# The Effects of pH on the Dissolution Rates of Common Painkillers

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## 1. Introduction

Ibuprofen, also known by one of its trade names as Advil, is an over-the-counter non-steroidal anti-inflammatory drug (NSAID) used for pain relief. It is a weak acid with an estimated pKa[1] of 4.45 (National Center for Biotechnology Information, n.d). Advil is sold in three forms where 200 mg of ibuprofen is the sole active ingredient: caplets, liquid gels and tablets. Caplets are similar to tablets but are longer in shape. Liqui-gels are composed of a soft-shell encapsulating dissolved ibuprofen in a liquid form.

Rate of dissolution is the rate at which a solute dissolves into a solvent. In the context of drug delivery, a higher rate of dissolution is correlated with a reduced need for additional doses, as well as faster absorption, and initial pain relief (Moore *et. al,* 2014). Factors such as temperature, pH and surface area are known to affect the rate of dissolution. Using the Henderson-Hasselbach equation, when the pH of the solvent is higher than the pKa of the solute, ibuprofen, (4.45) the main form of the solute is the deprotonated form which would have a lower stability and therefore a higher solubility and rate of dissolution than its stable organic form (Estime *et al.,* 2010). When taken orally, drugs are typically absorbed in the small intestine after passing through the stomach. The pH of gastric acid in humans is typically at pH of 1-2, and the pH of the small intestine is closer to a pH of 6. The acidity of these environments fluctuates with food consumption being a major factor (Koenigsknecht *et al.,* 2017). In our experiment, lemon juice is used as a solvent to emulate the pH of gastric acid and distilled water is used to emulate a neutral environment.

Using the in-vitro approach of dissolution we plan to explore the effects of solvent pH on the dissolution time of three forms of Advil. We hypothesize that the caplet form of 200 mg Advil in distilled water at an approximate pH of 7 will have the highest rate of dissolution among the three forms of Advil since it has the highest surface area to volume ratio.

## 2. Design of the Experiment

To determine the differences in the dissolution rates of common painkillers we used a 2-factor factorial design. Factor A is ibuprofen form with three levels: tablets, caplets, and liquid gels. Factor B is the solvent pH with two levels: distilled water with a pH of 7 and lemon juice with a pH of 2. The solvent temperature will be kept between 35.5-39 °C during the trials using a thermometer to replicate normal body temperature. The response variable will be the time required for the complete dissolution of the pills measured in minutes.

[1] The pKa helps predict what a molecule will do at a specific pH

The three levels of factor A (ibuprofen form) were chosen since they are all common/accessible forms of ibuprofen for consumer purchase. Also since they have the same active ingredient, the dissolution rate is a better proxy for the time taken for drug action compared to using painkillers with various active ingredients that might naturally differ in the time required to act. The three types of ibuprofen pills are all 200 mg, however, they do not all share the same surface area and this could affect the dissolution rates. The two levels of factor B (solvent pH) were chosen because lemon juice has a pH similar to the pH of stomach acid and distilled water is easily accessible and will allow for a comparison of dissolution times between the different forms of ibuprofen at neutral pH.

One nuisance factor of this experiment is that the lemon juice is quite opaque. The reduced clarity of the lemon juice interferes with the observation of the pill, making it more difficult to determine exactly when the pill is dissolved compared to the distilled water. This factor is uncontrollable since we are unable to alter the colour or clarity of the lemon juice without also changing the pH. However, to mitigate this factor, we looked at the pills through the bottom of the glass which allowed us better visibility than looking from the top-down. Another, nuisance factor is the different temperatures between each glass of solvent. We controlled this factor by placing all six glasses in a single, communal water bath. We allowed the temperature to range by 3.5 °C, there could be a temperature disparity of up to this amount between the solvents. Additionally, noise was reduced in our data collection by clearly defining what we considered dissolved for our experiment and having one person observe and determine when a pill is dissolved. Figure 9 depicts pills that meet our definition of dissolved. Finally, the solvents were all from the same batch (distilled water was from one large jug and multiple containers of lemon juice were combined and stirred to create a uniform batch before use).

This study addressed the three basic principles of experimental design: randomization, replication, and blocking.

1) Randomization
   In each trial, all six observations are taken simultaneously so the order of the observations within each trial were not able to be randomized.
2) Replication
   Each trial will contain six runs (all six treatment combinations) and we will conduct four trials to obtain a total of 24 observations.
3) Blocking
   We will block by trial since they will be temporally separated thus potentially introducing errors.

The statistical model for our design is as follows:

$$y_{ijk} = \mu + \tau_i + \beta_j + (\tau\beta)_{ij} + \gamma_k + \epsilon_{ijk}$$

Where $\mu$ denotes the overall mean effect, $\tau_i$ denotes the effect of the $i^{th}$ Ibuprofen form ($i$ = 1, 2, 3), $\beta_j$ denotes the effect of the $j^{th}$ solvent pH ($j$ = 1, 2), $(\tau\beta)_{ij}$ denotes the effect of the interaction between $\tau_i$ and $\beta_j$, $\gamma_k$ denotes the effect of the $k^{th}$ block ($k$ = 1, 2, 3, 4, 5, 6), and $\epsilon_{ijk}$ denotes the random error. The random error, $\epsilon_{ijk}$ , is normally distributed with mean 0 and variance $\sigma^2$ ($\epsilon_{ijk} \sim N(0, \sigma^2)$).

## 3. Data Collection

*3.1 Procedure*

Using a scale, 200 mL of solvent was measured and poured into a clear glass, for a total of six glasses; three holding 200 mL of distilled water each and three holding 200 mL of lemon juice each. Each trial consisted of all six treatment combinations of ibuprofen form and solvent pH. All six pills were simultaneously dropped into the glasses containing the solvents at which time a stopwatch was started. We observed the pills and recorded how long it took them to dissolve. For the tablets and caplets, dissolved was defined as the pills no longer maintaining their solid structure. For the liquid gels, dissolved was defined as when the structure of the pill became noticeably deformed and the majority of contents of the pill were released into the solvent. To reduce error, one person was assigned to watch the pills and determine when each was dissolved and to observe the pill through the bottom of the glass to mitigate the issue of the lemon juice's opacity.

