogD. Programs that calculate basic parameters of drug-likeness can be used as an introduction to this section. A basic lecture on biopharmaceutics and ADMET and a basic description of metabolism and transporters is also helpful.

Instructions

Learning to run ADMET Predictor™

(1) Use “Remote Desktop” to access ADMET Predictor™. For Apple laptops, there is a “Remote Desktop” app that can be used. Enter the username and password shown in class.

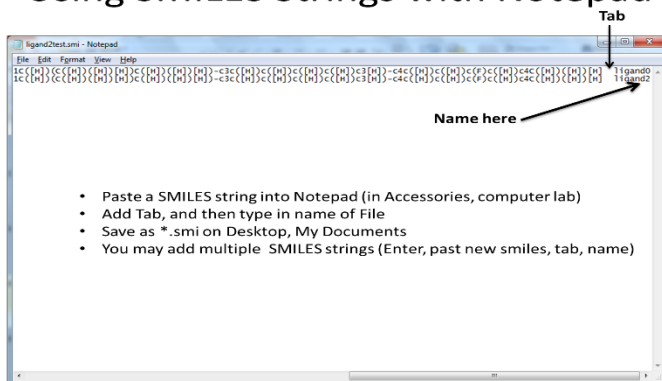


(2) Click on the ADMET Predictor™ icon to open the program.

(3) Create a folder on the “remote desktop” named ADMET and save all your ADMET Predictor™ files in this folder. You will be working with multiple input and output files and it is important for you to know where your files are.

(4) Create a SMILES string (simplified molecular-input line-entry system) in any text editor on your personal laptop. You may use a drug molecule from your project. Make sure you add the extension *.smi to the file name. You cannot import your structure file unless you give it the *.smi extension. Copy and paste the smiles string to your ADMET folder on the “remote desktop”.

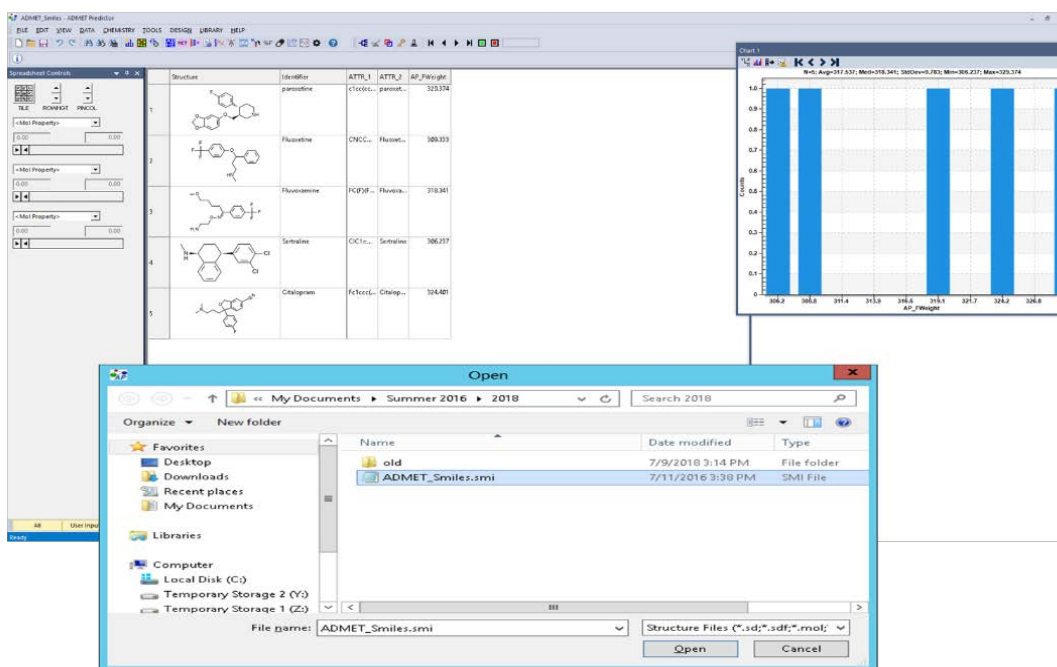
Using SMILES Strings with Notepad



(5) If you have not created a smiles string, you can download a sample smiles strings from Blackboard, named ADMET_Smiles.smi. Copy and paste the smiles string into your “remote desktop” ADMET folder.

(6) Click on the ADMET Predictor™ icon to open the program (see step 1). Once the program is open, open your smiles string from your “remote desktop” ADMET folder.

Click on icon; File Open > *.smi file (sdf and mol)



(7) Run an ADMET Predictor™ calculation by clicking on the icon shown below. The various columns generated can be exported as an excel file and are briefly explained in the Help Menu.

Calculate ADMET Properties

The screenshot shows the ADMET Predictor software interface. A spreadsheet displays various chemical properties for five compounds. A dialog box titled "Calculate ADMET properties" is open, showing the process status and options to calculate properties like Physicochemical, Metabolism, and Toxicity. The spreadsheet columns include Structure, Identifier, *Risk*, *PCP*, ADMET_Risk, ADMET_Code, S+Acidic_pKa, S+Mixed_pKa, S+Basic_pKa, DfPCof, MlogP, S+logP, S+logD, logHLIC, S+Peff, S+MDCK, Perm.Comes, Perm.Skin, S+Sw, S+H_Sand, S+L_Inhibin, SolFactor, S+5_pH, and S+5pD.

