Industrial Pharmacy (PHAR441)

Lab Report 4 (Experiments 7, 8, 9, 10, 11)

Tablet Coating, and Quality Control Tests

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Abstract

The objective of this experiment was to coat the tablets produced in earlier experiments with film-coating by spray-coating. The coated tablets were then tested for weight variation, hardness, friability, disintegration, and dissolution. The coated tablet didn't show any increase in weight after the coating process, and displayed mutiple defects of the coating process, including erosion, orange peel effect, sticking, twinning, and color variation. The coated tablets didn't display any weight variation by 5% from the average weight. The average hardness of the tablets was determined to be 12.01 Kp. The friability test showed an unusual slight increase in weight after processing the tablets. The disintegration test showed a disintegration time for the coated tablets of 4 minutes and 1 second. The dissolution test was done on two different batches, with the first batch showing a high percent dissolution, and the second batch showing a low one.

1 Introduction

1.1 Coating

Tablet coating is the process of applying a dry outer layer to the tablet's surface to achieve a number of outcomes including protection of the tablet against humidity or air, taste masking, modification of drug release, or simply for aesthetic purposes. Tablet coating types include **sugarcoating** and **film-coating**. [1]

Sugarcoating of tablets includes first sealing the tablets by polymers for waterproofing, then subcoating with sugar-based syrup, then addition of more layers of thick syrup for smoothing and final rounding. These processes are done in acorn-shaped, metal, rotating pans that operate at an angle that allows for visualization of the tablets in the pan, while the coating materials are poured or sprayed over the tablets, and warm air is blown for drying. After this process, the tablets can be colored and polished. However, the sugarcoating process requires high expertise, and results in large increase in the size and weight of tablet, and is more likely to produce weight and size variation in tablets of the same batch. Therefore, the film-coating process of tablets is more widely used. [1]

The film-coating process of tablets places a tight, thin coating of plastic-like material of the tablet. The coating is applied in similar pans as sugarcoating by spraying the coating solution or suspension with warm air for drying. The coating is sprayed as either aqueous or non-aqueous preparation. Non-aqueous preparations contain The coating preparation sprayed usually contains a film-coating polymer such as hydroxypropyl methylcellulose (HPMC) or cellulose acetate phthalate (CAP), a plasticizer to provide flexibility such as glycerin, polyethylene glycol, or castor oil, coloring agents, and the vehicle carrying the substances which is water in the case of aqueous preparations, or alcohols for non-aqueous preparations. Non-aqueous preparations also contain a surfactant to enhance the spreadability of the coating material, and an alloying substance to allow the bodily fluids to penetrate the coating. Coating with non-aqueous vehicles allows for faster adherence and drying due to the volatility of the vehicles compared to water as a vehicle. However, non-aqueous vehicles are more expensive and pose an environmental issue due to this volatility, and therefore water-based dispersions which don't require as much water as solutions are usually used. [1]

Many defects can occur during the film-coating process. These include **picking and peeling**, in which small (picking) or large (peeling) amounts of the film-coating flake off the tablet surface, the **orange-peel effect** in which the tablet surface appears rough after coating due to a problem in the spreading of the coating material, **mottling** which is unequal distribution of color, **bridging** in which the scoreline or logo produced on the tablet during compression is filled by coating material, **erosion** of the tablet surface during spraying, and **sticking** of the tablets to the sides of the pan and to each other (**twinning**). [1]

The coating material used in film-coating may also serve a function in drug-release rather than only be for protectinon or aesthetics. Enteric-coating of tablets is used to allow the tablet to pass through the stomach as it is, either to protect the tablet from the acidic environment of the stomach, or to protect the stomach from any side effect the drug might have on it. The materials used in enteric-coating include HPMC phthalate, CAP, and pharmaceutical shellac. [1]

Another process used to coat granules before tablet compression is fluid bed coating, in which the granules are suspended in a continuous flow of

air, while the coating material is sprayed downward (top-spray), upward (bottom-spray), or tangentially (tangential-spray). The fluid bed process can also be used for granulation. [1]

Tablets may also be coated by compression in special tablet compression machines. This method does not use a liquid solvent and therefore is useful for substances that are susceptible to moisture. [1]

In this experiment, the tablets were film-coated by spraying them with the coating material manually in a medium speed rotating pan. The amount of coating material that's required to increase the tablet weight by 3% was calculated before the coating process, and the change in tablet weight was monitored during the coating process. The coating material used is Opadry complete film-coating. A 15% of this coating material was dispersed in purified water.

