Optimization and Scale Up (Stage 1) of the Synthesis of a Medicinal Compound

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Abstract

This Thesis is the result of an effort to optimize the synthesis of succinyl disalicylic acid by esterification of salicylic acid and succinyl chloride. Conditions for the synthesis of the succinyl disalicylic acid, reaction time, addition rate of succinyl chloride, amount of catalyst, volume of solvent and type of solvent have been optimized for small-scale synthesis. These parameters are the most important factors affecting on yield. Increasing the addition rate and decreasing the reaction time results in higher yield. On the other hand, Increase of the volume of solvent resulted in lower yield. Increasing of the concentration of the reactants, i.e. lowering the volume of the solvent will increase the reaction rate. However, the relatively low solubility of salicylic acid will be the critical limiting factor. It was found that acetone gave higher yield than methyl ethyl ketone. The ratio of the catalyst to the starting materials is very important factor. The amount of catalyst has to be equivalent with the salicylic acid. For the larger-scale synthesis, scale was increased by a factor of 10. Reaction conditions for scale-up synthesis followed the same trend as the small-scale synthesis but some conditions have been changed to improve the yield. Decreasing the reaction time and volume of solvent result in higher yield. The mechanical-stirrer speed has been varied in order to solve the mixing problem. The results clearly indicated that higher mechanical-stirrer speed resulted in higher yield.

Keywords : optimization, succinyl disalicylic acid, scale up

1. Introduction

Analgesics (pain relievers) are among the most important worldwide medicinal applications. One of the oldest analgesics, a drug that is amazing for its continuing and varied usefulness is Aspirin, or acetyl salicylic acid, the salicylate ester of acetic acid. As an antipyretic, Aspirin reduces fever but does not lower normal body temperature. Its analgesic properties are effective against pain accompanying colds, flu, nervous tension, rheumatism, and arthritis. Recent evidence suggests that continuous small doses over long periods could decrease the chances of heart problems and increase the chances of surviving a heart attack should one occur. An important disadvantage of Aspirin is the deleterious effect on the stomach by inducing gastric ulceration. These gastrointestinal effects are due to the abstraction of succinate from the citric acid cycle. For this reason succinyl disalicylic acid has been developed [1] as a non-ulcerogenic, non-steroidal anti-inflammatory drug. It does not effect the stomach because a succinic acid residue is built into the molecule [1]. This Thesis is aimed as the development of the most efficient synthesis of succinyl disalicylic acid on a pre-industrial scale.

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2. Experimental

2.1 Synthesis of Succinyl Chloride

Succinic anhydride (10 g, 0.1 mole) was poured into the mixture of thionyl chloride (24.6 g, 0.2 mole) and anhydrous zinc chloride ($ZnCl_2$), weighed out accurately 4 decimals (variable), and refluxed with stirring for variable time. The solution was then filtered through glass wool, the excess thionyl chloride removed under vacuum, and the remaining liquid distilled under vacuo (80 ^oC/ 20 mm.) to yield a clear liquid [2].

2.2 Synthetic Methods for Succinyl Disalicylic Acid

Salicylic acid (13.8 g, 0.1 mole) and pyridine (7.6 g, 0.1 mole) were dissolved in 22.5 mL acetone. To the resulting clear solution, succinyl chloride (8.4 g, 5.3×10^{-2} mole) in 22.5 mL of acetone was added with stirring at a rate 15 mL/min to keep acetone refluxing. During the addition, the mixture turned dark purple. The reaction slurry was stirred for 30 minutes after all of the succinyl chloride has been added. The acetone evaporated from the slurry using a rotary evaporator at 45 ^oC and the desired product collected on a suction filter, washed with water and dried under vacuum at 65 ^oC. A brown solid was first crystallized from ethanol melted at 171-173 ^oC and weighed 9.76 g, (55%). It was then recrystallized from glacial acetic acid to give a white crystalline product, m.p. 176-178 ^oC (177-177.5 ^oC, [3]), (8.26 g, 46%) and its NMR spectrum is shown in Figure 1.

2.3 Optimization of the Production of Succinyl Chloride

Two processes the variables in the study were the reaction time and the quantity of zinc chloride used.

2.4 Optimization of the Production of Succinyl Disalicylic Acid

The optimum conditions were determined as follows.

