Drug Dissolution Rate Analysis Using the Noyes-Whitney Model: Effect of Surface Area and Solubility on Pharmaceutical Dissolution

A Technical Project Report

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Abstract

Dissolution is the process of solid substance dissolving , which is critical in bioavailability of active pharmaceutical ingredients in the early stages of drug development. Drug dissolution is the prerequisite for drug absorption which in turn influences the rate and extent at which the administered dose of a drug reaches the general circulation. Noyes-Whitney model, a cornerstone of pharmaceutical science, is a theoretical framework for predicting dissolution rate based on diffusion, surface area, solubility and diffusion layer thickness. Parameters were selected based on standard USP dissolution test conditions , paracetamol as reference drug , V=0.0009m^3, C_s = 40mg/L. The base case obtained from this study was that the dissolution rate constant k = 0.0133 min^{-1} , 55% dissolved at 60 minutes. It was also concluded that increasing the surface area from 0.0005 to 0.005 m^2 significantly increased dissolution rate . higher solubility was found to be directly proportional to concentration achieved at any given time. The tools used were Microsoft Excel for calculations, Python (matplotlib) for visualization.

1. Introduction

Dissolution is a process in which a solid substance dissolves in a given solvent i.e. mass transfer from the solid surface to the liquid phase. It is a fundamental process in pharmaceutics where the oral bioavailability of a drug is determined by mainly the drug dissolution rate. It is an important parameter to be studied and considered as poor dissolution means poor drug absorption which in turn leads to an ineffective treatment. Dissolution is therefore a critical quality attribute in pharmaceutical formulation and manufacturing. Dissolution testing is mandatory in drug development and quality control. The factors affecting dissolution are the particle sizes, solubility, diffusion coefficient stirring conditions. This study applies the Noyes-Whitney model to analyse the effect of particle surface area and solubility on drug dissolution rate using Microsoft Excel for calculations and Python for visualization. In this study, paracetamol is used as the reference drug, as it is one of the most widely studied compounds in pharmaceutical dissolution testing. Paracetamol is a BCS class I drug, meaning it has high solubility and high permeability making it an ideal reference for dissolution studies. The dissolution behaviour is studied over a period of 120 minutes, consistent with the standard USP dissolution test duration.

2. System Specifications & Assumptions

This analysis is based on the Noyes-Whitney model. All the parameters used in this study are based on standard USP dissolution test conditions. The reference drug taken is paracetamol. The following table summarizes all input parameters that serves as the foundation for subsequent calculations and performance evaluations in this study.

Parameter	Symbol	Value	Unit
Diffusion Coefficient	D	1.00E-09	m^2/s
Particle Surface Area	A	0.002	m^2
Diffusion layer thickness	h	1.00E-05	m
Saturation solubility	C_s	40	mg/L
Initial concentration	C_0	0	mg/L
Volume of dissolution medium	V	0.0009	m^3

Table 1 : Design Parameters and Input Specifications

The diffusion coefficient D was taken to be $1.0x10^{-9}$ m^2/s, a typical value for small drug molecules in aqueous solution at 37°C which aligns with the literature values for paracetamol. The surface area A was taken to be 0.002 m^2, which is a standard value for 500mg paracetamol tablet under normal dissolution conditions. The diffusion layer thickness h was taken to be $1.0x10^{-5}$ m which is a typical value under moderate stirring conditions consistent with USP dissolution apparatus specifications. The saturation solubility C_s was taken to be 40 mg/L at 37°C, taken from the standard pharmaceutical literature. Initial concentration C_o was assumed to be zero, as at the start of the test, representing a fresh dissolution medium. The volume was taken as 0.0009m^3 (900mL), a standard value specified by USP dissolution apparatus II (paddle method), universally used in pharmaceutical dissolution testing. All experiments were conducted at 37°C, body temperature, a standard condition for all USP dissolution tests simulating in vivo conditions. All particles are assumed to have a sphericity of 1 and uniform. The sink conditions are maintained throughout, and the fluid is assumed to be well mixed. The assumptions are consistent with standard Noyes-Whitney model conventions and are widely accepted for theoretical dissolution analysis.