To ensure that the solvent was kept approximately at body temperature throughout the duration of the trials, the glasses were placed in a baking dish filled with warm water. Every two minutes, the temperature of the solvents in each of the six glasses was taken and the dish was replenished with hot water as needed to maintain a solvent temperature of 35.5-39 °C. This procedure was replicated three times for a total of four trials.

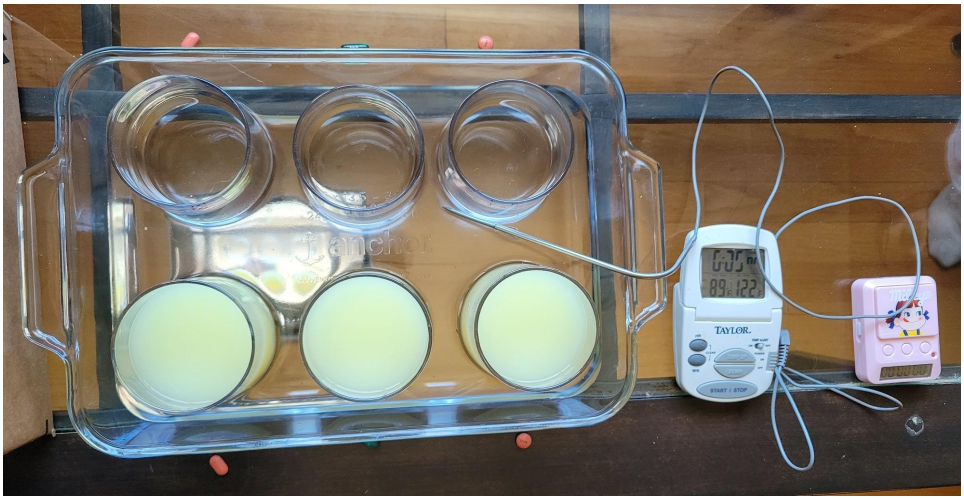



**Figure 1.** Experimental design setup with six glasses for the six treatment combinations sitting in a warm water bath monitored with a thermometer.

A nuisance factor that appeared during the execution of this experiment was a disparity in the solvent temperature. While both the lemon juice and the water were within our defined temperature range throughout the entire duration of the trial, the water tested consistently higher than the temperature of the lemon juice. This difference in temperature could affect the dissolution rates of the Advil, thus creating error in our data. Due to the design of our experiment with all glasses being placed in the same water bath, this factor was uncontrollable. Another nuisance factor in the experiment was that due to the size of the water bath dish, water could only be added to the sides and not in the center of the dish to ensure that water did not enter the glasses containing the solvents. Although we did stir the water in the baking dish after adding the hot water to distribute it, the glasses closer to the side where the hot water was added may have been heated more than the glasses farther away. The order of the glasses in the water bath was not randomized since we did not anticipate this problem so this uni-lateral addition of water could have a systematic effect on our results. In future experiments, we would randomize the glass positions in the water bath to reduce the effect of this nuisance factor. Lastly, we had difficulty determining when precisely the liquid gels were dissolved despite our specific definitions of dissolved for the sake of our experiment. For the liquid gels, it was harder to see when it had escaped from its capsule, compared to the powder form in the caplets and tablets. Error from this nuisance factor should be minimized since only one person was looking for when the pills had dissolved.

## 4. Data Analysis

*4.1 Visualization of the data*

The response variable, dissolution time, was measured in minutes. The data from this experiment are summarized in Table 1. By looking at this summary we can see that caplets had the lowest average dissolution time, followed by tablets and then liquid gels. Liquid gels had a much longer average dissolution time than both caplets and tablets (Figure 2, Figure 3). We also notice that the average dissolution takes longer in lemon juice (pH 2) compared to distilled water (pH 7) (Table 1, Figure 4). We will investigate if these differences are significant using ANOVA and Tukey tests.

**Table 1.** Dissolution times (minutes) for all replicates of each treatment combination. Average dissolution times for each treatment combination, each level of factor A (ibuprofen form), each level of factor B (solvent pH) and an overall average dissolution time are also shown in bold.

| Factor A: Ibuprofen Form | Factor B: Solvent pH | | |
|---|---|---|---|
| | Level 1: pH 7 (distilled water) | Level 2: pH 2 (lemon juice) | |
| Level 1: Caplets | 4.95<br>6.55<br>7.25<br>4.78<br>$\bar{y}_{11.}$= **5.8825** | 7.45<br>11.83<br>8.55<br>10.3<br>$\bar{y}_{12.}$= **9.5325** | $\bar{y}_{1..}$= **7.7075** |
| Level 2: Liquid Gels | 19.07<br>15.07<br>19.77<br>15.95<br>$\bar{y}_{21.}$= **17.465** | 26.3<br>18.58<br>17.4<br>19.55<br>$\bar{y}_{22.}$= **20.4575** | $\bar{y}_{2..}$= **18.96125** |
| Level 3: Tablets | 7.45<br>9.18<br>6.72<br>5.92<br>$\bar{y}_{31.}$= **7.3175** | 11.33<br>13.82<br>11.9<br>12.15<br>$\bar{y}_{32.}$= **12.3** | $\bar{y}_{3..}$= **9.80875** |
| | $\bar{y}_{.1.}$= **10.22167** | $\bar{y}_{.2.}$= **14.0967** | $\bar{y}_{...}$= **12.1592** |