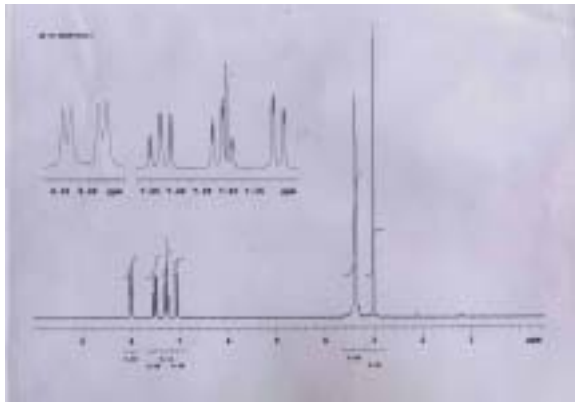


Figure 1 200 MHz ^1H NMR spectrum of succinyl disalicylic acid ($CD_3OD/CDCl_3$).

2.4.1 Addition Rate and Reaction Time

Since volume of solvent and the amounts of the catalyst were fixed, there are two process variables in the study; addition rate and reaction time.

2.4.2 Volume of Solvent and Catalyst

There are two process variables in this part of the study; volume of solvent and amounts of catalyst. These were done under the already optimized addition rate and reaction time.

2.4.3 Type of Solvent

The experiments were done under optimized conditions: addition rate, reaction time, volume of catalyst, and volume of solvent. And MEK was used instead of acetone in order to determine type of solvent; that most appropriate to the synthesis.

2.5 Scale-up Synthesis

2.5.1 Succinyl Chloride

Reaction conditions for scale-up synthesis were the same as the small-scale synthesis, but the scale was increased by a factor of 10. Succinic anhydride (100 g, 1 mole), thionyl chloride (246 g, 2.1 mole), and zinc chloride (8.1×10^{-3} mole) were used as reactants and catalyst. Reaction time was 6 hrs using a 500-mL two neck round-bottomed flask. The experiments were done under different adding

conditions; slow adding and all-at-once adding in order to investigate the mixing problem.

2.5.2 Succinyl Disalicylic Acid

2.5.2.1 Reaction conditions for scale-up synthesis were the same but carried out on 10 times as the small scale. Reactants and catalyst contained salicylic acid (138 g, 1 mole), succinyl chloride (84 g, 0.53 mole), and pyridine (79 g, 1 mole). The reaction time was half an hour using a 1-liter three neck round-bottomed flask with mechanical stirrer at speed 120 rpm.

2.5.2.2 The experiments were done in the same way as 2.5.2.1 but reaction time was reduced to 15 minutes and 100 mL acetone was decreased correspond to the amounts used in experiment 2.5.2.1.

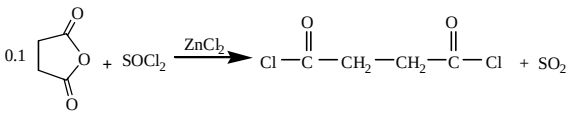
To investigate the mixing problem, the experiments were determined as follows.

2.5.2.3 The experiments were carried out in the same as experiment 2.5.2.2 but they were done under three-speed mechanical stirrer; 120 rpm, 200 rpm and 280 rpm.

3. Result and Discussion

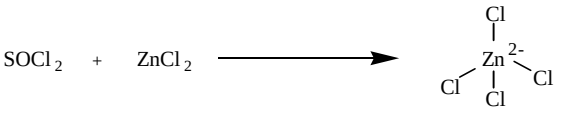
3.1 Synthesis of Succinyl Chloride

The reaction has been carried out many times using dimethyl formamide (DMF) as catalyst [4] and it has been found that DMF is not easy and convenient to remove. Therefore, succinyl chloride was synthesized by refluxing succinic anhydride in thionyl chloride using zinc chloride as catalyst.



(1)

Anhydrous zinc chloride is a powerful Lewis acid with empty orbitals that can accept electrons from chloride ions. The formation of a complex of zinc chloride with the chloride ions weakens the S-Cl bond and thus enhances the leaving ability of the chloride group. The complexation of $ZnCl_2$ and $SOCl_2$ is as follows.