Click on "Edit", "Find Column", To navigate the Spreadsheet

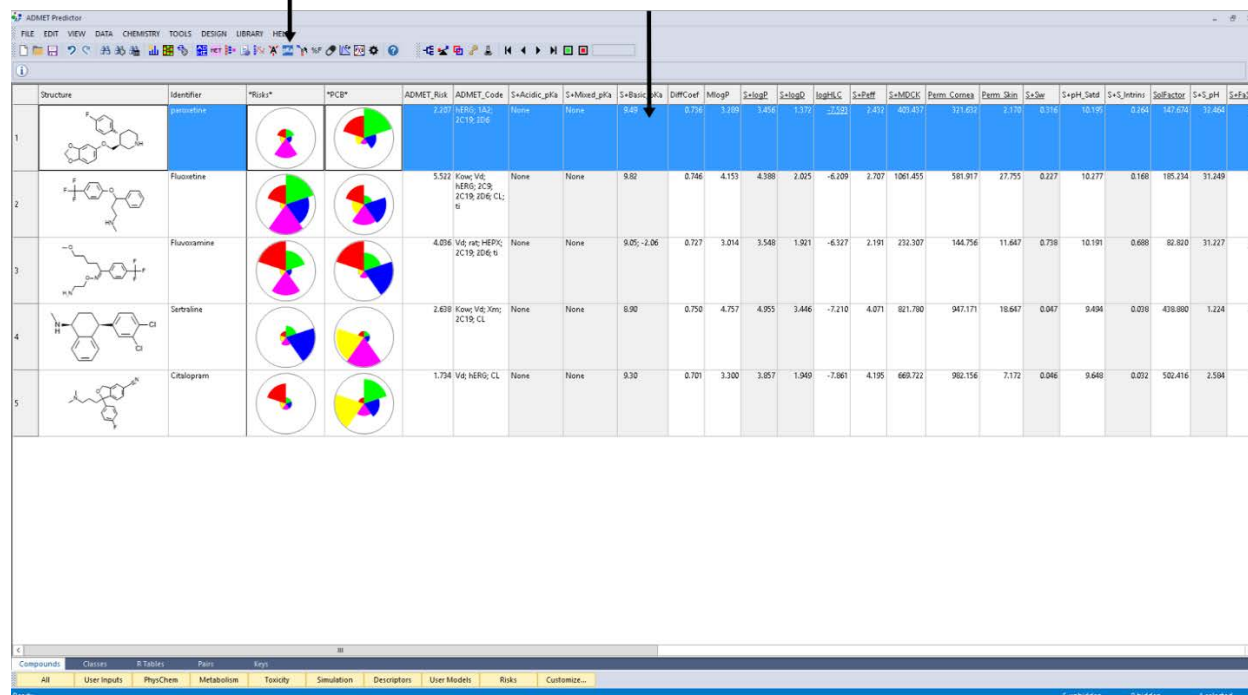
(8) To view the atomic sites of metabolism, click on the icon shown below, and the enzyme. Atomic sites of metabolism are shown as red circles. To copy the image, click on the clipboard.

View Sites of Metabolism

The screenshot shows the ADMET Predictor software interface with the "Atomic Properties Display - paroxetine" window open. This window displays the chemical structure of paroxetine with red circles indicating metabolic sites. The sites are categorized by enzyme: CYP1A2_Sites of metabolism, CYP2C19_Sites of metabolism, CYP2D6_Sites of metabolism, and CYP3A4_Sites of metabolism. The background spreadsheet is visible, showing the same data as in the previous screenshot.

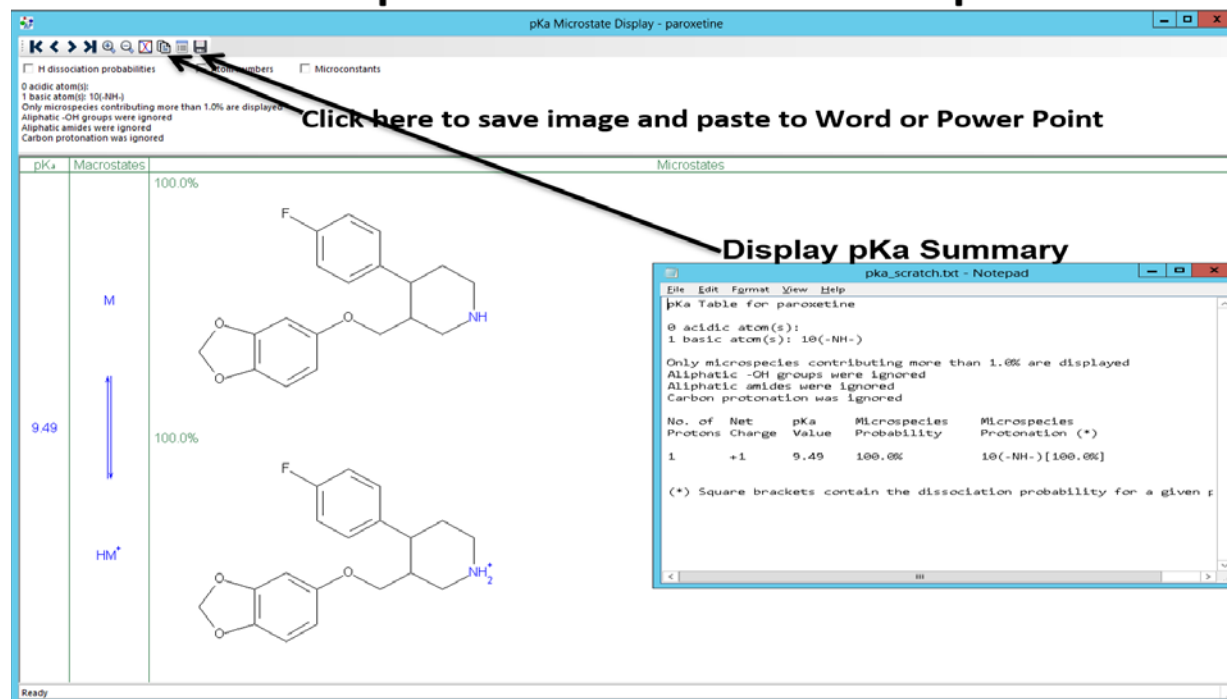
(9) To view the pKa, click on the icon shown below or double click on the pKa cell.

Calculate pKa (or dbl click on pKa in spread sheet)