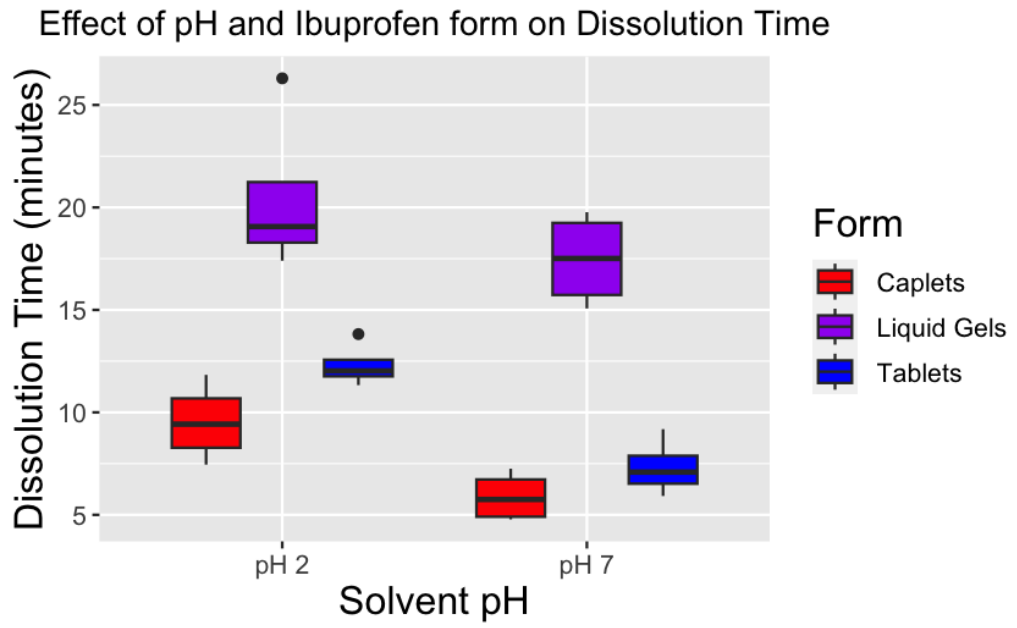



**Figure 2.** Boxplot showing variation in dissolution time by solvent pH and ibuprofen form. Lemon juice was the solvent that had a pH of 2 and distilled water had a pH of 7.

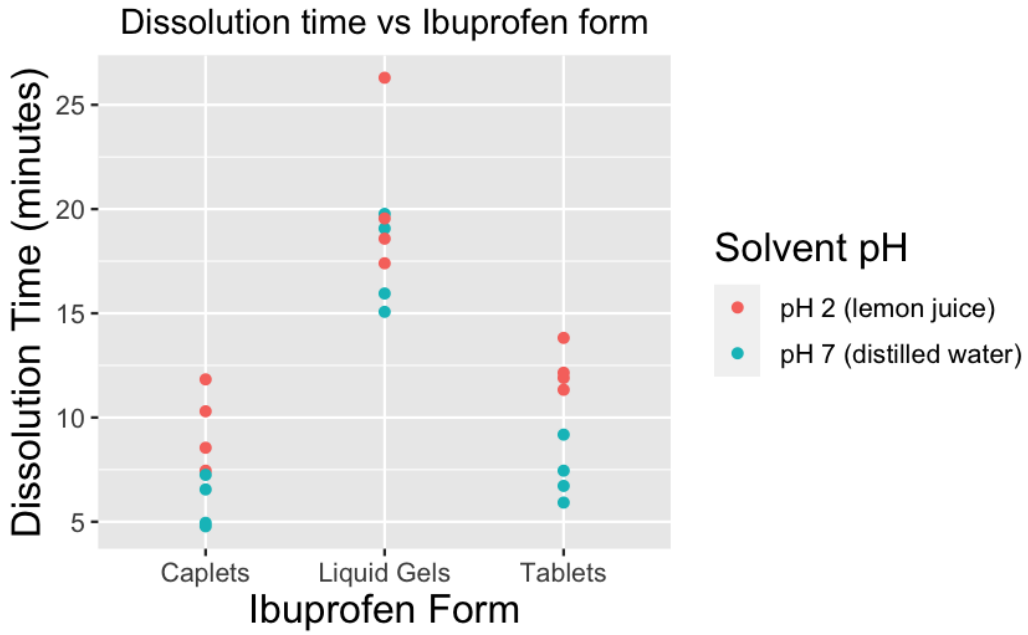



**Figure 3.** Scatterplot showing the different dissolution times for each ibuprofen form under both solvent pH treatments. It shows the overall range of dissolution time for each ibuprofen form. In general all three ibuprofen forms dissolved slower in a pH of 2 compared to a pH of 7.

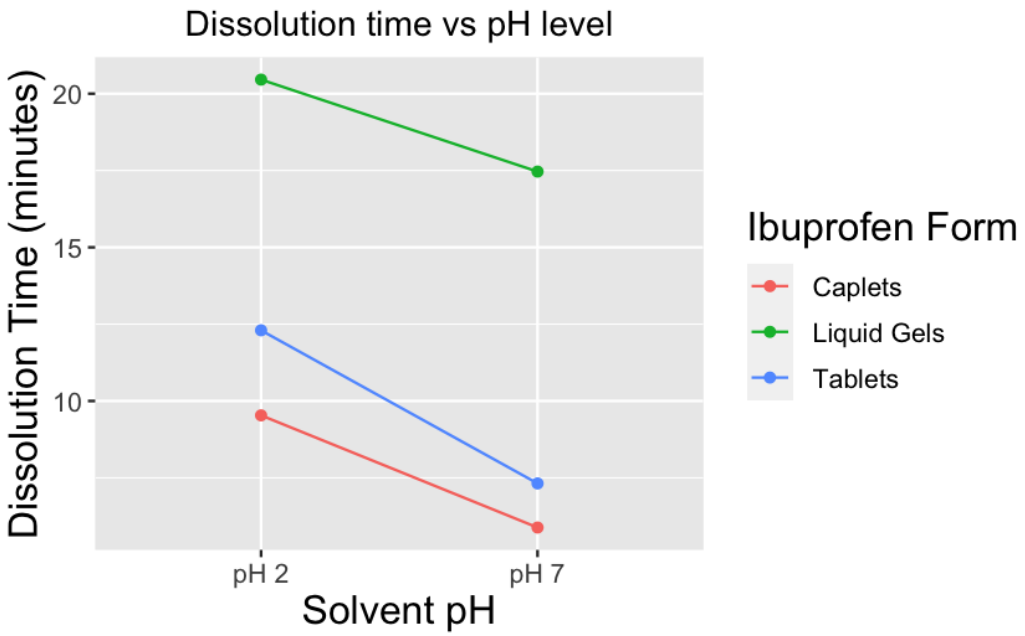



**Figure 4.** Plot of dissolution time vs pH level.

*4.2 ANOVA Model*

To get an understanding of how the form of ibuprofen and solvent pH affect dissolution time, we conducted an ANOVA test, the output of which is displayed below.

```
                          Df Sum Sq Mean Sq F value   Pr(>F)
factor(Form)               2  572.9  286.44  52.218 1.75e-07 ***
factor(Solvent)            1   90.1   90.09  16.424  0.00104 **
factor(Block)              3    6.3    2.09   0.381  0.76809
factor(Form):factor(Solvent)  2    4.1    2.06   0.375  0.69368
Residuals                 15   82.3    5.49
---
Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
```