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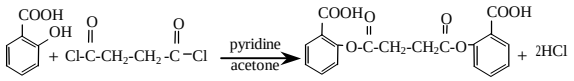
3.2 Synthesis of Succinyl Disalicylic Acid in the Course of the Present Project

Succinyl disalicylic acid was synthesized by esterification of salicylic acid and succinyl chloride. The synthesis of succinyl disalicylic acid has been carried out exactly as in the literature [5-6] but this was not successful. The Gaffar et al. Method [3] avoids the use of benzene and dimethylaniline by employing pyridine and acetone instead. It is easy to work up and uses inexpensive chemical reagents. Therefore, this method was chosen to the optimization in this Thesis. The product was obtained as white crystals (176-178 °C, 46%), (177-177.5 °C, [3]).



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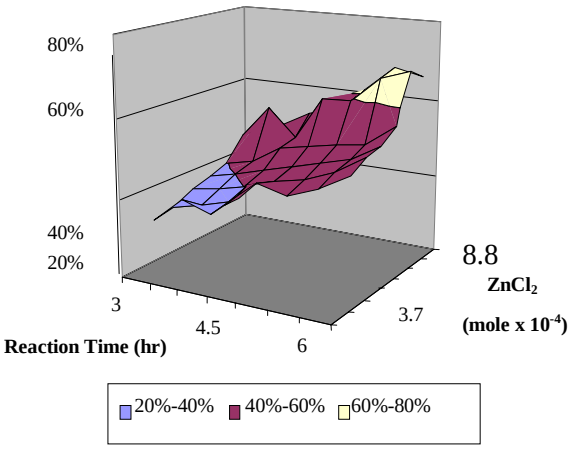

Figure 2 Effects of the amount of zinc chloride and the reaction time on percentage yield.

Table 1 Effects of amount of zinc chloride and the reaction time on percentage yield

$ZnCl_2$(mole x10^{-4}) / RT(hr)	3.7	4.4	5.1	5.9	6.6	7.4	8.1	8.8
3.0	31%	33%	34%	37%	39%	40%	46%	45%
3.5	33%	40%	36%	38%	40%	42%	55%	48%
4.0	36%	37%	38%	40%	42%	46%	47%	52%
4.5	38%	43%	44%	42%	44%	48%	59%	55%
5.0	38%	43%	42%	44%	46%	49%	59%	61%
5.5	43%	48%	45%	47%	49%	50%	66%	67%
6.0	47%	51%	49%	52%	53%	56%	68%	66%

3.3 Optimization of the Production of Succinyl Chloride

The process variables in this part of the study were the amount of zinc chloride and the reaction time. The percentage yields are shown in Table 1. Figure 2 shows in three-dimensional plots of the process variables; amounts of zinc chloride and reaction time, against the percentage yield.

Table 1 and Figure 2, shows that the amount of zinc chloride has a stronger effect on the percentage yield than the reaction time. Increasing the amount of zinc chloride to 8.10×10^{-4} mole resulted in the highest percentage yield. It appears therefore that the optimum amount of zinc chloride was 8.10×10^{-4} mole.

Table 2 shows the effect of the reaction time on the percentage yield at the optimum amount of zinc chloride. The longer the reaction time the higher the percentage yield up until 6 hrs, after that the percentage yield decreases. The lower in percentage yield at longer period of time may be the result of decomposition of succinyl chloride. Technically, the optimum reaction time should be 6 hrs. Therefore, a plot of the reaction time and the profit would be helpful to determine optimum reaction time in economic aspect.

Table 3 and Figure 3 clearly indicated the effect of the reaction time on the profit. At the reaction time 6 hrs resulted in highest profit. Therefore, the reaction time 6 hrs is suitable in both of technical and economic aspects.