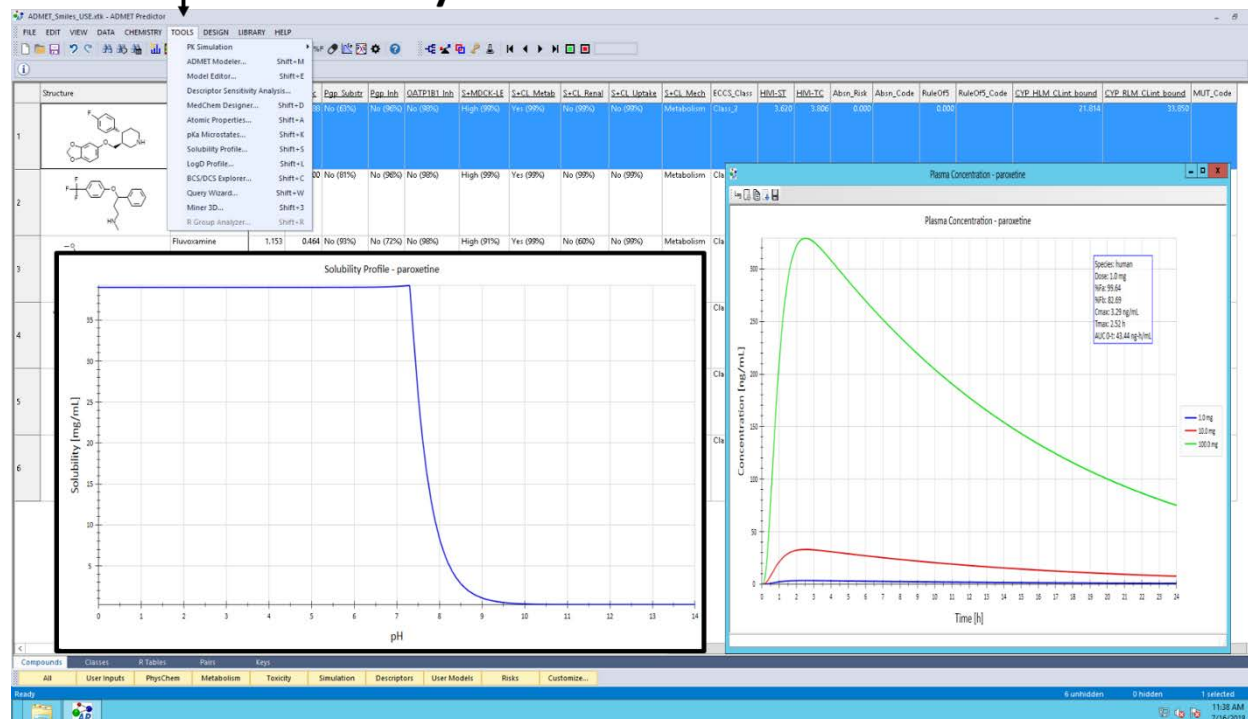
| Structure | Identifier | *Risks* | *PCB* | ADMET_Risk | ADMET_Code | S+Acidic_pKa | S+Mixed_pKa | S+Basic_pKa | DiffCoef | MlogP | S+logP | S+logD | logHLS | S+Peff | S+MDCK | Perm_Cornea | Perm_Skin | S+Ser | S+H_Setd | S+S_Intens | SelfFactor | S+S_pH | S+FaSS |
|-----------|-------------|---------|-------|---|------------|--------------|-------------|-------------|----------|-------|--------|--------|--------|--------|----------|-------------|-----------|-------|----------|------------|------------|--------|--------|
| | Paroxetine | | | 2.07 (NR0; 1A); 2C19; 2D6 | None | None | None | 9.49 | 0.796 | 3.396 | 3.404 | 3.372 | -2.531 | 2.412 | 401.451 | 171.435 | 2.139 | 0.316 | 10.195 | 0.164 | 147.674 | 31.464 | 0 |
| | Fluoxetine | | | 5.522 (Low VB; NR0; 2C9; 2C19; 2D6; CL; S) | None | None | None | 9.82 | 0.786 | 4.153 | 4.398 | 2.025 | -6.209 | 2.707 | 1061.455 | 581.917 | 27.755 | 0.227 | 10.277 | 0.168 | 185.234 | 31.249 | 0 |
| | Fluvoxamine | | | 4.096 (Vg rat; HEPG; 2C19; 2D6; S) | None | None | None | 9.05; -2.06 | 0.727 | 3.014 | 3.548 | 1.911 | -6.527 | 2.191 | 232.307 | 144.756 | 11.647 | 0.738 | 10.191 | 0.688 | 82.820 | 31.227 | 0 |
| | Sertraline | | | 2.638 (Low VB; 10m; 2C19; CL) | None | None | None | 8.90 | 0.750 | 4.757 | 4.955 | 3.446 | -7.210 | 4.071 | 821.780 | 947.171 | 18.647 | 0.047 | 9.494 | 0.078 | 418.880 | 1.224 | 0 |
| | Citalopram | | | 1.734 (Vg; NR0; CL) | None | None | None | 9.30 | 0.701 | 3.300 | 3.857 | 1.949 | -7.061 | 4.195 | 669.722 | 982.156 | 7.172 | 0.046 | 9.648 | 0.072 | 502.416 | 2.584 | 1 |

Example of Paroxetine pKa



(10) The Solubility curve and a simple pharmacokinetic (PK) simulation can be found in tools.

Solubility Curve and PK Simulation



(11) Export as an excel file or save the file in ADMET Predictor™ format. A brief explanation of each column is in the Help Menu and Manual.

Save File as (ADMET Predictor *.xtk) or Export as an Excel File

| Structure | Identifier | *Risk* | *PCP* | ADMET_Risk | ADMET_Code | S-Acidic_pKa | S-Mixed_pKa | S-Basic_pKa | DHPCof | MlogP | S-logP | S-logD | logHLG | S-Peff | S-MICCK | Perm_Carbox | Perm_Skin | S-Sw | S-pH_Satd | S-S_Introin | SolFactor | S-S_pH | S-SaSS |
|---|-------------|--------|-------|------------|--------------------------------------|--------------|-------------|-------------|--------|-------|--------|--------|--------|--------|----------|-------------|-----------|-------|-----------|-------------|-----------|--------|--------|
| <chem>C1=CC=C(C=C1)C2=CC=CC=C2C3=CC=CC=C3C4=CC=CC=C4C5=CC=CC=C5C6=CC=CC=C6C7=CC=CC=C7C8=CC=CC=C8C9=CC=CC=C9C10=CC=CC=C10</chem> | paroxetine | | | 2.007 | HERG; J02; 2C19; J04 | None | None | 9.69 | 0.736 | 3.300 | 3.604 | 3.372 | -2.501 | 2.810 | 403.431 | 111.620 | 1.170 | 0.316 | 10.135 | 0.268 | 161.674 | 10.464 | 8 |
| <chem>C1=CC=C(C=C1)C2=CC=CC=C2C3=CC=CC=C3C4=CC=CC=C4C5=CC=CC=C5C6=CC=CC=C6C7=CC=CC=C7C8=CC=CC=C8C9=CC=CC=C9C10=CC=CC=C10</chem> | Fluoxetine | | | 5.522 | Kow; V6; HERG; J02; 2C19; J04; CL; b | None | None | 9.62 | 0.746 | 4.153 | 4.388 | 2.025 | -6.209 | 2.707 | 1061.455 | 581.917 | 27.755 | 0.227 | 10.277 | 0.168 | 185.234 | 31.249 | 0 |
| <chem>C1=CC=C(C=C1)C2=CC=CC=C2C3=CC=CC=C3C4=CC=CC=C4C5=CC=CC=C5C6=CC=CC=C6C7=CC=CC=C7C8=CC=CC=C8C9=CC=CC=C9C10=CC=CC=C10</chem> | Fluvoxamine | | | 4.096 | Vd; rat; HEPK; 2C19; J04; b | None | None | 9.05-2.06 | 0.727 | 3.054 | 3.548 | 1.921 | -6.327 | 2.191 | 232.387 | 144.756 | 11.647 | 0.738 | 10.191 | 0.688 | 82.820 | 31.227 | 0 |
| <chem>C1=CC=C(C=C1)C2=CC=CC=C2C3=CC=CC=C3C4=CC=CC=C4C5=CC=CC=C5C6=CC=CC=C6C7=CC=CC=C7C8=CC=CC=C8C9=CC=CC=C9C10=CC=CC=C10</chem> | Sertraline | | | 2.638 | Kow; V6; Xmc; 2C19; CL | None | None | 8.90 | 0.750 | 4.757 | 4.955 | 3.446 | -7.210 | 4.071 | 821.788 | 947.171 | 18.647 | 0.047 | 9.494 | 0.070 | 438.890 | 1.224 | 0 |
| <chem>C1=CC=C(C=C1)C2=CC=CC=C2C3=CC=CC=C3C4=CC=CC=C4C5=CC=CC=C5C6=CC=CC=C6C7=CC=CC=C7C8=CC=CC=C8C9=CC=CC=C9C10=CC=CC=C10</chem> | Citalopram | | | 1.734 | Vd; HERG; CL | None | None | 9.30 | 0.701 | 3.300 | 3.857 | 1.949 | -7.861 | 4.195 | 669.722 | 982.156 | 7.172 | 0.046 | 9.648 | 0.072 | 520.416 | 2.504 | 1 |