The hypotheses that this ANOVA is testing are below:

For the effect of the $i^{th}$ Ibuprofen form: $H_0$: $\tau_1 = \tau_2 = \tau_3 = 0$, $H_1$: $\tau_i \neq 0$ for at least one $i$

For the effect of the $j^{th}$ solvent pH: $H_0$: $\beta_1 = \beta_2 = 0$, $H_1$: $\beta_j \neq 0$ for at least one $j$

For the effect of the interaction between $\tau_i$ and $\beta_j$: $H_0$: $(\tau\beta)_{ij} = 0$ for all $i, j$, $H_1$: $(\tau\beta)_{ij} \neq 0$ for at least one $i, j$

For the effect of the $k^{th}$ block: $H_0$: $\gamma_1 = \gamma_2 = \gamma_3 = \gamma_4 = \gamma_5 = \gamma_6 = 0$, $H_1$: $\gamma_k \neq 0$ for at least one $k$ Essentially each row of the ANOVA is testing the significance of the effect of one of, ibuprofen form, solvent pH, the interaction between ibuprofen form and solvent pH, and block on the response variable.

Looking at the ANOVA table above we can see that the interaction between solvent pH and ibuprofen form is not significant at a significance level of $\alpha$=0.05 (p=0.69368) so we can remove it from the final model. Although the blocking factor is not significant at a significance level of $\alpha$=0.05 (p=0.76809) we keep it in the final model to account for the fact that the replicates were temporally separate. The final statistical model for our experiment is as follows:

$$y_{ijk} = \mu + \tau_i + \beta_j + \gamma_k + \epsilon_{ijk}$$

Where all the symbols denote the same effect as before but the interaction term is dropped. We conducted another ANOVA test this time without the interaction term and the output of that test is displayed below.

```
                Df Sum Sq Mean Sq F value   Pr(>F)
factor(Form)     2  572.9  286.44  56.364 3.15e-08 ***
factor(Solvent)  1   90.1   90.09  17.728 0.000588 ***
factor(Block)    3    6.3    2.09   0.411 0.746958
Residuals       17   86.4    5.08
---
Signif. codes:  0 ’***’ 0.001 ’**’ 0.01 ’*’ 0.05 ’.’ 0.1 ’ ’ 1
```

From the ANOVA without the interaction term, we can see that both ibuprofen form and solvent pH have significant effects on dissolution time. The block for replicates still does not have a significant effect on dissolution time even with the interaction term dropped.

*4.3 Multiple Comparisons*

To further investigate which levels of the factors, ibuprofen form and solvent pH, differ in dissolution time we conducted a Tukey test. The output of which is displayed below.

```
  Tukey multiple comparisons of means
    95% family-wise confidence level

Fit: aov(formula = Dissolution_time ~ factor(Form) + factor(Solvent) + factor(Block), data = Dissolution_data)

$`factor(Form)`
                         diff         lwr       upr     p adj
Liquid Gels-Caplets 11.25375   8.3621773 14.145323 0.0000000
Tablets-Caplets      2.10125  -0.7903227  4.992823 0.1794576
Tablets-Liquid Gels -9.15250 -12.0440727 -6.260927 0.0000009

$`factor(Solvent)`
            diff       lwr       upr     p adj
pH 7-pH 2 -3.875 -5.816714 -1.933286 0.0005882

$`factor(Block)`
          diff       lwr      upr     p adj
2-1 -0.2533333 -3.953021 3.446355 0.9972822
3-1 -0.8266667 -4.526355 2.873021 0.9192159
4-1 -1.3166667 -5.016355 2.383021 0.7449505
3-2 -0.5733333 -4.273021 3.126355 0.9705592
4-2 -1.0633333 -4.763021 2.636355 0.8456337
4-3 -0.4900000 -4.189688 3.209688 0.9812028
```

From the Tukey test, we can observe that the differences in dissolution time between liquid gels and caplets, as well as between liquid gels and tablets are significant since their p-values are smaller than 0.001, which suggests that there is very strong evidence that liquid gels are significantly different from both caplets and tablets. However, the p-value for the difference between caplets and tablets is larger than 0.1, therefore there is no evidence that the mean dissolution time differs between caplets and tablets. But caplets have smaller standard deviations than tablets as shown in Table 2.

The p-value for the difference in dissolution time between the different pH levels is smaller than 0.001, thus there is very strong evidence that the mean dissolution time differs between pH 2 and pH 7. The p-values for the differences between different replicates are very large (> 0.10), therefore there is no evidence that the mean dissolution time differs between different replicates as shown by the ANOVA table.

*4.4 Assumptions*

To assess the adequacy of our model, we performed a residual analysis to check for the validity of the assumptions required for an ANOVA model. These assumptions are that the data are normally distributed, have constant variance, and that all the observations are independent.

Looking at the normal probability plot (Figure 5), the residuals appear to fall along the line suggesting that our data are at least approximately normally distributed. We also conducted a Shapiro-Wilks test that had a p-value of 0.2799. The null hypothesis of this test is that the data is

normally distributed, and since the p-value is larger than 0.01, there is little evidence against this null hypothesis. Therefore, we can conclude that our data is likely normally distributed.

We can assess the validity of the constant variance assumption by looking at the residual vs fitted value plot (Figure 6). The points on this plot generally appear to be approximately randomly distributed around the line and despite some slight narrowing at the beginning, the constant variance assumption overall appears to be valid.

To determine if the observations are independent, we can examine the plot of residuals against the run order (Figure 8). From Figure 8, it is noticeable that the fifth observation from the first replicate has a larger residual than the others. This is likely because when we first conducted the experiment, it was not evident what we should be looking for to consider it dissolved, especially for the liquid gels. Despite this mild outlier, the observations are still generally independent.