Table 2 Effects of the reaction time at 8.1×10^{-4} mole of zinc chloride on percentage yield

RT (hr)	1st experiment	2nd experiment	3rd experiment	Average
3.0	54%	37%	49%	51%
3.5	56%	53%	50%	53%
4.0	38%	57%	60%	58%
4.5	58%	60%	63%	60%
5.0	56%	62%	62%	62%
5.5	68%	63%	67%	68%
6.0	74%	63%	70%	72%
6.5	49%	54%	54%	54%
7.0	47%	49%	47%	48%
7.5	33%	36%	31%	35%

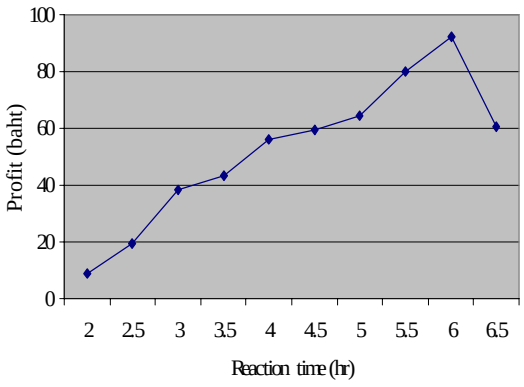

Figure 3 Effects of the reaction time at 8.10×10^{-4} mole of zinc chloride on the profit

Table 3 Relationships between the reaction time, cost of electricity, cost of refrigerator, capital, and cost of recovery

RT(hr)	[1]cost of electricity (baht)	[2]cost of refrigerator (baht)	[3]cost of succinyl chloride (baht)	[4]investment (baht)	[5]cost of recovery (baht)	[6]net investment (baht)	[7]profit (baht)
2.0	4.56×10^{-2}	4.2	168.2	340.6	181.0	159.6	9.0
2.5	5.70×10^{-2}	5.2	188.4	341.6	172.7	168.9	19.5
3.0	6.84×10^{-2}	6.2	228.0	342.7	153.1	189.5	38.5
3.5	7.98×10^{-2}	7.3	236.0	343.7	149.5	192.4	44.0
4.0	9.12×10^{-2}	8.3	259.2	344.8	141.5	203.3	56.0
4.5	10.26×10^{-2}	9.4	267.2	345.8	138.0	207.8	59.0
5.0	11.40×10^{-2}	10.4	276.4	346.9	135.1	211.8	65.0
5.5	12.54×10^{-2}	11.4	300.0	347.9	128.1	219.9	80.0
6.0	13.68×10^{-2}	12.5	317.6	349.0	123.4	225.6	92.0
6.5	14.82×10^{-2}	13.5	240.0	350.0	170.6	179.5	61.0

[1]cost of electricity = rate/unit x electrical energy electrical energy (kWhr) = power of heating mantle (kW) x time (hr) rate/unit was assumed as 2 baht/unit

[2]cost of refrigerator = rate/unit x refrigerator energy refrigerator energy (kWhr) = power usage of refrigeration (kW) x time (hr) rate/unit was assumed as 2 baht/unit

[3]cost of succinyl chloride = price/unit in mL (40 baht) x volume (mL)

[4]investment = cost of electricity + cost of refrigeration + cost of succinic anhydride 0.1 mole (17.3 baht) + cost of $ZnCl_2$ 8.10×10^{-4} mole (6.82×10^{-2} baht) + cost of $SOCl_2$ 15 mL (319.0 baht)

[5]cost of recovery = cost of recovered $SOCl_2$

[6]net investment = investment - cost of recovery

[7]profit = cost of succinyl chloride - net investment

Table 4 Effects of the addition rate and the reaction time on percentage yield

RT(hr) / AR(mL/min)	0.5	1.0	1.5
0.5	30%	22%	26%
3.0	29%	30%	31%
6.0	42%	35%	33%
10.0	47%	39%	40%
15.0	46%	49%	38%

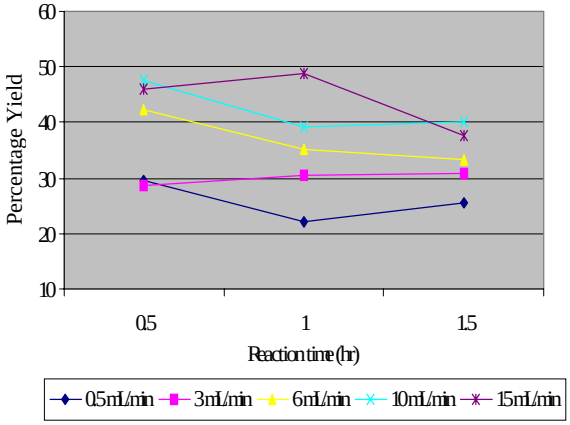

Figure 4 Effects of the addition rate and the reaction time on percentage yield.

