Formulation and Testing of a Seaweed-based, Oral Tablet to Treat the Symptoms of Acid Reflux.

BY

SAWITTA SRIWORALAKKHANA 62011245

A PROJECT SUBMITTED IN PARTIAL FULFILLMENT OF THE REQUIREMENTS FOR THE DEGREE OF BACHELOR OF ENGINEERING IN BIOMEDICAL ENGINEERING
KING MONGKUT'S INSTITUTE OF TECHNOLOGY LADKRABANG
ACADEMIC YEAR 2022

SCHOOL OF ENGINEERING

KING MONGKUT'S INSTITUTE OF TECHNOLOGY LADKRABANG

PROJECT CERTIFICATE

Project Title	Formulation and Testing of a Seaweed-based, Oral Tablet to Treat the Symptoms of Acid Reflux
Student Name	Sawitta Sriworralakkhana 62011245
Degree	Bachelor of Engineering in Biomedical Engineering
Project Advisor	Signed: _____ (Assoc. Prof. Dr. Matthew Paul Gleeson)
Committee	Signed: _____ (Assoc. Prof. Dr. Chuchart Pintavirooj)
Committee	Signed: _____ (Assoc. Prof. Dr. Wibool Piyawattanamatha)
Committee	Signed: _____ (Asst. Prof. Dr. Treesukon Treebupachatsakul)
Committee	Signed: _____ (Asst. Prof. Dr. Kasama Srirussamee)
Head of Department	Signed: _____ (Assoc. Prof. Dr. Sarinporn Visitsattapongse)

Project Title	Formulation and Testing of a Seaweed-based, Oral Tablet to Treat the Symptoms of Acid Reflux
Student Name	Sawitta Sriworalakkhana 62011245
Degree	Bachelor of Engineering in Biomedical Engineering
Project Advisor	Assoc. Prof. Dr. Matthew Paul Gleeson, International Program, Ph.D.
Academic Years	2022

ABSTRACT

Gastroesophageal reflux (GERD) disease is designated as the involuntary flow of stomach content back into the esophagus, causing the esophageal tract to be wounded and inflamed. This disease affects more than 44% of the world's population. The symptom of GERD is burning pain in the chest, also known as heartburn, which can be soothed by making use of an antacid. Antacid helps neutralize the acid in the stomach which reduce the effect of heartburn but this method also has a negative side effect. But by neutralizing the acidity, the bacteria can infect the body easier, which can cause other illnesses. So, another method of treatment was invented. Without offsetting the stomach acid, Gaviscon has made medicine with the property of stopping the acid from flowing back to the esophageal tract and not disturbing the immune system. Instead of neutralizing acid, the pills interact with stomach acid and form a gel-like raft that floats on top of stomach content, preventing them from fluxing back. This method turns out to be highly effective. However, due to the high price of this product, the medicine cannot be accessed by a lot of people. This project is made to replicate the same or better effect of the Gaviscon tablets with a lower price and use the ingredient that we have in the Thai medical market, for the easiest access to people in our country and nearby.

ACKNOWLEDGEMENTS

The author would like to thank their own family who provide them support and care during the making of this study. Also, I would like to thank my advisor Assoc. Prof. Dr. Matthew Paul Gleeson who have been very supportive and understanding provide me with resource and advice throughout the making of this project.

Sawitta Sriworalakkhana

TABLE OF CONTENTS

	Page
ABSTRACT	**III**
ACKNOWLEDGEMENTS	**IV**
LIST OF TABLES	**VII**
LIST OF FIGURES	**VIII**
LIST OF SYMBOLS/ABBREVIATIONS	**XIII**
CHAPTER 1 INTRODUCTION	**1**
1.1 Background and significance of Research	1
1.2 Research Objectives	2
1.3 Research Hypothesis	2
1.4 Research Scope	2
CHAPTER 2 REVIEW OF SURFACE PLASMON RESONANCE	**4**
2.1 Tablet making	5
2.2 Material processing	8
2.3 Tablet testing	14
2.4 Mechanic	17
CHAPTER 3 METHODOLOGY	**19**
3.1 Introduction	19
3.2 Materials and methods	19
3.2.1 Ingredients and Formula developing	19
3.2.2 Tablet making Process	20