3. Methodology

3.1 Noyes-Whitney Model Overview

Noyes-Whitney equation proposed in 1897 by Noyes and Whitney is a simplified yet remains the cornerstone of pharmaceutical science. It is based on Fick's first law of diffusion, as it illustrates that the dissolution rate is proportional to concentration gradient between solid surface and bulk solution. It is the most widely used model in pharmaceutical dissolution testing and drug formulation design. This model provides a theoretical basis for understanding how physical and chemical properties of a drug influence its dissolution behaviour. The model assumes that the diffusion later thickness remains constant, particles are spherical and uniform in size and the sink conditions are maintained throughout the dissolution process.

3.2 Dissolution Rate Constant Calculation

The dissolution rate constant k represents the speed at which a drug dissolves under given conditions. It was calculated using the following expression:

$$k = \frac{DA}{hV}$$

Where:

- k = dissolution rate constant (min^{-1})
- D = diffusion coefficient (m^2/s)
- A = particle surface area (m^2)
- h = diffusion layer thickness (m)
- V = volume of dissolution medium (m^3)

k is directly proportional to surface area and diffusion coefficient. Hence, larger surface area and higher diffusion coefficient increases the value of k . k is inversely proportional to diffusion layer and volume. Hence, thicker diffusion layer and larger volume decreases the value of k. Therefore, smaller particles have large surface area which in turn increases the value of the dissolution rate constant (k), hence faster dissolution. This is the fundamental reason why pharmaceutical companies micronize drug particles to improve bioavailability .

3.3 Dissolution Profile Calculation

The concentration of drug dissolved at any given time t was calculated using the integrated form of the Noyes-Whitney equation as follows:

$$C(t) = C_s\left(1 - e^{-kt}\right)$$

Where:

- C(t) = concentration at time t (mg/L)
- C_s = saturation solubility (mg/L)
- k = dissolution rate constant (min^{-1})
- t = time (min)

At time t = 0, the concentration C is zero, representing a fresh dissolution medium with no drug dissolved. As t increases, C approaches $C_{s\_}$ asymptotically, however it will never fully reach saturation. This indicates rapid initial dissolution, and then gradual flattening which demonstrates that the rate of increase slows down over time. This behaviour is characteristic of first order dissolution kinetics.

3.4 Sensitivity Analysis

Sensitivity analysis was performed to study the effect of two key parameters - particle surface area (A) and saturation solubility (C_s) on the dissolution profile . In this study , surface area was varied from 0.0005 to 0.005 m^2, simulating different degrees of particle micronization used in the pharmaceutical manufacturing. Smaller particles have higher surface area, hence increasing the dissolution rate constant (k), as a result faster dissolution rate. The saturation solubility was varied from 10 to 60 mg/L, representing drugs with different solubility profiles. This demonstrates that, higher solubility increases the concentration gradient between the solid surface and bulk solution, which is the primary driving force for dissolution. Both the analyses were performed using Python - matplotlib used for visualization. The base case dissolution profile was generated using k = $0.0133 min^{-1}$, calculated from standard USP parameters, and each sensitivity analysis varied one parameter at a time while keep all others constant.

4. Results & Discussion

4.1 Dissolution Rate Constant

Parameter	Formula Used	Result	Unit
Dissolution rate constant(k)	Noyes-Whitney	2.22E-04	s^{-1}
k converted	Noyes-Whitney	0.0133	min^{-1}

Table 2 : Calculated Dissolution Rate Constant

The dissolution rate constant (k) was calculated to be 0.0133 min^{-1} at base conditions. This demonstrates that 1.33% of the remaining concentration difference dissolves per minute. This value aligns with the literature values for paracetamol dissolution. The above attained value for k serves as the base case for all subsequent dissolution profile calculations.