1.2 Quality Control Tests

After the coating process, the tablets were tested for weight variation, hardness, friability, and disintegration in the same manner the uncoated tablets were tested before coating. The tablets were also tested for their dissolution this time as well.

Dissolution rate of the drug is rate at which the drug is released from a dosage form and solubilized in the bodily fluids. The determination of the dissolution of a dosage form is important to give an indirect measure of the bioavailability of the API in the given dosage form. Any error in bioavailability can cause an ineffective treatment, or in worse cases, a toxic overdose. Therefore, the dissolution of a dosage form must be determined in vitro first to estimate how it would dissolve in the body, to optimize the therapeutic efficacy of the product, and such tests are also important for bioequivalence studies. [2]

In dosage form dissolution testing, a dosage form is placed in a specified fluid at body temperature (around 37°C), and mixed for a specified time. The concentration of the API in the fluid is then determined using UV spectroscopy, chromatography, or any other methods. Many apparatuses exist for this test, including type 1: Basket, type 2: Paddle, type 3: Reciprocat-

ing cylinder and type 4: Flow-through cell. Each apparatus is suitable for certain dosage forms. The method used for determination of concentration depends on the availability of the devices required, and the API, as some APIs do not have an absorbance range in the UV spectrum. [2]

The dissolution rate of a dosage form is affected by the dosage form type itself, its size and shape, the excipients used from disintegrants to binders and others, the pH, and other factors. Due to these differences between dosage forms, the Pharmacopeias (USP, BP, EP ...) assign regulations of the fluid that must be used in the dissolution test, the apparatus, the time, and the tolerable results of the test. [2]

Parameters involved in the dissolution test include the rotation speed of the basket or paddle. Also the amount of API in the dosage form shouldn't be higher than the ability of the fluid to dissolve, since this will cause some of the amount to remain in the dosage form due to the limitation of the dissolving fluid. [2]

For testing the dissolution of paracetamol tablets, the USP specifies the use of pH= 5.8 phosphate buffer as the dissolving fluid. 7 paracetamol tablets, 4 from the first batch, and 3 from the second batch, were placed in 900 mL of the specified fluid. UV spectroscopy was used to measure the percent of dissolution of the tablets, as compared to a standard solution of paracetamol prepared for the test. The USP specifies that the dissolution shouldn't be less than 80%. Apparatus 2 (Paddle) was used, and the time for the test was 30 minutes. [3]

2 Experimental

2.1 Procedure

The procedure is the same as the one in the Industrial Pharmacy (PHAR441) Lab Manual, with the following changes and notes:-

1. During the coating process, the weight of the tablets was checked multiple times. There was no 3% increase in the weight of the tablet, however, and the process was stopped when it seemed that the tablets cannot be coated further. (discussed in "Discussion").

2. Seven tablet were tested for dissolution instead of the six specified in the S1 stage of the dissolution test. A sample was only taken at the end of the test, and not at the specified intervals in the Lab Manual.

3. A standard solution of acetaminophen was prepared to allow for calculation of % dissolution of the tablets through UV spectroscopy. The solution's concentration was 0.0111 mg/mL, and it was prepared by dissolving acetaminophen in sufficient amount of phosphate buffer (pH = 5.8, the specified solvent for dissolution testing in the USP). The samples taken for dissolution testing after the test was done for 30 minutes were diluted to 0.01 mg/mL, and using the the absorbance of both the standard solution and the sample solutions and their concentrations, the % dissolution was calculated.