3.2.3 Tablet quality testing 21

CHAPTER 4 EXPERIMENTAL RESULT **22**

4.1 Introduction 22

4.2 Progression map 22

4.3 Experiment 23

CHAPTER 5 CONCLUSION **33**

5.1 Conclusions 33

5.2 Discussion 34

REFERENCES 35

LIST OF TABLES

Tables	Page
Figure3: Steps required for each type of tablet processing method	4
Figure22: The mole of bases in 3 Gaviscon tablets, from titration	24
Figure24: weight of each ingredients of each batch number	26
Figure25: The table showing qualitative data of tablet that has been measured out and being produced differently.	26
Figure26: The table showing quantitative data of hardness of tablets made from granule in 4 particle ranges	27
Figure27: The table showing moles of bases in tablets made from granule in 3particle ranges	27
Figure28: The table showing hardness value and Disintegration time of 6 tablet formula from 2 different brand of Sodium alginate	28
Figure29: The table showing the titration results of 3 controlled factor for future reference	28
Figure30: The table showing weight of CaCO3 and NaHCO3	29
Figure31: The table comparing mole of bases from calculation and from titration	29
Figure32: The table showing weight of ingredients in each flask	29
Figure33: The table comparing mole from calculation and titration	30
Figure34: The table shows moles per tablet of each particle range	30
Figure35: The table shows moles per tablet for each particle range	31
Figure36: The table shows speed of raft formation of each particle batch	31
Figure37: The table shows quantitative quality of raft by each particle range	31
Figure39: The table shows thickness of raft from each particle range	32

LIST OF FIGURES

Figures	Page
Figure1: Gastroesophageal reflux disease (GERD) infographic	1
Figure 2: Example 8 of 2003 Gaviscon (WO 03/ 068246 A2)	2
Figure4: The parameter and incidence used in determining quality of tablets	6
Figure5: Showing automated tapped density device and the difference between bulk and tapped density.	7
Figure6: Difference angle of repose in terms of particle size and table of flowability calculated from angle repose.	8
Figure7: Ball milling process	9
Figure8: V-shape powder mixer	9
Figure9: Granulation process.	10
Figure10: Tablet compression process	10
Figure11: image of starch particles	12
Figure12: micro crystalline cellulose particles	13
Figure13: Vernier caliper	14
Figure14: Tablet friability tester	15
Figure15: Tablet hardness testers	16
Figure16: Tablet disintegration test	16
Figure17: raft structure	17
Figure 18: Example 8 of 2003 Gaviscon (WO 03/ 068246 A2)	20
Figure19: Flowchart of project workflow	22
Figure20: Flowchart of workflow of each category of evaluation	23
Figure 23: Example 8 of 2003 Gaviscon (WO 03/ 068246 A2)	25
Figure25: The table showing qualitative data of tablet that has been measured out in figure20 after being produced differently.	26
Figure26: The table showing quantitative data of hardness of tablets made from granule in 4particle ranges	27
Figure38: The photo showing raft from each particle batches (from left to right: active ingredients, >1mm, 1mm-0.6mm, 0.6mm-0.45mm, <0.45mm)	32

CHAPTER 1
INTRODUCTION

1.1 Background and significant of research

Gastroesophageal reflux is a normal physiologic process. It is defined as the involuntary flow of stomach content back into the esophagus. Gastroesophageal reflux disease (GERD) occurs when reflux causes discomfort, troublesome symptoms or, complications. Most people can manage the discomfort of GERD with lifestyle changes and over-the-counter medications. But in the case of high severity, the patient may need stronger medications or surgery to ease symptoms. Gastroesophageal reflux disease (GERD) affects more than 11.9% of the world's population. Antacids reduce the acid reaching the duodenum by neutralizing the acid present in the stomach. The salts' mechanism of neutralization of acid varies, and each salt has a different approach to achieving the ultimate goal of acid neutralization. This neutralization makes the stomach contents less corrosive, thus the content becomes less harmful to the organs. This can help to relieve the pain associated with ulcers and the burning sensation in acid reflux. However, the complete neutralization of stomach acid can negatively affect digestion as well as remove an important barrier preventing bacterial and viral infections.