4.2 Dissolution Profile

Time(min)	Concentration(mg/l)	% Dissolved
0	0.00	0.00
10	4.99	12.47
20	9.35	23.39
30	13.18	32.94
45	18.03	45.09
60	22.01	55.03
90	27.94	69.84
120	31.91	79.78

Table 3 : Dissolution Profile Data

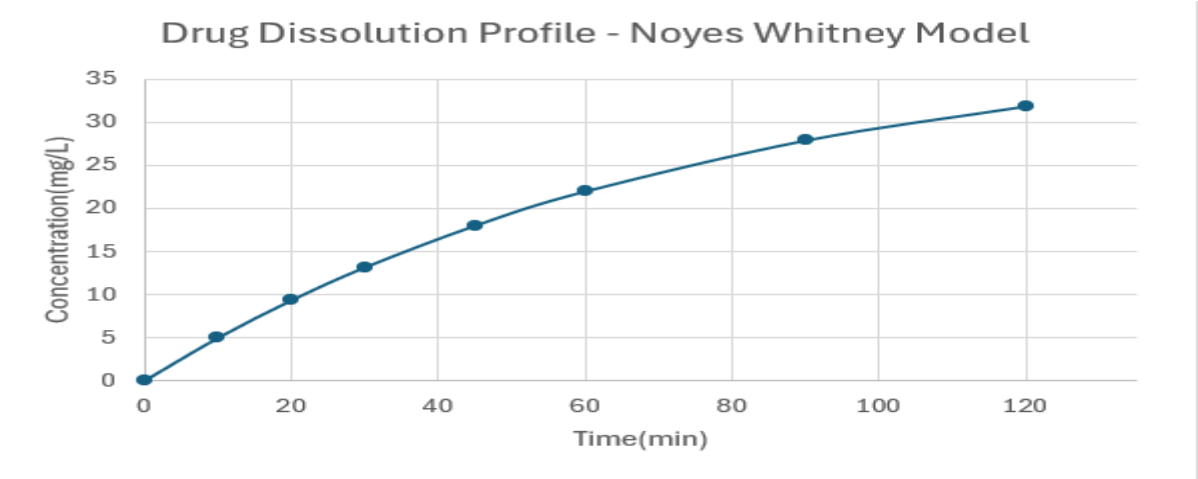

Figure 1 : Drug Dissolution Profile (Excel)