3.4 Optimization of the Production of Succinyl Disalicylic Acid

The volume of acetone was 22.5 mL and amount of pyridine was 0.1 mole, Table 4 and Figure 4 show the effect of the addition rate and reaction time on percentage yield. The increase in addition rate and decrease in reaction time resulted in high percentage yield due to the highly reactive

Table 5 Effects of amount of catalyst and volume of solvent on percentage yield

Pyridine (mole) \ Acetone(mL)	17.5	22.5	27.5
0.050	35%	37%	15%
0.075	43%	39%	25%
0.100 (equivalent)	41%	55%	27%
0.125	35%	36%	20%
0.150	22%	29%	7%

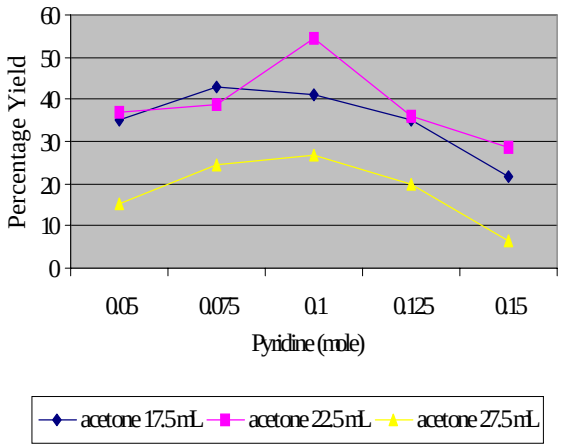

Figure 5 Effects of amounts of pyridine and volume of acetone on percentage yield

of the reactants salicylic acid and succinyl chloride in the esterification reaction. Amounts of pyridine and volume of acetone were evaluated in the same manner at the addition rate of 15 mL/min and the reaction time half an hour. These results are based on the first recrystallized product because some reactions could not be purified even when recrystallized twice. The results are shown in Table 5 and Figure 5

When the amount of pyridine was low, the percentage yield decreased because the amounts of catalyst were inadequate to react with the salicylic acid. On the other hand, higher amount of pyridine than an equivalent caused the percentage yield to decrease. Because the excess pyridine would react with the highly reactive succinyl chloride. Therefore, there is not enough succinyl chloride to react with salicylic acid.

Increase in the volume of acetone resulted in lower percentage yield because of the lower concentration of reacting species. Therefore, at lower volume of acetone, the percentage yield was higher, may due to the higher opportunity for reacting species to encounter each other. However, a lower volume of acetone would not be enough to dissolve the salicylic acid resulting a lower percentage yield. It appears therefore that theoptimum volume of acetone was 22.5 mL and the optimum amounts of pyridine were 0.1 mole.

The effect of the type of solvent was also examined. The experiments were carried out using the optimized conditions; addition rate 15 mL/min, reaction time half an hour, volume of acetone 22.5 mL and amount of pyridine 0.1 mole. The results showed that acetone gave higher percentage yield than MEK. This is probably due to their higher boiling point of MEK than that of acetone, leading to a higher reflux temperature. Then succinyl chloride may be decomposed prior to react.

3.5 Large Scale Synthesis

3.5.1 Succinyl Chloride

To investigate the optimum scale up condition, the experiments were carried out under the optimized reaction time. There were two experiments, one was

Table 6 Effect of type of solvent on percentage

Solvent	% Yield
Acetone	46%
MEK	24%

Table 7 Percentage yield of succinyl chloride in small scale and large scale synthesis

Scale (mole) \ Addition	slow addition	all- at- once addition
0.1 (8.1×10^{-4} mole $ZnCl_2$)	79%	72%
1.0 (8.07×10^{-3} mole $ZnCl_2$)	64%	55%

slow addition and the other was all-at-once addition. Slow addition resulted in higher percentage yield than that of all-at-once adding because of more efficient mixing. However, the percentage yield from large scale was still lower than small scale. The results are shown in Table 7.

3.5.2 Succinyl Disalicylic Acid

To investigate the optimum scale up condition, the experiments were carried out under the following the optimized conditions; addition rate 15 mL/min, reaction time 0.5 hr and mechanical-stirrer speed 120 rpm. The reaction scale was increased by a factor of 10. Percentage yield was 25 %. This reaction has been carried out several times but only the highest yield is reported here.