## 5. Conclusion

Based on our analysis, ibuprofen form and solvent pH were both found to have a significant effect on dissolution time. However, the interaction between ibuprofen form and solvent pH was determined to not have a significant effect on dissolution time which makes sense since the order in which the ibuprofen form dissolved was the same for lemon juice and distilled water.

From the Tukey test, we found that the mean dissolution time of liquid gels is significantly different than both caplets and tablets. Looking at Figures 2 and 3 we can see that liquid gels dissolve slower than the other two pill forms. And the difference between caplets and tablets is found to not be statistically significant. But since caplets have smaller standard deviations than Tablets as shown in Table 2, caplets might be a better option if you are looking for the pill that dissolves the fastest. We also found that the mean dissolution time differs significantly between lemon juice (pH 2) and distilled water (pH 7). Dissolution occurred slower in lemon juice compared to distilled water (Figure 4).

If we consider solely dissolution as a proxy for the time required for ibuprofen to dissolve and enter the bloodstream, caplets and tablets would be the best options for fast pain relief while liquid gels would likely be better for extended pain relief. However, other factors contribute to the action time of ibuprofen and liquid gels are suggested to provide meaningful pain relief faster than tablets but the two forms do not appear to differ too much in the time until first perceptible pain relief (Al Lawati & Jamali, 2016).

## 6. Appendix - R code

### Input data

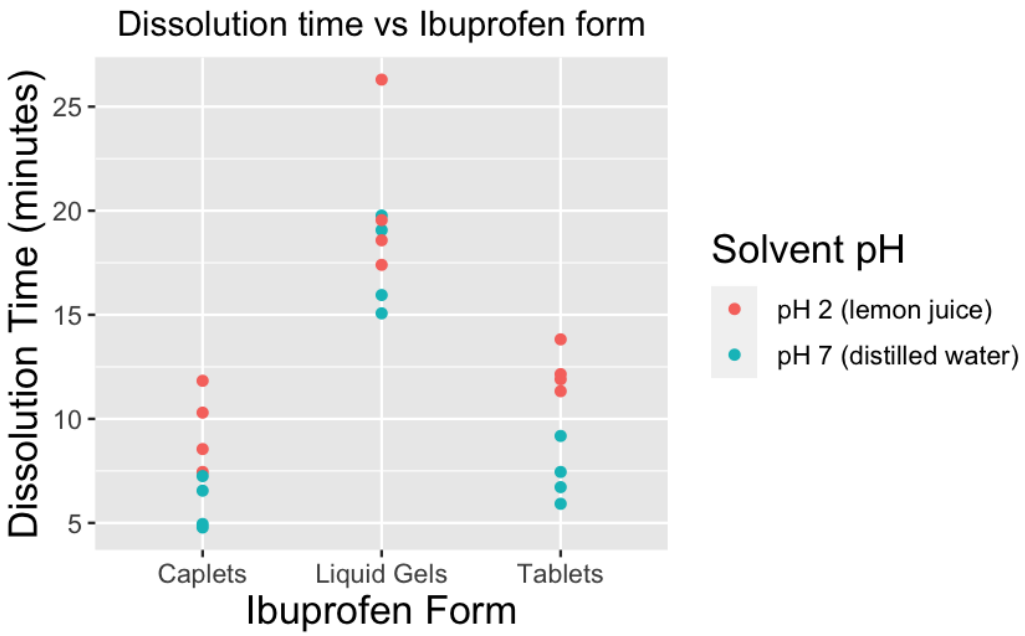
```
Dissolution_time=c(4.95,19.07,7.45,7.45,26.30,
                   11.33,6.55,15.07,9.18,11.83,18.58,
                   13.82,7.25,19.77,6.72,8.55,17.4,
                   11.9,4.78,15.95,5.92,10.30,19.55,12.15)
Form=rep(c("Caplets","Liquid Gels","Tablets"),8)
Solvent=rep(c(rep("pH 7",3),rep("pH 2",3)),4)
Block=c(rep(1,6),rep(2,6),rep(3,6),rep(4,6))
Runs=c(1:24)

Dissolution_data<-data.frame(Runs, Form, Solvent, Dissolution_time, Block)
```

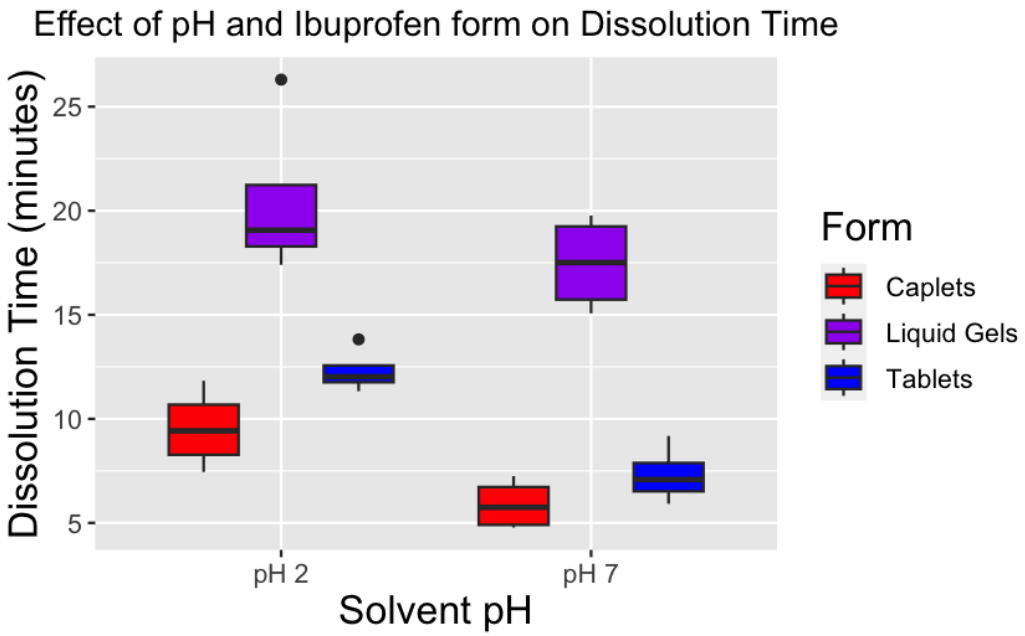
### Visualize data

```
library(ggplot2)

ggplot(Dissolution_data, aes(x=Form,y=Dissolution_time,color=Solvent)) +
  geom_point()+
  ggtitle("Dissolution time vs Ibuprofen form")+
  theme(plot.title = element_text(hjust = 0.5))+
  xlab("Ibuprofen Form")+
  ylab("Dissolution Time (minutes)")+
  labs(color="Solvent pH")+
  scale_color_discrete(labels=c("pH 2 (lemon juice)","pH 7 (distilled
water)"))+
  theme(axis.text=element_text(size=10))+
  theme(axis.title=element_text(size=15))+
  theme(legend.title=element_text(size=15))+
  theme(legend.text=element_text(size=10))
```