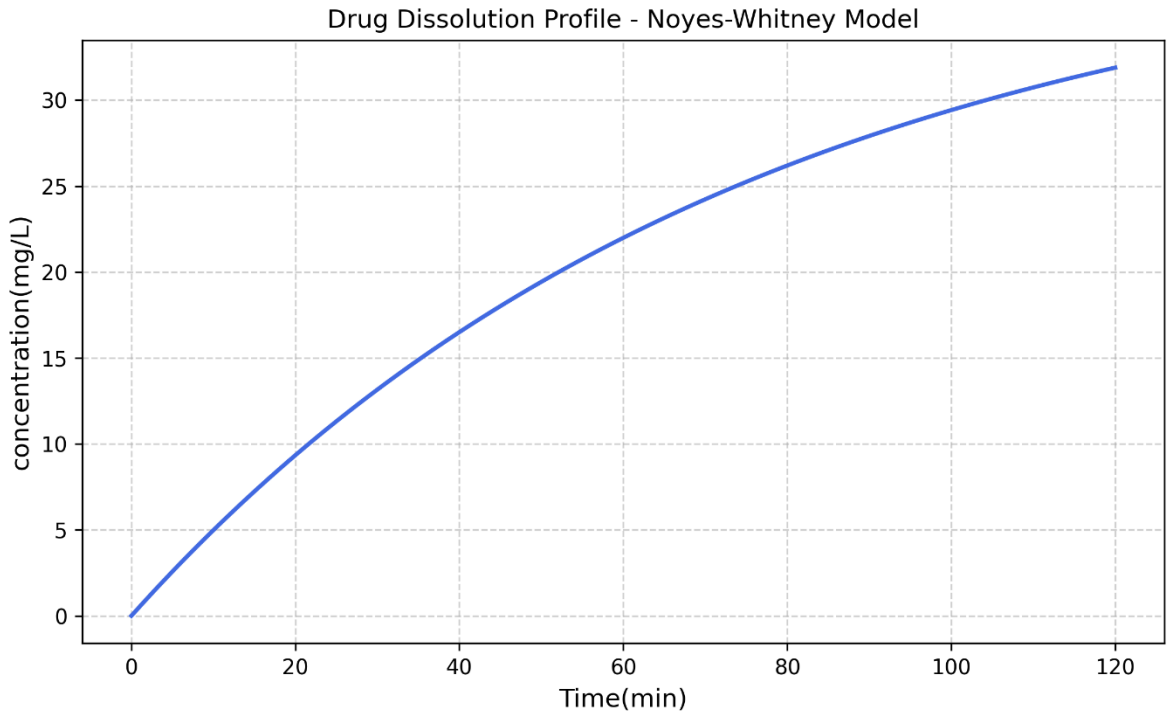

Figure 2 : Drug Dissolution Profile – Noyes-Whitney Model (Python)

The profile starts from t = 0 and concentration = 0 demonstrating that there is no drug dissolved yet and slowly it increases with time. At t = 60 minutes, the concentration reaches 22.03 mg/L indicating that it is 55% dissolved. At t = 120 minutes, the concentration is 31.85 mg/L, indicating that it is 79.78 % dissolved. The above dissolution profiles curve shows asymptotic behaviour, where it will never reach C_s= 40mg/L, only approach. The python generated graph confirms the Excel results producing a smoother continuous curve with 500 data points compared to Excel's 8 data points. The dissolution profile obtained aligns with first order dissolution kinetics where the rate of dissolution decreases as the concentration approaches saturation solubility. The rapid initial dissolution observed in the first 30 minutes is important in the pharmaceutical field as it determines the onset of drug action. Beyond 60 minutes, the rate of dissolution slows down, indicating that the concentration gradient between the solid surface and bulk solution , which is the primary driving force for dissolution diminishes as the bulk concentration approaches saturation solubility. These findings are consistent with the theoretical predictions of the Noyes-Whitney model and validate the accuracy of the Excel calculations. The dissolution profile serves as the foundation for the sensitivity analysis conducted in Sections 4.3 and 4.4 .