When the reaction was scaled up, the conditions were changed to improve the percentage yield. The amount of the acetone was decreased, the percentage yield was higher, follow the same trend as those of small scale. In addition, the reaction time set for 15 minutes, the percentage yield was higher. The longer reaction time caused the product hydrolyzed by the moisture. Moreover, there was an obvious mixing problem. Since succinyl chloride is quite reactive and is readily hydrolyzed. When succinyl chloride was added to the reaction mixture of salicylic acid and pyridine, it should diffuse to the matrix of salicylic acid as fast as possible. Otherwise succinyl chloride will be hydrolyzed or reacted with other reagents instead of salicylic acid. The mechanical-stirrer speed has been varied in order to solve the mixing problem. It should be carefully investigated and should not be too high because by-product in this reaction is HCl gas caused the reaction to blow up. The results clearly indicated that higher mechanical-stirrer speed resulted in higher percentage yield. It appears therefore that mixing problem could be solved by increasing mechanical-stirrer speed. The results are shown in Table 8 and Figure 6.

Table 8 Effect of speed of mechanical stirrer on percentage yield

Mechanical-stirrer Speed (rpm)	% Yield
120	27%
200	30%
280	36%

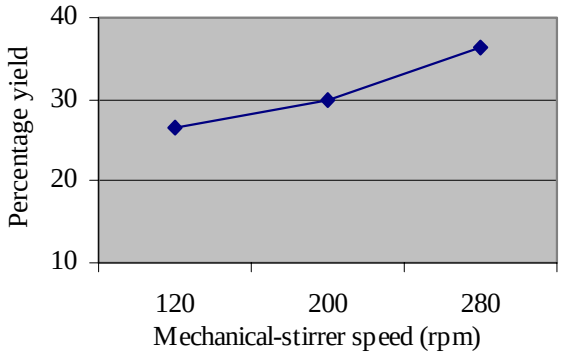

Figure 6 Effects of mechanical-stirrer speed on percentage yield

4. Conclusion

From the work, it can be concluded that, increasing the addition rate and decreasing the reaction time result in higher yield since the esterification of salicylic acid with succinyl chloride, which is highly reactive. Shorter reaction time results in higher percentage yield. When the amounts of catalyst was low, the percentage yield decreased because the amounts of catalyst were inadequate to react with the salicylic acid. On the other hand, when the amounts of catalyst is more than an equivalent of the salicylic acid the percentage yield was decreased, because the excess catalyst reacted with succinyl chloride instead. Therefore, there is not enough succinyl chloride to react with salicylic acid. The optimization of the ratio of the catalyst to the starting materials is very important.

Increase in the volume of solvent would result in the lowering percentage yield because of the decrease concentration of reacting species. Therefore, increasing the concentration of the reactants, i.e.

lowering the volume of the solvent will increase the reaction rate. However, the relatively low solubility of salicylic acid will be the critical limiting factor.

Effect of the type of solvent showed that acetone gave higher percentage yield than MEK. This is probably due to the higher boiling point of MEK as compared to that of acetone leading to higher reflux temperature.

Therefore, optimum condition for small-scale synthesis of succinyl disalicylic acid were: salicylic acid : succinyl chloride : catalyst : solvent (0.1 : 0.05 : 0.1 : 0.3 mole ratio), reaction time 0.5 hr, addition rate 15 mL/min, and suitable solvent was acetone.

For the larger-scale synthesis, the scale was increased by a factor of 10. The amount of the acetone was decreased, the percentage yield was higher, this is due to the higher opportunity for reacting. In addition, the reaction time set for 15 minutes, the percentage yield was higher. The longer reaction time caused the product was hydrolyzed by the moisture. However, there was an obvious mixing problem. This problem could be minimized by increasing the mechanical-stirrer speed.

Therefore, optimum condition for large-scale synthesis of succinyl disalicylic acid was assigned to the mole ratio of : salicylic acid : succinyl chloride : catalyst : solvent equal to 1 : 0.5 : 1 : 2.38 with the reaction time 15 min, addition rate 15 mL/min, and mechanical-stirrer speed 280 rpm.

5. Acknowledgement

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