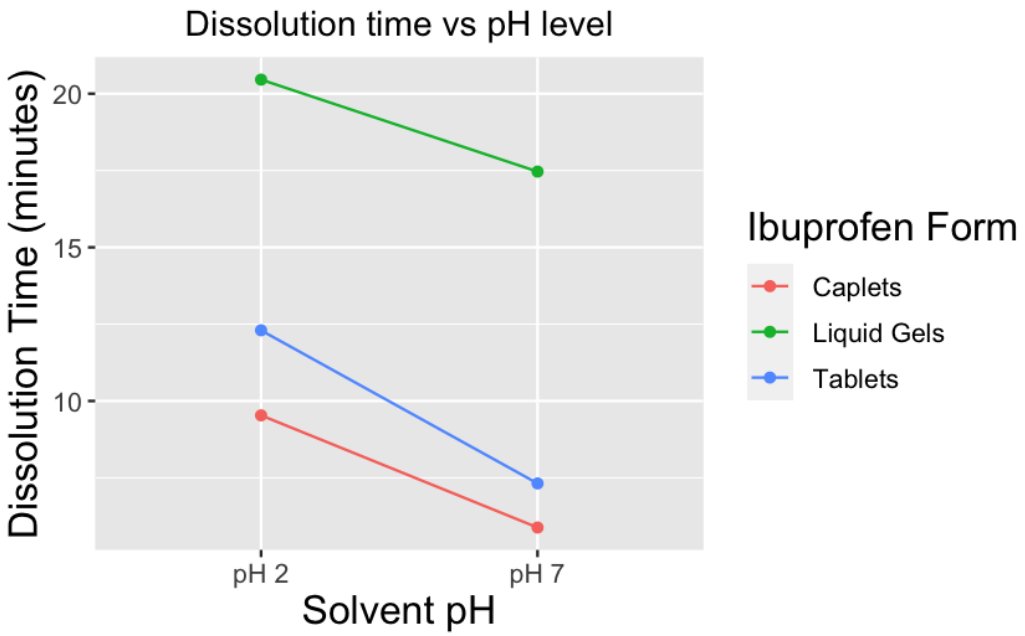

```
ggplot(Dissolution_data, aes(x=Solvent,y=Dissolution_time, fill=Form))+
  geom_boxplot()+
  ggtitle("Effect of pH and Ibuprofen form on Dissolution Time")+
  theme(plot.title = element_text(hjust = 0.5))+
  xlab("Solvent pH")+
  ylab("Dissolution Time (minutes)")+
  scale_fill_manual(values=c("red","purple","blue"))+
  theme(axis.text=element_text(size=10))+
  theme(axis.title=element_text(size=15))+
  theme(legend.title=element_text(size=15))+
  theme(legend.text=element_text(size=10))
```




Another graph with averages

```
Dissolution_time2<-c(5.8825,17.465,7.3175,9.5325,20.4575,12.3)
Form2<-c("Caplets","Liquid Gels","Tablets","Caplets","Liquid Gels","Tablets")
Solvent2<-c("pH 7","pH 7","pH 7","pH 2","pH 2","pH 2")
Dissolution_data2<-data.frame(Form2,Solvent2,Dissolution_time2)

ggplot(Dissolution_data2, aes(x=Solvent2,y=Dissolution_time2,color=Form2,
group=Form2))+
  geom_point()+
  ggtitle("Dissolution time vs pH level")+
  theme(plot.title = element_text(hjust = 0.5))+
  xlab("Solvent pH")+
  ylab("Dissolution Time (minutes)")+
  labs(color="Ibuprofen Form")+
  geom_line()+
  theme(axis.text=element_text(size=10))+
  theme(axis.title=element_text(size=15))+
  theme(legend.title=element_text(size=15))+
  theme(legend.text=element_text(size=10))
```




Analyse data with ANOVA

```
# run anova
res.aov1<-aov(Dissolution_time~factor(Form)*factor(Solvent)+factor(Block),data
=Dissolution_data)
summary(res.aov1)
```

```
##                            Df Sum Sq Mean Sq F value   Pr(>F)
## factor(Form)                2  572.9  286.44  52.218 1.75e-07 ***
## factor(Solvent)             1   90.1   90.09  16.424  0.00104 **
## factor(Block)               3    6.3    2.09   0.381  0.76809
## factor(Form):factor(Solvent)  2  4.1   2.06   0.375  0.69368
## Residuals                  15   82.3   5.49
## ---
## Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
```

```
# drop interaction term that was not significant
res.aov2<-aov(Dissolution_time~factor(Form)+factor(Solvent)+factor(Block),data
=Dissolution_data)
summary(res.aov2)
```

```
##                Df Sum Sq Mean Sq F value   Pr(>F)
## factor(Form)    2  572.9  286.44  56.364 3.15e-08 ***
## factor(Solvent)  1   90.1   90.09  17.728 0.000588 ***
## factor(Block)  3    6.3   2.09   0.411 0.746958
## Residuals      17   86.4   5.08
## ---
## Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
```