4.3 Sensitivity Analysis – Surface Area

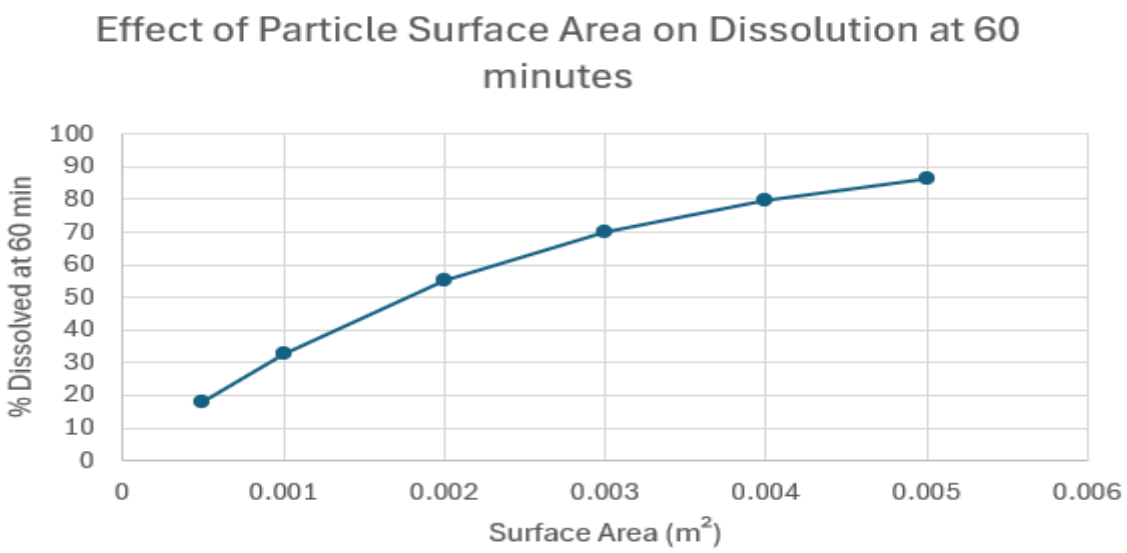

Table 4 : Effect of Particle Surface Area on Dissolution at 60 Minutes

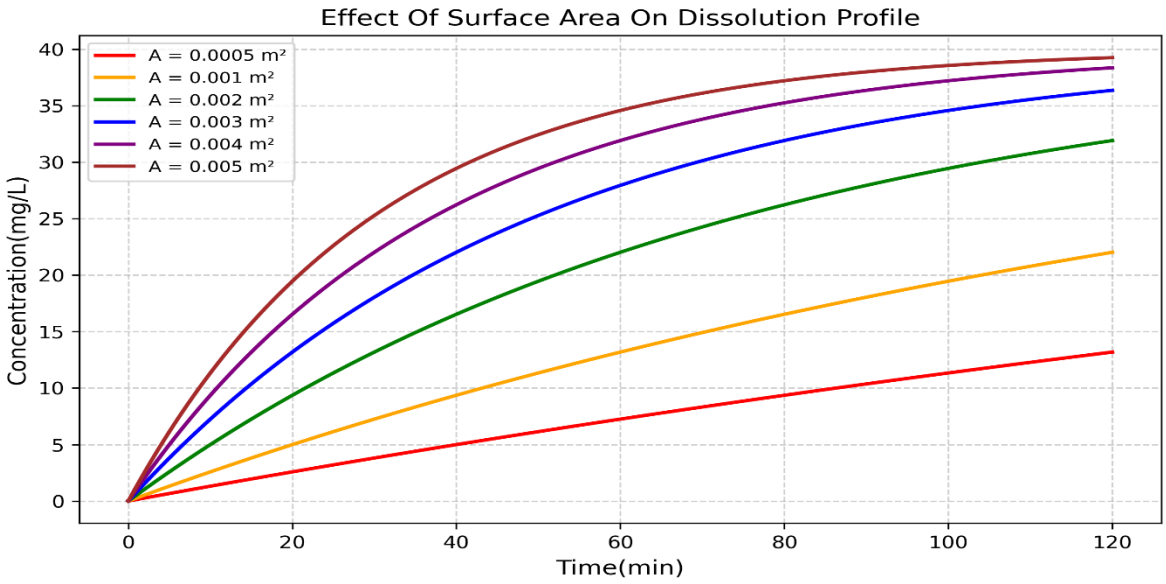

Figure 3 : Effect of Particle Surface Area on Dissolution Profile (Python)

As surface area (A) increases from 0.0005 to 0.005m², dissolution increases significantly. At A = 0.0005 m² , it was observed that only 18.13% dissolved at 60 min. At A = 0.005 m², it was observed that 86.47% dissolved at 60 min, representing nearly 5x improvement in dissolution. This directly demonstrates why micronization is critical in pharma manufacturing. Smaller particles have larger surface area, hence higher dissolution rate constant k. Therefore, faster dissolution and better bioavailability. These results highlight the

important of particle size control as a critical formulation parameter in pharmaceutical manufacturing.