Activity for ADMET Predictor™

Part 1: Examine an ADMET Predictor™ Output File in Excel

- Download from Blackboard the “ADMET_Excel.xlsx” file exported from the ADMET Predictor™ demonstration/lecture.
- Find the following in the “ADMET_Excel.xlsx” file:
 - (1) pKa (acid or base?) Compare it with an experimental pKa value from the primary literature and draw the charged structure. Are the experimental values similar?
 - (2) LogP and LogD (why are they different?)
 - (3) Intrinsic Solubility (S+S_Intrins in mg/mL); Compare this value with a value from the primary literature (the intrinsic solubility is the solubility of the drug when it is neutral).
 - (4) Solubility Factor (the solubility factor is the ratio of ionic solubility to intrinsic solubility)
 - (5) MW (AP_FWeight)
 - (6) Permeability (S+Peff in cm/s×10⁴)
 - (7) Lipinski Hydrogen bond donors and acceptors (can you count them yourself?)
 - (8) Rotatable Bonds (N_FrRotB; how many? Can you count them?)
 - (9) Polar Surface Area (T_PSA; why is this important?)
 - (10) Metabolism and CYPs (or other enzymes) that metabolize your drug
 - (11) Transporters? Is your drug an inhibitor or substrate? (Compare with the literature)
 - (12) Any issues with toxicity?

View the Help Menu to see a brief explanation of the abbreviations for each column.

Part 2: Running an ADMET Predictor™ Calculation

- (1) Run ADMET Predictor™ for your group's drugs and analogues (make a SMILES string file or use the ADMET_Smiles.smi provided on Blackboard).
 - (2) Produce an Excel file with all the properties (name the Tab “Properties”)
 - (3) Make a graphic image of the metabolic sites and paste the structures into Excel (name the Tab “Metabolism”).
 - (4) Make a graphic image of the pKa equilibrium and the solubility profiles and paste the images into Excel (name the Tab “Solubility”).
 - (5) Make a graphic image of the plasma concentration-time profile and paste the images into Excel (name the Tab “PK”).
 - (6) Review your exported Excel file and determine the following:
 - a. Are any of your analogues more soluble than your group's drug?
 - b. Do any of your analogues have a higher LogP than your group's drug?
 - c. Are any of your analogues more permeable than your group's drug?
 - d. Were any sites of metabolism changed? Deleted? Added? Different enzyme?
 - (7) Describe how the changes in a, b, c, and d, in part (6) might affect the ADMET properties and the bioavailability of the analogues (compare to your original group's drug)
- Submit part 2-5 as an excel file and part 6 as a Word Document or Power Point file.
- Upload to Blackboard by the due date and be prepared to explain your group's results to the class.

Objectives for GastroPlus™

- Learn how to run a simulation on GastroPlus™ software to calculate pharmacokinetic parameters
- Identify and explain the various tabs in GastroPlus™

- Describe how Fa (Fraction absorbed; fraction of the concentration of drug in enterocytes), FDp (fraction of the concentration of drug in the portal vein), and F (fraction of the concentration of drug in the systemic circulation/blood) affect bioavailability
- Identify which ADMET or biopharmaceutical properties might affect Fa, FDp, and F (Describe how pKa, pH dependent solubility, dissolution, permeability and metabolism affects the amount of drug absorbed)
- Explain the Absorption and Dissolution curves
- Identify important pharmacokinetic parameters from a GastroPlus™ simulation
- Explain how a modification to a drug structure might alter the ADMET properties and the bioavailability of the drug

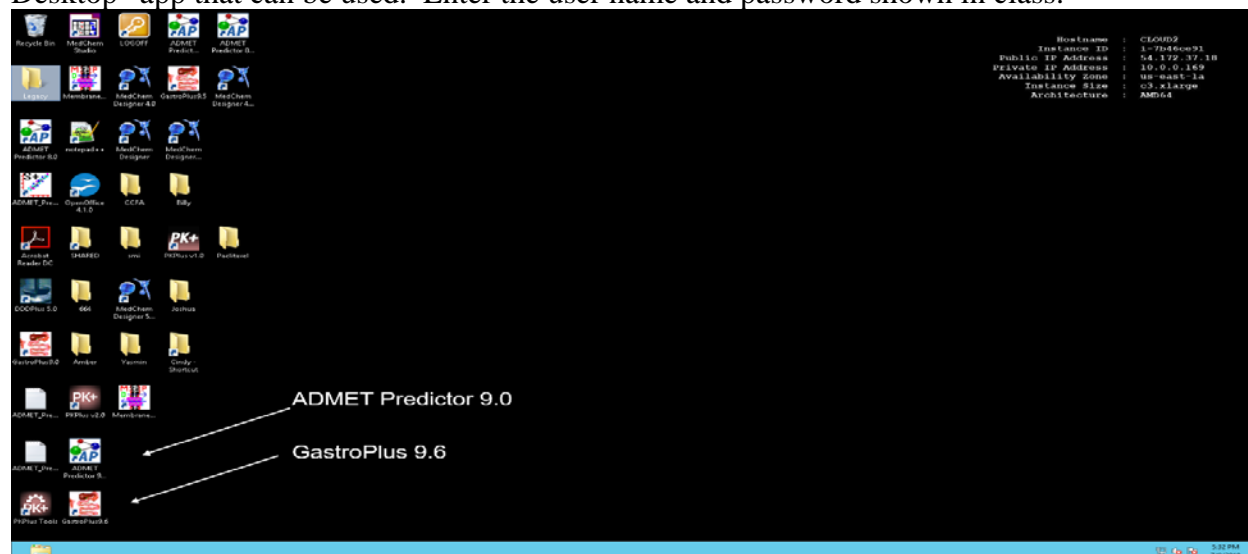
Preparation

- SMILES string: You will need to create a simplified molecular-input line-entry system, or a SMILES string for input into the program. A SMILES string may also be copied from PubChem. Other molecular or chemical formats can also be used as input, such as Structure Data Format (sdf extension) files and Molfile (mol extension), and also MedChem Designer™ (freely available program from Simulations Plus).
- Students should have lectures about pKa, solubility, and how this affects dissolution and the Biopharmaceutical Classification System (BCS), a system to differentiate drugs based on their solubility and permeability. A lecture on the basic anatomy and physiology of the GI tract and how drugs are made bioavailable to the body is essential, including basic biopharmaceutical or ADMET properties and basic pharmacokinetic parameters such as Cmax, Tmax, AUC, and t_{1/2}.