## Multiple comparisons

```
#multiple comparisons
TUKEY <- TukeyHSD(x=res.aov2, conf.level=0.95)
TUKEY
```

```
##   Tukey multiple comparisons of means
##    95% family-wise confidence level
##
## Fit: aov(formula = Dissolution_time ~ factor(Form) + factor(Solvent) +
factor(Block), data = Dissolution_data)
##
## $`factor(Form)`
##                       diff        lwr   upr   p adj
## Liquid Gels-Caplets 11.25375   8.3621773 14.145323 0.0000000
## Tablets-Caplets      2.10125  -0.7903227  4.992823 0.1794576
## Tablets-Liquid Gels -9.15250 -12.0440727 -6.260927 0.0000009
##
## $`factor(Solvent)`
##          diff        lwr   upr   p adj
## pH 7-pH 2 -3.875 -5.816714 -1.933286 0.0005882
##
## $`factor(Block)`
##          diff        lwr   upr   p adj
## 2-1 -0.2533333 -3.953021 3.446355 0.9972822
## 3-1 -0.8266667 -4.526355 2.873021 0.9192159
## 4-1 -1.3166667 -5.016355 2.383021 0.7449505
## 3-2 -0.5733333 -4.273021 3.126355 0.9705592
```

```
## 4-2 -1.0633333 -4.763021 2.636355 0.8456337
## 4-3 -0.4900000 -4.189688 3.209688 0.9812028
```

```
# Mean and standard deviation values for each term
library("tidyverse")
```

```
group_by(Dissolution_data, factor(Form)) %>%
      summarise(
      count = n(),
      mean = mean(Dissolution_time, na.rm = TRUE),
      sd = sd(Dissolution_time, na.rm = TRUE),
      )
```

```
## # A tibble: 3 × 4
##   `factor(Form)` count  mean     sd
##   <fct>        <int> <dbl> <dbl>
## 1 Caplets          8  7.71  2.46
## 2 Liquid Gels      8 19.0   3.42
## 3 Tablets          8  9.81  2.90
```

**Table 2**. Mean and standard deviation values for each form

## Residual Analysis

```
#residual analysis
residuals=res.aov2$residuals
qqnorm(residuals, ylim=c(min(residuals)-1,max(residuals)+1), main = "Normal
Q-Q Plot for Residuals",
      xlab = "Theoretical Quantiles", ylab = "Sample Quantiles- Modified",
      plot.it = TRUE, datax = FALSE)

qqline(residuals, datax = FALSE, distribution = qnorm)
```

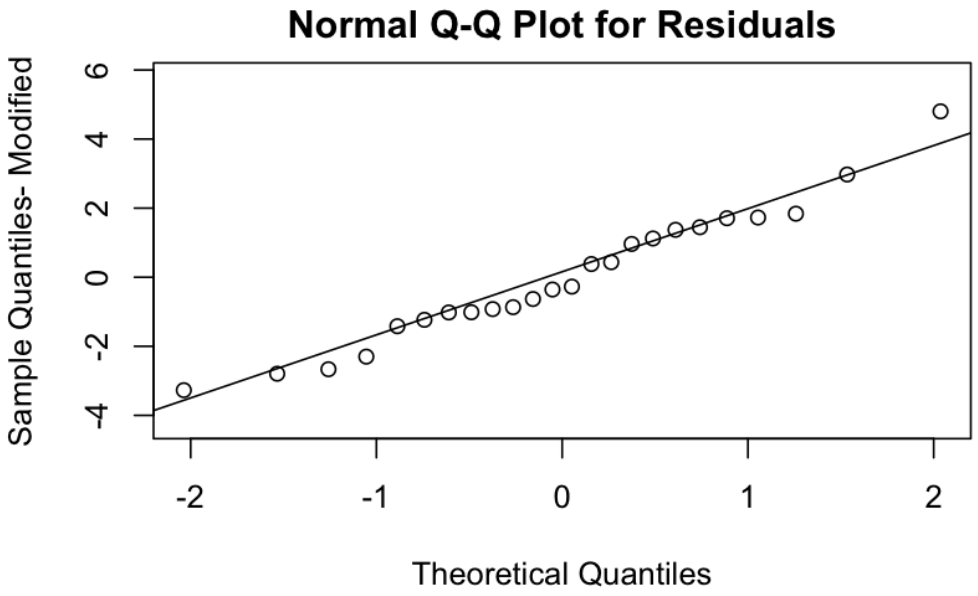



**Figure 5.** Normal probability plot used to check the assumption of normality. The points fall closely along the line suggesting the data is approximately normally distributed.

```
#Test normality using Shapiro Wilks
shapiro.test(residuals) #0.1253 therefore approximately normal

##
##  Shapiro-Wilk normality test
##
## data:  residuals
## W = 0.9709, p-value = 0.6893

#Check Variance
Fitted_values=res.aov2$fitted.values
plot(Fitted_values,residuals,main="Residuals vs Fitted
values",ylab="Residuals",xlab="Fitted Values")
abline(h=0)
```

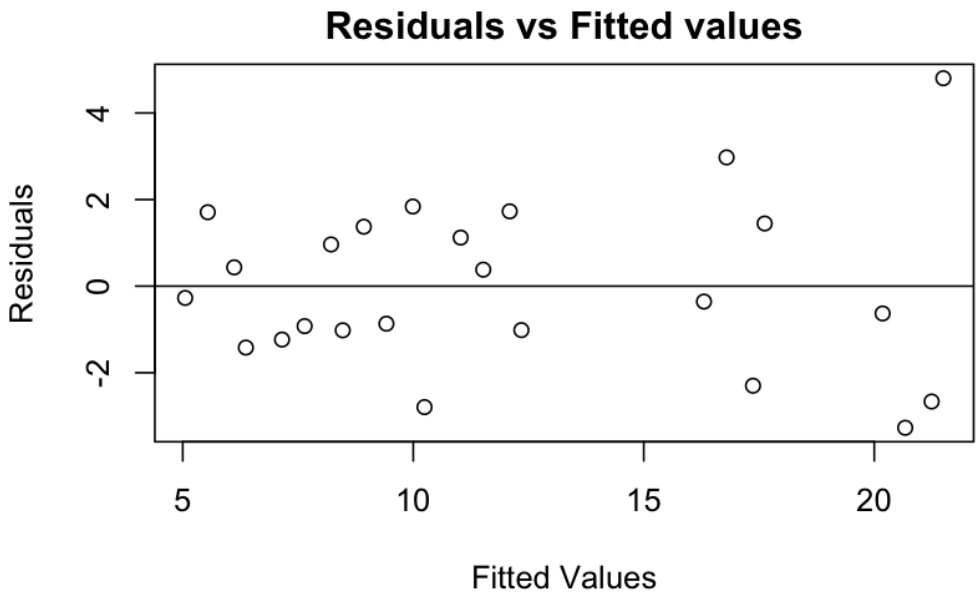



**Figure 6.** Residuals vs fitted values plot used to check the constant variance assumption. The points appear to be randomly distributed above and below the line thus the constant variance assumption appears to be valid.

```
#Check Independence
plot(seq(1:length(residuals)),residuals,main="Residuals vs
Order",ylab="Residuals",xlab="Order",col=Dissolution_data$Block)
abline(h=0)
```