4.4 Sensitivity Analysis – Effect of Solubility

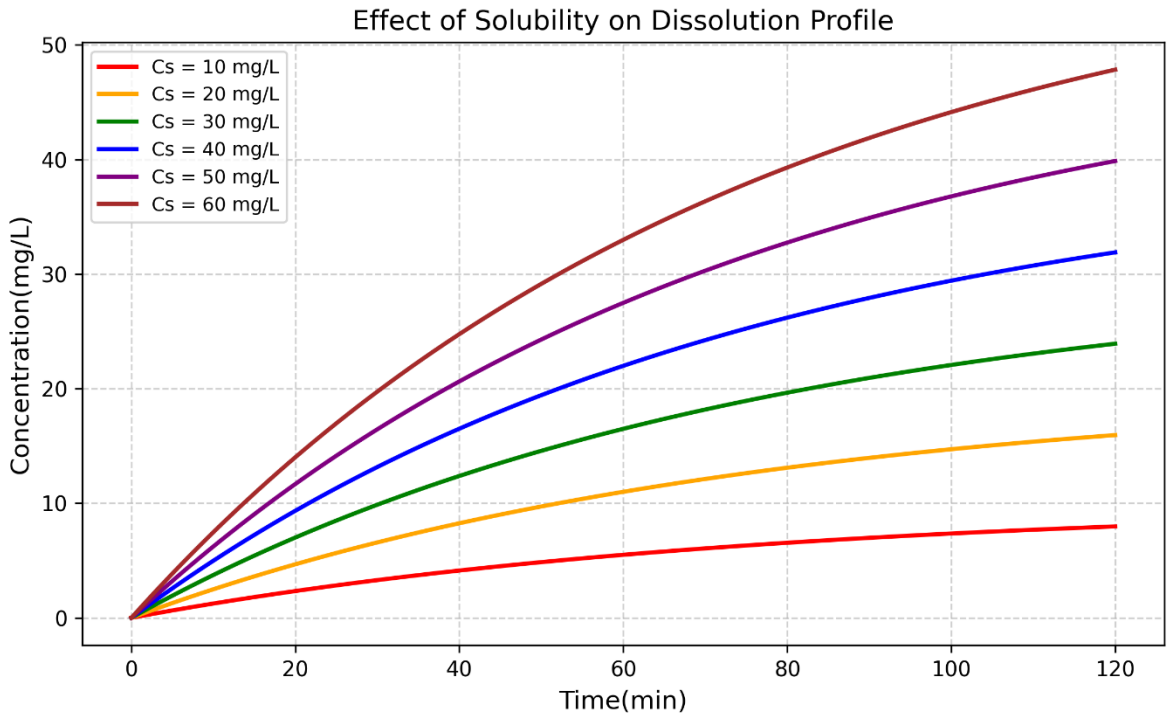

Figure 4 : Effect of Solubility on Dissolution Profile (Python)

As saturation solubility (C_s) increases from 10 to 60 mg/L, since solubility is directly proportional to concentration, the maximum concentration achievable increases proportionally. At C_s = 10 mg/L only 8.19 mg/L was achieved at 120 minutes. At 120 minutes, 48.13 mg/L was achieved at C_s= 60 mg/L. This is due to the fact that higher solubility increases the concentration gradient between the solid surface and the bulk solution, which is the primary driving force for dissolution. All the six curves in the profile follow asymptotic shape, which confirms the first order dissolution kinetics regardless of solubility. This analysis highlights that drugs with poor solubility present a significant formulation challenge, as low solubility directly limits the concentration achievable in the dissolution medium. These findings provide valuable insights for pharmaceutical scientists in selecting and optimizing drug candidates during the early stages of formulation development.

5. Conclusions & Recommendations

5.1 Conclusions

This study presented a theoretical dissolution rate analysis of paracetamol using the Noyes-Whitney model. The calculations were carried out in Microsoft Excel and visualization in python based on the Noyes-Whitney's model covering dissolution rate, surface area and solubility. The dissolution rate constant k was calculated to be 0.0133 min-1 at base conditions. At 60 minutes, it was observed that 55% of drugs were dissolved , meanwhile at 120 minutes 79.78 % was dissolved. The profile/curves follows an asymptotic behaviour which confirms the first order dissolution kinetics

Furthermore, Increasing the surface area (A) from 0.0005 to 0.005 m^2, resulted in nearly a 5x improvement in dissolution at 60 minutes. Increasing the solubility from 10 to 60 mg/L, the maximum concentration achievable increases the proportionally. This demonstrates that solubility and surface area are most crucial formulation parameters for getting a faster dissolution rate. these results highlight the important of micronization and solubility enhancement in the pharmaceutical filed. The Noyes-Whitney model despite its simplicity serves as a reliable tool for preliminary dissolution analysis.