Instructions

Part1: Practice Simulation

(1) Use “Remote Desktop” to access GastroPlus™. For Apple laptops, there is a “Remote Desktop” app that can be used. Enter the user name and password shown in class.



(2) Click on the GastroPlus™ icon to open the program and the demonstration database.

Demonstration Database

Select Drug by Clicking Here Or Here

Compound

Selected Compound: Propranolol HCl

Current= 1; Total= 3

Chemical Structure: CC(C)NCC(O)Cc1ccccc1

Molecular Formula: C₁₆H₂₁N_O₂

Molecular Weight (g/mol): 259.34

Reference logD: 1.54 @pH: 7.4

pKa Table

Enzyme Table

Transporter Table

ver. 8.0.0002

SI Trans Time (h) = 3.3 Mean Abs Time (h) = 0.571

Longest Diss. Time (h) is @ pH 1.0 = 0.001 hours

Max Abs Dose (S+) = 1.664E+6 mg Max Abs Dose (R) = 7.828E+5 mg

Support Files

Propranolol HCl.opd

Dosage Form: IR: Tablet

Initial Dose (mg): 140.28

Subsequent Doses (mg): 0

Dosing Interval (h): 0

Dose Volume (mL): 250

pH for Reference Solubility: 3

Solubility (mg/mL @pH=3): 125

Mean Precipitation time (sec): 900

Diff. Coeff. (cm²/s x 10⁻⁵): 0.829

Drug Particle Density (g/mL): 1.2

Particle Size: R=25.00, D=50.00

Effective Permeability

Source: Human

Peff (cm/s x 10⁻⁴): 2.91

Sim Peff x10⁻⁴ (Human): 2.91

Convert from User Data

Biorelevant Solubilities

Dose No. = 0.0309

Absorption No. = 5.783

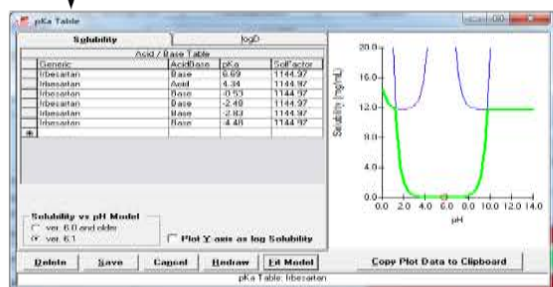
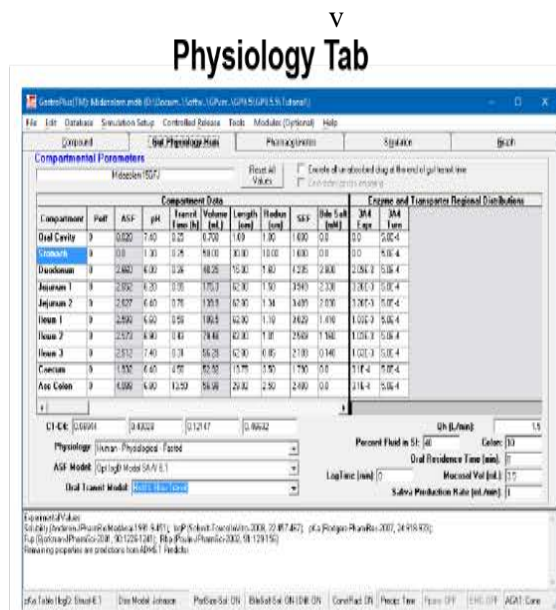
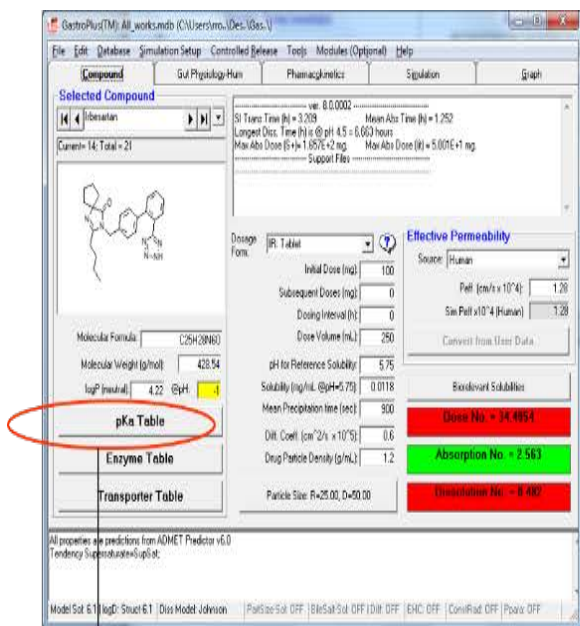
Dissolution No. = 4.924E+3

Notes

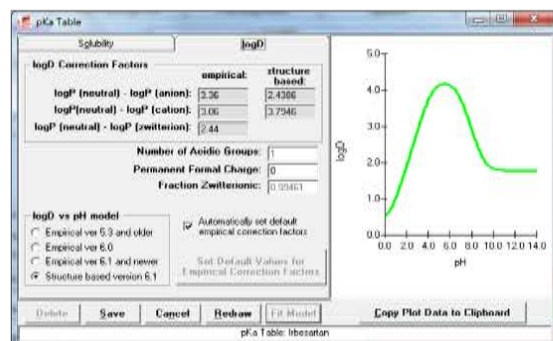
Model Sol: 6.1 | logD: Struct:6.1 | Diss Model: Johnson | PartSize:Sol: OFF | BileSalt:Sol: OFF | Diff: OFF | EHC: OFF | ConstRad: ON | Ppara: OFF

(3) The demonstration database contains various drug molecules with various properties. You may select and view each drug by clicking on the arrows shown above. The example screen shot shows propranolol and the “Compound” tab indicating the MW, LogP (or LogD), dose, dosage form, permeability and the solubility at a reference pH. Also shown are the Dose, Absorption and Dissolution Numbers (No.) in green. These are values related to the Biopharmaceutical Classification System (BCS), a system to differentiate drugs based on their solubility and permeability. The Dose Number is the ratio of the dose per volume (250 mL) divided by the lowest solubility of the drug from pH 1- 8. A value of <1 is good and means the drug can completely dissolve in 250 mL. The Absorption Number is the ratio of the small intestine transit time divided by the small intestine absorption time. A value >1 is good and means that the transit time in the small intestines is longer than the absorption time, which means that there is enough time for absorption. The Dissolution Number is the transit time divided by the small intestine dissolution time. A value >1 is good and means that the transit time in the small intestines is longer than the dissolution time, which means there is enough time for dissolution.