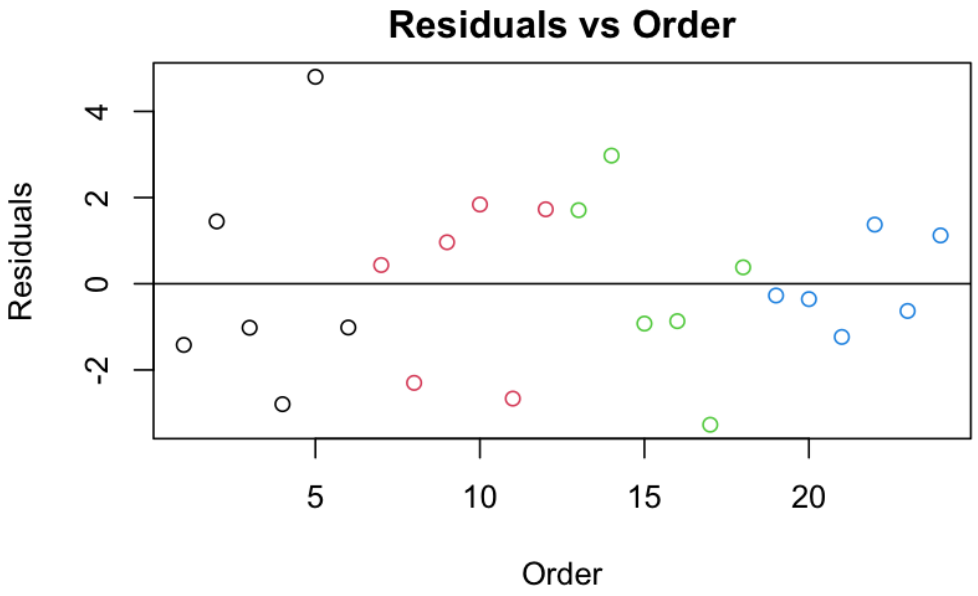



**Figure 8.** Residual vs order plot used to check the assumption of independent observations. The various colours denote the different replicates of our experiment.

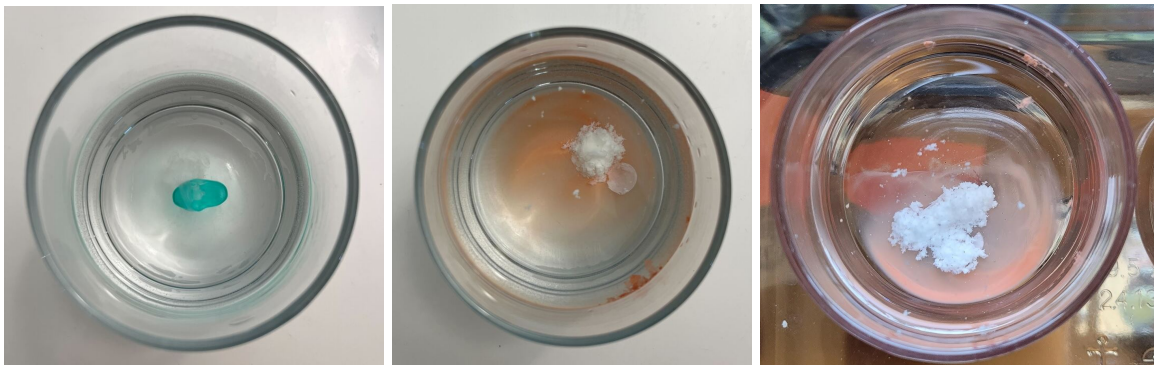


**Figure 9.** Pills that meet our definition of dissolved. The picture on the left is an example of a dissolved liquid gel. The picture in the center is a tablet that has dissolved. The picture on the right shows a caplet that has dissolved.

## 7. References


1. National Center for Biotechnology Information. PubChem Bioassay Record for Bioactivity AID 781326 - SID 103174500, Bioactivity for AID 781326 - SID 103174500, Source: ChEMBL. Retrieved March 28, 2023 from https://pubchem.ncbi.nlm.nih.gov/bioassay/781326#sid=103174500.
2. Estime, N., Teychené, S., Autret, J.-M., & Biscans, B. (2010). Influence of pH, Temperature and Impurities on the Solubility of an Active Pharmaceutical Ingredient (API). International Journal of Chemical Reactor Engineering, 8(1), 2099–2099. https://doi.org/10.2202/1542-6580.2099
3. Koenigsknecht, M. J., Baker, J. R., Wen, B., Frances, A., Zhang, H., Yu, A., Zhao, T., Tsume, Y., Pai, M. P., Bleske, B. E., Zhang, X., Lionberger, R., Lee, A., Amidon, G. L., Hasler, W. L., & Sun, D. (2017). In Vivo Dissolution and Systemic Absorption of Immediate Release Ibuprofen in Human Gastrointestinal Tract under Fed and Fasted Conditions. Molecular Pharmaceutics, 14(12), 4295–4304. https://doi.org/10.1021/acs.molpharmaceut.7b00425
4. Moore, R. A., Derry, S., Straube, S., Ireson-Paine, J., & Wiffen, P. J. (2014). Faster, higher, stronger? Evidence for formulation and efficacy for ibuprofen in acute pain. *Pain (Amsterdam)*, *155*(1), 14–21. https://doi.org/10.1016/j.pain.2013.08.013
5. Al Lawati, H., & Jamali, F. (2016). Onset of Action and Efficacy of Ibuprofen Liquigel as Compared to Solid Tablets: A Systematic Review and Meta-Analysis. Journal of Pharmacy & Pharmaceutical Sciences, 19(3), 301–311. https://doi.org/10.18433/J3B897