5.2 Recommendations

1. Extend the analysis to BCS class II and class IV drugs which have poor solubility, as these present greater formulation challenges.
2. Validate the results using ASPEN Plus or similar pharmaceutical simulation software.
3. Investigate how diffusion layer thickness and saturation solubility gets affected by varying the stirring conditions
4. Study the effect of dissolution medium temperature on diffusion coefficient and saturation solubility for high temperature industrial applications.
5. Conduct experimental validation using the USP dissolution apparatus II (paddle method) to verify the theoretical Noyes-Whitney predictions.

6. References

1. Noyes, A.A. and Whitney, W.R. (1897). *The rate of solution of solid substances in their own solutions.* Journal of the American Chemical Society, 19(12), 930-934.
2. United States Pharmacopeia (USP). (2023). *General Chapter <711> Dissolution.* USP-NF.
3. Aulton, M.E. and Taylor, K.M.G. (2013). *Aulton's Pharmaceutics: The Design and Manufacture of Medicines.* 4th ed. Churchill Livingstone.
4. McCabe, W.L., Smith, J.C. and Harriott, P. (2017). *Unit Operations of Chemical Engineering.* 7th ed. McGraw-Hill.

7. Appendix

```
import matplotlib.pyplot as plt
import numpy as np


Cs = 40
k = 0.0133

t =np.linspace(0,120,500)
C= Cs * (1- np.exp(-k * t))
plt.figure(figsize=(8,5))
plt.plot(t,C,color='royalblue', linewidth= 2)
plt.xlabel('Time(min)', fontsize = 12)
plt.ylabel('concentration(mg/L)',fontsize= 12)
plt.title('Drug Dissolution Profile - Noyes-Whitney Model', fontsize = 12)
plt.grid(True, linestyle = '--',alpha = 0.6)
plt.tight_layout()
plt.savefig('Dissolution_Profile.png', dpi = 300)
plt.show()

# Sensitivity Analysis - Surface Area Effect

colors = ['red', 'orange', 'green', 'blue', 'purple', 'brown']
surface_areas = [0.0005, 0.001, 0.002, 0.003, 0.004, 0.005
plt.figure(figsize=(8,5))
```

```
for A, color in zip(surface_areas, colors):
        k_new = (1e-9 * A)/(1e-5 * 0.0009) * 60
        C_new = Cs * (1- np.exp(-k_new * t))
        plt.plot(t, C_new, color=color, linewidth = 2, label=f'A = {A} m²')

plt.xlabel('Time(min)', fontsize = 12)
plt.ylabel('Concentration(mg/L)', fontsize = 12)
plt.title('Effect Of Surface Area On Dissolution Profile', fontsize = 13)
plt.legend(fontsize = 9)
plt.grid(True, linestyle = '--', alpha = 0.6)
plt.tight_layout()
plt.savefig('Surface_Area_Sensitivity.png', dpi=300)
plt.show()

#Effect of Solubility
colors2 = ['red', 'orange', 'green', 'blue', 'purple', 'brown']
solubilities = [10,20,30,40,50,60]
plt.figure(figsize=(8,5))

for Cs_new , color in zip(solubilities, colors2):
       Cs_sol = Cs_new * (1 - np.exp(-k * t))
       plt.plot(t, Cs_sol, color=color , linewidth = 2, label = f'Cs =
{Cs_new} mg/L')

plt.xlabel('Time(min)', fontsize = 12)
plt.ylabel('Concentration(mg/L)', fontsize = 12)
plt.title('Effect of Solubility on Dissolution Profile', fontsize = 13)
plt.legend(fontsize = 9)
plt.grid(True, linestyle = '--', alpha = 0.6)
plt.tight_layout()
plt.savefig('Solublity_effect.png', dpi=300)
plt.show()
```