(4) Examine the various tabs in GastroPlus™ and the calculated properties. The Compound tab has the MW, LogP (or LogD), dose, dosage form, permeability and the solubility at a reference pH, along with a solubility curve and pKa (and LogD), which can be accessed by clicking on “pKa Table”. The Physiology tab has information for each section of the GI tract (pH, transit time, pH, etc.) and the physiology (human, dog, rat, etc. and fasted or fed) and various information for metabolizing enzymes (CYP in the GI tract) and transporters. The Pharmacokinetic tab has information about the model (Compartment, etc.), fraction unbound (fu), FPE (fraction extracted from the oral cavity, GI tract or liver), information on clearance (renal or systemic), volume of distribution, half-life, observed values (these are observed experimental values that can be typed in) and correction values or “Scale Factors” for metabolizing enzymes and transporters. Note that the windows can be captured using “print screen” or any capturing software and pasted to a document for an oral presentation or a report.

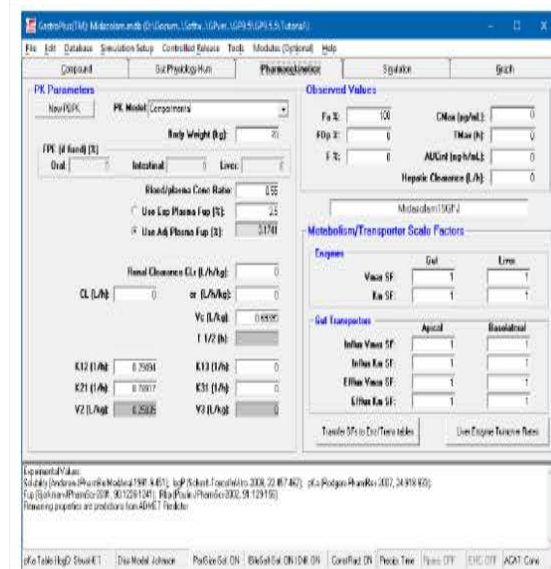


pKa, Solubility Factor
Solubility Curve
Check
Experimental values



Log D Curve

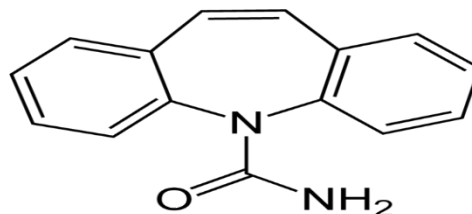
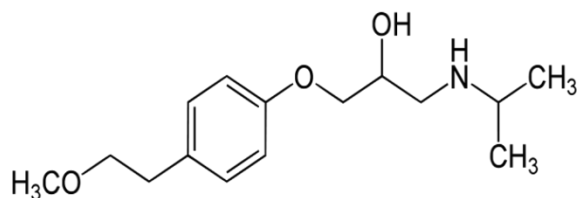
Pharmacokinetic Tab



(5) Go back to the Compound Tab and select Metoprolol Tartrate. Find the dose, dosage form, pKa, LogP or logD (indicate pH), reference solubility (pH?), solubility curve, intrinsic solubility (lowest solubility, when the drug is neutral).