2.2 Machines

Table 1: Machines used in the experiment

Machine	Model and/or S/N	Function	Involved Parameters
PharmaTest Mixer	S/N: 10.00499	Rotate the pan in which the tablets reside during the coating process to allow for uniform coating and drying.	Rotation speed of the pan Air flow and temperature Capacity
Spraying Gun	N/A	Atomization and spraying of the coating material over the tablets.	Atomizing air pressure Pattern air diameter Distance from the tablets Angle at which it's held Spraying rate
Homogenizer Mixer	L5M-A	Dispersion of coating material in water.	Rotation speed
PharmaTest Tablet Hardness Tester	PTB-111 PHDTH1021	Measures the hardness of tablets by Kp, by applying pressure to the tablet.	N/A
PharmaTest Friability Tester	PTF PHDFR1022	Tests for tablet friability by dropping the tablets in drums multiple times.	Number of rotations Rotation speed
PharmaTest Tablet Disintegration Tester	DIST-3	Tests the disintegration time of tablets by immersing them in a fluid continuously.	Immersion cycles per minute Immersion fluid Temperature of immersion fluid Amount of immersion fluid
Dissolution Tester Type 2 Apparatus: Paddle	N/A	Tests for the dissolution of tablets by continuously mixing the tablet in a fluid.	Volume of fluid used Temperature of fluid used Type of apparatus used Rotation speed Time of test

3 Results and Calculations

3.1 Coating

Amount of coating suspension required for tablets to gain 3% weight:-
80 g of Opadry coating material were dissolved in 533.3 mL of water to produce a 15% (w/w) suspension of coating material.
The average weight of one tablet before coating was determined to be 0.7936 g (Table 1). 3% * 0.7936 g = **0.0238 g** (each tablet must have a 0.0238 g increase in weight after coating)
Weight of all tablets produced = 1476.67 g
Number of tablets produced = 1476.67 g / 0.7936 g = **1860 tablets**
Amount of coating material needed to coat all tablets = 1860 * 0.0238 g = **44.268 g**
This amount of coating material is contained in **339.5 g of the coating suspension** prepared.

Table 2: Weight of 10 tablets before and after coating

No.	Weight of 10 Tablets Before Coat (g)	Weight of 10 Tablets After Coat (g)
1	7.92	7.84
2	7.93	7.86
3	7.95	7.89
4	7.90	7.89
5	7.97	7.89
6	7.94	7.91
7	7.90	7.83
8	7.97	7.90
9	7.92	7.88
10	7.96	7.91
Avg.	7.936	7.88

The tablets lost weight after the coating process (possible causes are disscused in "Discussion").

Table 3: In process weighing of tablets to check for weight gain

Tablet No.	1	2	3	4	5	6	7	8	9	10	Avg.
In-Process Weighing 1 (g)	0.77	0.78	0.77	0.77	0.77	0.79	0.77	0.78	0.79	0.79	0.778
In-Process Weighing 2 (g)	0.80	0.80	0.78	0.77	0.79	0.80	0.78	0.78	0.79	0.80	0.789
In-Process Weighing 3 (g)	0.79	0.80	0.80	0.79	0.79	0.78	0.79	0.78	0.79	0.79	0.790

During no point of the coating process have the tablets showed any weight gain (possible causes discussed in "Discussion").

3.2 Weight Variation

Table 4: Weight Variation Data

Tablet Number	Tablet Weight (g)	% Deviation	Acceptance
1	0.80	1.39%	Accepted
2	0.80	1.39%	Accepted
3	0.78	1.14%	Accepted
4	0.77	2.41%	Accepted
5	0.79	0.13%	Accepted
6	0.80	1.39%	Accepted
7	0.78	1.14%	Accepted
8	0.78	1.14%	Accepted
9	0.79	0.13%	Accepted
10	0.80	1.39%	Accepted

Average weight of tablets = 0.789 g
Deviation of each tablet from the average:-

1. (0.80 - 0.789) / 0.789 = 1.39%
2. (0.80 - 0.789) / 0.789 = 1.39%
3. (0.789 - 0.78) / 0.789 = 1.14%
4. (0.789 - 0.77) / 0.789 = 2.41%
5. (0.79 - 0.789) / 0.789 = 0.13%

6. (0.80 - 0.789) / 0.789 = 1.39%
7. (0.789 - 0.78) / 0.789 = 1.14%
8. (0.789 - 0.78) / 0.789 = 1.14%
9. (0.79 - 0.789) / 0.789 = 0.13%
10. (0.80 - 0.789) / 0.789 = 1.39%

No tablets deviate more than 5% from the average weight.