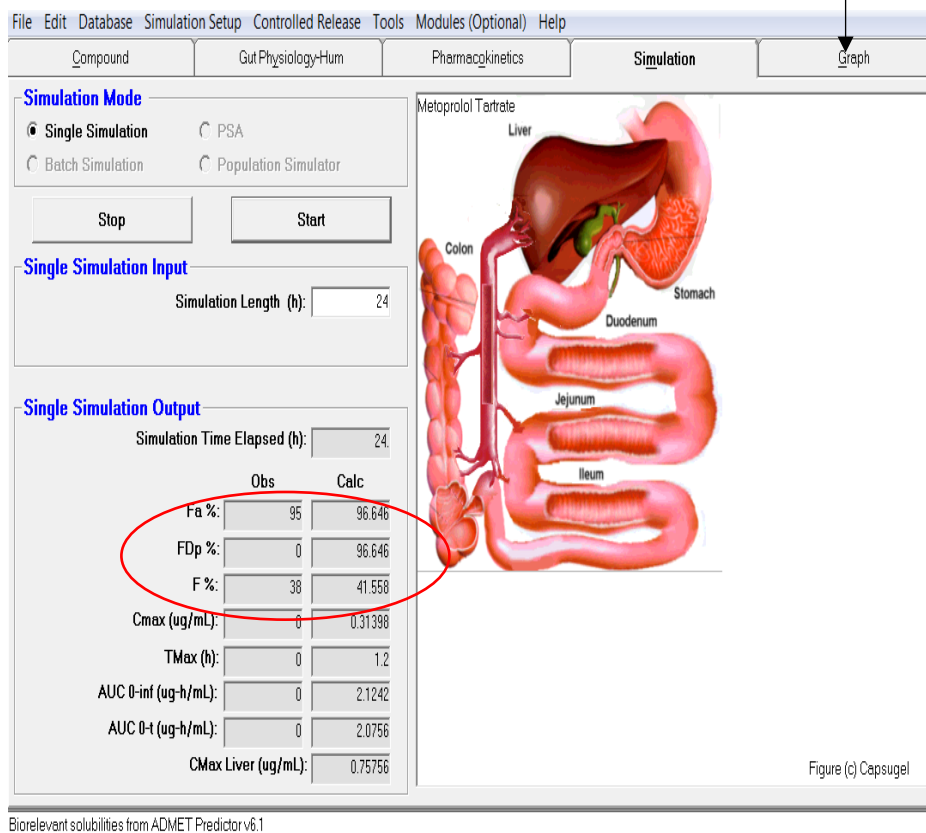
Practice Simulation

Try Simulation with Metoprolol and Carbamazepine

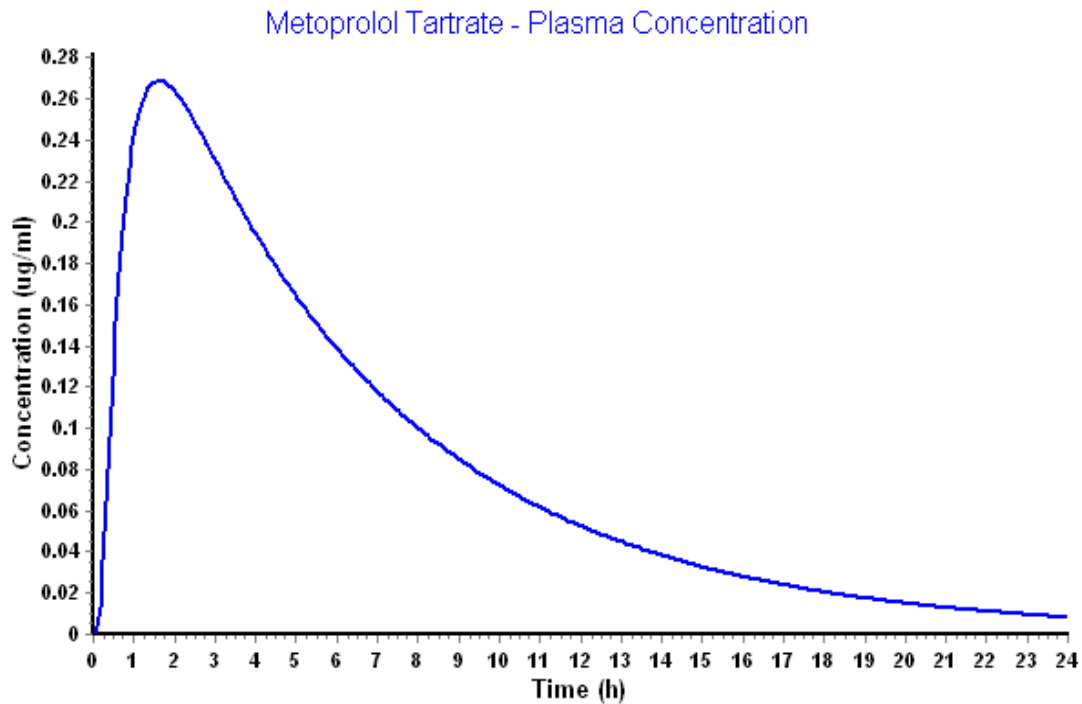


(6) Examine the Physiology and Pharmacokinetic tabs and look for Observed values.

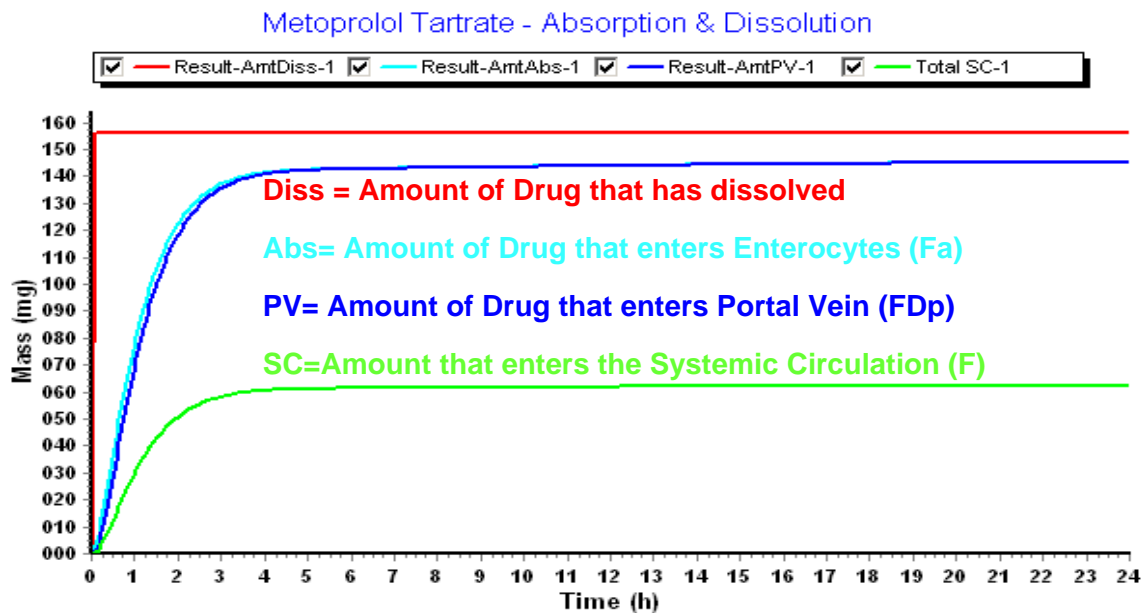
(7) Click on the Simulation tab to run an oral simulation for Metoprolol. Enter 24 hours (h) for the Simulation Length and click on “Start”. The simulation will show the observed (Obs) and calculated (Calc) values for Fa% (fraction absorbed into the enterocytes), FDP% (fraction absorbed into the portal vein) and F% (bioavailability), Cmax, Tmax, and AUC (area under the curve). To see the plasma concentration time curve and other graphs, click on the Graph tab. Repeat the Simulation for Carbamazepine.



(a) Plasma concentration time curve for metoprolol on the Graph tab.



(b) Amount per time of Metoprolol: Dissolved (AmtDiss=red curve); Absorbed in the enterocytes (Fa, AmtAbs=light blue curve); Absorbed into the portal vein (FDp, AmtPV=dark blue curve), and Absorbed into the systemic circulation (F, SC=green curve), on the Graph tab.

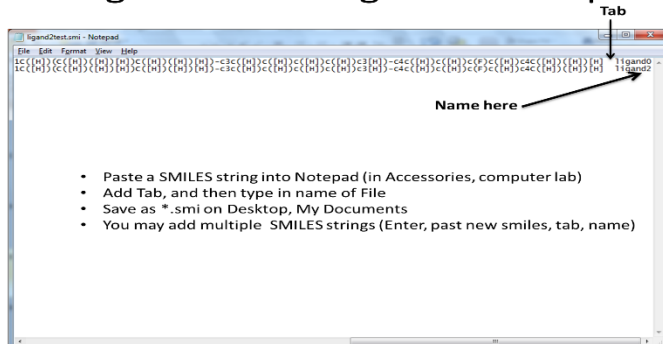


Part2: Importing a Structure

(1) Create a folder on the “remote desktop” named GastroPlus and save all your GastroPlus™ files in this folder. You will be working with multiple input and output files and it is important for you to know where your files are.

(2) Create a SMILES string in any text editor on your personal laptop. Make sure you add the extension *.smi to the file name. You cannot import your structure file unless you give it the *.smi extension. Copy and paste the smiles string to your GastroPlus folder on the “remote desktop”.

Using SMILES Strings with Notepad



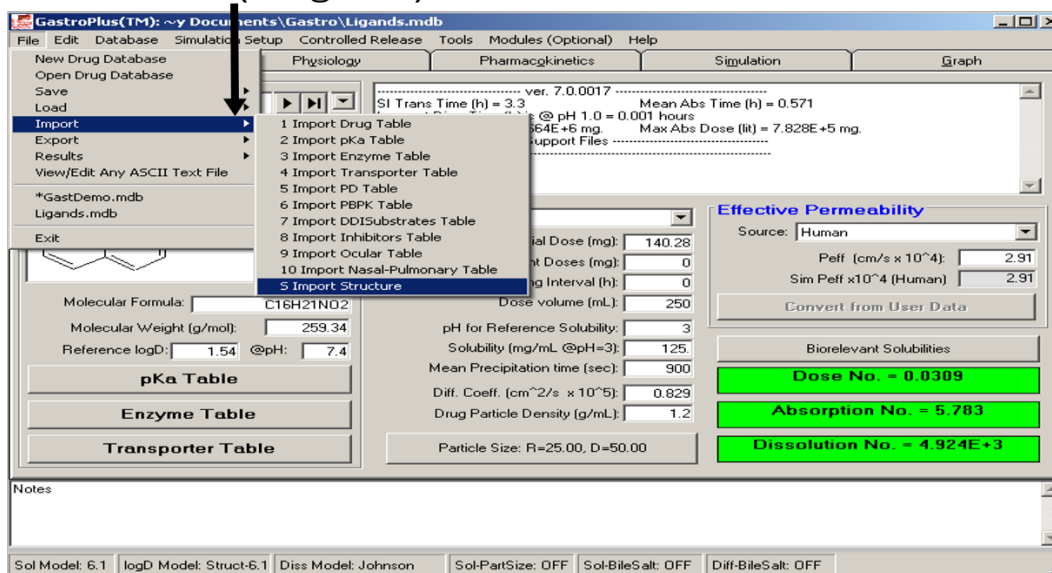
(3) If you have not created a smiles string, you can download a sample smiles strings from Blackboard, named ADMET_Smiles.smi. Copy and paste the smiles string into your “remote desktop” GastroPlus folder.

(4) Click on the GastroPlus™ icon to open the program (see step 1, practice simulation). Once the program is open, create a new GastroPlus™ database, name it “Practice” and save it in your GastroPlus™ folder on your “remote desktop”. Once the new database is created, import your SMILES string by clicking on File>Import>Import Structure. **Please note** that a structure cannot be imported until you create a new database.

Create a New Gastro Plus Database

File> New Drug Database (Click open, name it Practice.mdb)

Import Structure (drug.smi)



(5) The window shown below will appear if your imported file has the correct format. Click OK and do not change any properties (default calculation). All the calculated properties are from ADMET Predictor™.

Importing To GastroPlus Import SMILES string *.smi file

**Do Not Change
Any Properties
or Parameters;
Leave Default
and Predicted
values as is.**

**Click
OK**

(6) After clicking OK, examine the various tabs and run a simulation. Note: A systemic clearance (CL) will be estimated from the ADMET Predictor™ predicted hepatic metabolism if the CL values in the window shown above are used.

Activity for GastroPlus™

Part1: Sample Database Simulation

- (1) Run a simulation on the demonstration database for Metoprolol and Carbamazepine.
 - (2) Note the pKa, LogP and LogD (pH?), solubility curves, reference solubility (pH?), intrinsic solubility (the solubility of the drug when it is neutral or at its lowest solubility). Paste images into a document and compare the various parameters for Metoprolol and Carbamazepine.
 - (3) Examine the graphs of the Absorption and Dissolution curves. Can you explain why one drug dissolves slower than the other in the GI tract (AmtDiss)?
 - (4) Examine the graphs for Fa (AmtAbs), FDp (AmtPV), and F (SC). Paste images into a document and compare the parameters for Metoprolol and Carbamazepine.
 - (5) Would you predict one drug to be absorbed better into the enterocytes? If yes, why? Which values give you this information?
 - (6) Can you explain why the F% curves are different for Metoprolol and Carbamazepine?
 - (7) Identify important pharmacokinetic parameters in the plasma concentration-time curve (absorption phase, elimination phase, Cmax, Tmax, t_{1/2}, AUC)
 - (8) The observed F% for Carbamazepine is 70% but the simulated GastroPlus™ value for F% is 99%. Can you explain what might cause this difference for Carbamazepine in the simulation?
- Upload to Blackboard by the due date and be prepared to explain your groups results to the class using images, tables, etc. Include legends for all figures.

Part2: Importing a Structure and Running a Simulation

- (1) Import a drug structure into GastroPlus™ and examine the pH solubility curve for one of your drugs (your drug for the project or one of the ADMET_Smiles.smi). Do they look correct? Does the pKa look correct? Can you explain the shape of the solubility curve? Paste an image of the solubility curves for your drugs into a document.
 - (2) Run an oral GastroPlus™ simulation for an immediate release (IR) tablet, 24 hours, for your drug.
 - (3) Explain, Fa, FDp and F; Are they different? If yes, why are they different? Paste an image of the simulation tab showing the values for Fa, FDp and F for your drugs into a document.
 - (4) Explain the Diss, Ab, PV, and SC Curves. Paste an image of these curves for your drugs into a document.
 - (5) Can you find the absorption phase, elimination phase, Cmax, Tmax, t_{1/2}, AUC? Paste an image of the Plasma concentration time curve for your drug into a document and clearly label these parameters on the graph.
 - (6) Explain your drugs oral bioavailability? You should compare your drugs bioavailability to the primary literature (this is only for the unmodified version). How well did GastroPlus™ predict the Bioavailability of your drug?
 - (7) Look up the dose for your drug and change the dose on the compound tab. Does this change the results?
 - (8) Run a GastroPlus™ simulation for two modified structures of your drug. Is there a difference between the original and the unmodified drug? Are you improving or reducing the ADMET properties and the oral bioavailability? Explain your answer.
 - (9) Assume the modified structures will use the same dose as the original, unmodified drug and run the simulation again. Does this change the results?
 - (10) Advanced Exercise: Can you import a *.mol, *.sdf file? Can you import an excel smiles strings? Paste the ADMET_Smiles.smi strings into an excel file, save it as a tab delimited file, give the file the correct smile extension, and import it. Did it work?
- Upload to Blackboard by the due date and be prepared to explain your groups results to the class. Include legends for all figures.