3.3 Hardness

Table 5: Tablet Hardness Data

Tablet	Weight (g)	Thickness (mm)	Hardness (Kp)
1	0.7887	6.28	12.1
2	0.7884	6.34	12.3
3	0.7981	6.29	13.1
4	0.7917	6.32	12.4
5	0.7852	6.28	11.8
6	0.7821	6.32	12.0
7	0.7865	6.31	10.6
8	0.7933	6.29	12.9
9	0.7876	6.36	11.5
10	0.7822	6.28	11.4
Avg. Hardness		12.01Kp	

Average hardness of the tablets is above 4 Kp.

3.4 Friability

Table 6: Tablet Friability Data

Weight of Tablets Before Processing (W1) (g)	7.855 g
Weight of Tablets After Processing (W2) (g)	7.860 g
Friability (%loss)	(W1-W2)/W1 = -0.064%

Results are less than 1%, but unusual.

3.5 Disintegration

The six tablets used in the disintegration test disintegrated in 4 minutes and 1 second (240 seconds).

3.6 Dissolution

A standard solution of paracetamol of concentration 0.0111 mg/mL was prepared, and its absorbance was determined to be 0.860 nm.
Percent dissolution of each sample is calculated through the formula:-
$\%Dissolution = \frac{Absorbance of sample}{Absorbance of standard} * \frac{Conc. of standard}{Conc. of sample} * 100\%$

1. (0.968/0.860) * (0.01/0.0111) * 100% = 101.4%
2. (1.012/0.860) * (0.01/0.0111) * 100% = 105.9%
3. (1.033/0.860) * (0.01/0.0111) * 100% = 108.1%
4. (1.077/0.860) * (0.01/0.0111) * 100% = 112.7%
5. (0.675/0.860) * (0.01/0.0111) * 100% = 70.6%
6. (0.693/0.860) * (0.01/0.0111) * 100% = 72.5%
7. (0.726/0.860) * (0.01/0.0111) * 100% = 76.0%

Table 7: Dissolution Data

Sample	Absorbance (nm)	% Dissolution
1	0.968	101.4%
2	1.012	106.0%
3	1.033	108.2%
4	1.077	112.8%
5	0.675	70.7%
6	0.693	72.6%
7	0.726	76.1%

4 Discussion

4.1 Coating

The coated tablets have shown many defects that occurred during the coating process. The first issue noted was that the tablets didn't show any increase in weight after the coating process. The goal was for the tablets to gain a 3% increase in weight, and the amount of coating material that's required for this gain was calculated. However, after the amount was sprayed in full after the tablets, 10 tablets were weighed and had an average weight slightly lower than the average weight calculated before the coating process. The coating process was continued afterwards with the remaining amount of coating material to try and achieve weight gain for the tablets. In-process weighing of the tablets also showed no weight gain as well. Eventually, the process was stopped as to not overcoat the tablets. This failure of the tablets to gain weight is likely to be due to erosion of the tablets during the spraying process. This erosion could have caused weight loss and the coating weight gain, which is why the tablets showed no significant weight change after the coating process. Another factor that may have contributed to this is the moisture content of the tablets. If the drying of the tablets before the coating process was insufficient, the tablets may have lost more moisture, and therefore weight through the coating process, which may explain the unchanging weight throughout the process.

The coated tablets surfaces were also rough, and showed the orange peel effect. Possible causes of the orange peel effect include a high viscosity of the coating suspension, which prevents the coating droplets from coalescing effectively on the tablet surface and being applied in a uniform, smooth manner. It may have also been cause by ineffective atomization of the coating suspension, or over wetting of the tablets with the coating suspension due to un-optimized spraying and drying parameters (distance of the gun from the tablets, rotation speed of the pan, temperature of the drying air, diameter of the spraying on the tablets, ...). All these factors can affect the amount of coating material that reaches each tablet, so some tablets may come in contact with more fluid than others, and can also affect whether there was sufficient time for drying of the coating material on the tablets. Erosion of the tablets may have also contributed to the roughness of the tablets' surfaces after coating. The droplet size may have also been large during spraying due

to the atomizing air pressure and the pattern air diameter of the spraying gun. The atomizing air pressure decreases droplet size as it increases, while the pattern air diameter controls the area of spraying on the tablets, which would affect the distribution of the coating material on the tablets. [4]

The tablets have also displayed sticking and twinning problems during the coating process. The sticking defect was probably caused by incorrect spraying which hit the sides of the pan at times instead of the tablets, which would have caused the tablets to stick to the sides of the pan. The twinning problem could have been caused by over wetting or insufficient drying time or temperature during the process, which would have caused the tablets to gain too much moisture on their surfaces and stick to each other during the process.

The tablets have also displayed color variation, which was probably caused by uneven spraying of the coating material on the tablets as well.

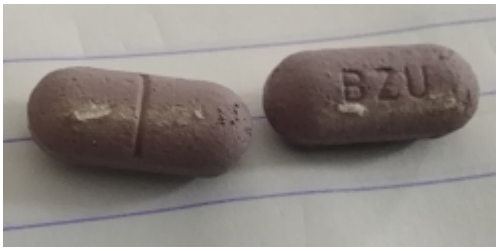

Figure 1: Result of sticking and twinning

Figure 2: Orange peel effect and erosion

4.2 Weight Variation

All tablets tested after coating for weight variation didn't display significant deviation from the average weight of the 10 tablets taken in the test. The USP specifies that when tablets weigh more than 324 mg, no more than 2 tablets should deviate by 5% from the average weight of tablets, and so all the tablets tested here are successful.

4.3 Hardness

The average hardness of the tablets produced after coating was determined to be 12.01 Kp. The USP only specifies that tablets should have a hardness greater than or equal to 4 Kp. A note worthy of mention is the increase in hardness of the tablets after coating. The average hardness of the tablets determined before coating was 10.04 Kp. Therefore, the coating around the tablets contributed to nearly 2 Kp increase in hardness of the tablets. After this test, it's important to test for disintegration and dissolution to determine whether this increase in hardness may affect the disintegration and dissolution of the tablets negatively.

4.4 Friability

The friability test showed an unusual increase in tablet weight (by 0.064%) after they were proccessed with the friability tester. This result indicates that the tablets are indeed resistant to abrasion during handling and such, but the increase in weight is unusual. This increase in weight may have been caused by insufficient dedusting of the tablets after the friability test was done, as well as random error from the balance used for weighing the tablets.

4.5 Disintegration

After coating disintegration time increased from 2 minutes and 19 seconds to 4 minutes and 1 seconds and this because coating increase the strength between tablet particles, increasing the time needed for disintegration, this also indicates good coating.

4.6 Dissolution

Before doing the test the 900 ml of phosphate buffer (pH = 5.8) was placed in all tubes and the temperature was checked to ensure that it's equal to 37°C +/- 0.5. Then the stirring speed was set to 50 rpm.

The first batch showed high % dissolution, however, since there dissolution were higher than the specified tolerance in the USP (80%), the test on that batch can be considered a success. The second batch, however, showed a % dissolution lower than the specified tolerance, and so should have moved to later stages of dissolution testing. The variation in dissolution between batches, whether high or low, can be attributed to poor mixing. Poor mixing may have resulted in higher or lower amounts of API in certain tablets, which may have caused an increase or decrease in the dissolution. The excipients used in the tablets may have also caused problems in the dissolution of the tablets, including the binder and the disintegrant. The coating material can also slow down the disintegration, and thus the dissolution of the tablets. Low temperature may also had a role, however the temperature was checked before the test was began.

Another source of bias is UV device that may has variation.

5 Questions

1. Dissolution of the drug product is the basis for its release and absorption in the body. Therefore, it's important to determine to get a measure of the bioavailability of the drug. Also, the dissolution pattern of an API has an impact on its pharmacological activity.

2. Before the API dissolves in a fluid, the drug product must break down and disintegrate to release the API and allow it to dissolve in the fluid. Therefore, when a disintegrant allows for a faster disintegration process, it also increases the dissolution rate of the API from the drug product.

3. - Ibuprofen immediate tablets. Medium: 900 mL Phosphate buffer (pH = 7.2). Apparatus 2: Paddle 50 rpm. Time: 60 minutes. Tolerance: Not less than 80% dissolved. [5]

- Cefuroxime suspension: 900 mL Phosphate buffer (pH = 7.0). Apparatus 2: Paddle 50 rpm. Time: 30 minutes. Tolerance: Not less than 60% dissolved. [6]
- Medium: 900 mL water. Apparatus 1 on 100 rpm for 250mg, or apparatus 2 on 75 rpm for 500mg. Time: 60 minutes. Tolerance: Not less than 80% dissolved. [7]

6 References

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