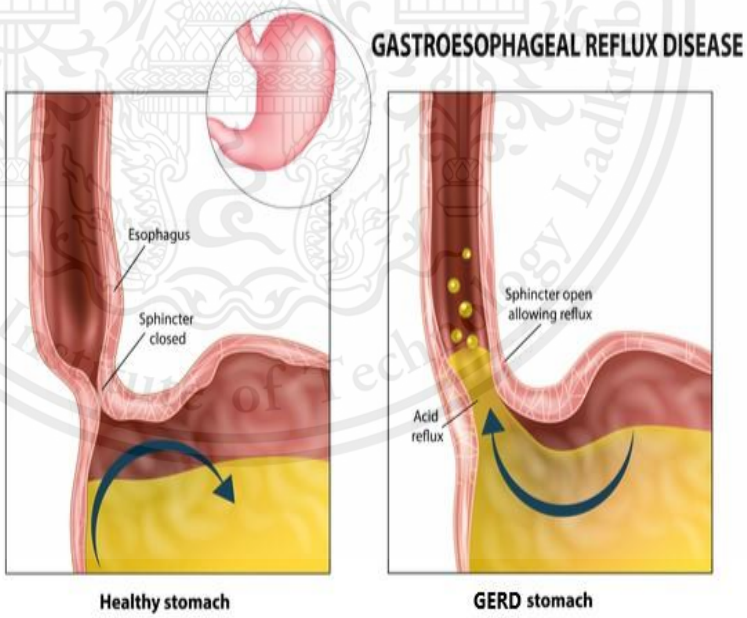


***Figure1**: Gastroesophageal reflux disease (GERD) infographic*
(https://www.straighthealthcare.com/gerd.html)

The anti-ulcer drugs work as a treatment for GERD, usually by preventing stomach content from spilling into the esophageal or reducing acidity of stomach content, therefore reducing the infection rate in the lower esophageal tract. In this project, we focus on the anti-ulcer drugs that are formulated such that a floating raft is formed upon reacting with stomach acid, hovering over stomach content. A raft formed

by the product of the present invention will form a physical barrier to acid refluxing into the esophagus, thereby preventing or reducing the continuous damage to the esophageal lining.

1.2 Objectives

One of the medical brands that use the raft method and prove it to be incredibly successful in treating GERD is Gaviscon. However, due to differences in money value, this medicine is hardly accessible in within Thailand and other south east Asian countries. For that reason, this project was made. Aiming to replicate the therapeutic effect of Gaviscon tablet with ingredient that are acquirable in Thai market and have the price of final product be more affordable to Thai citizen and neighbor countries.

Properties that we wanted to achieves are:

- Gel-like raft that is strong enough to prevent reflux
- Has good tablet properties.
- A formula of tablets that are reproduceable in mass product.

1.3 Hypothesis

Due to limited tools in making and compressing tablets and wide range of patents mentioned, this project will be focusing on the medical properties of one of the mentioned patents in Gaviscon 2003 patents.

Ingredient	Example	
	Comparative 2	8
	mg/tablet	mg/tablet
Sodium alginate LFR5/60	250.00	250.00
Sodium bicarbonate	133.50	133.50
Calcium carbonate	80.00	80.00
Mannitol	607.75	432.75
Polyethylene Glycol 20000	0.00	175.00
Flavour 1	5.50	5.50
Flavour 2	1.10	1.10
Sweetener 1	5.50	5.50
Sweetener 2	1.65	1.65
Magnesium stearate	15.00	15.00
Tablet weight	1100mg	1100mg

Figure 2: *Example 8 of 2003 Gaviscon (WO 03/ 068246 A2)*

1.4 Research scope

- All the experiment conducted each time are done in one sitting, unless mentioned otherwise.

- Using Gaviscon as reference tablet due to the effective medical properties
- The tablet compressor used in this project are smaller in size in comparison to our reference.
- Human error might be made in production.
- Referencing tablet formula from Gaviscon2003 patent.

CHAPTER 2
THEORY

Introduction

Tablet making

Tablets are the most economical means of administering drugs to humans because they are inexpensive to manufacture and transport and their physical properties can be easily altered. Tablets consist of an active ingredient mixed with additional inactive pharmaceutical ingredients (API)selected to ensure good ingredient mixing, physical strength, chemical stability, and physiological properties when ingested. The characteristics of the excipients are:

Pharmacologically inert.

- Inexpensive and commercially Available
- High purity and Commercially stable
- Free from bacteria and fungi
- Acceptable to regulatory agencies

Excipients for tablets can be divided into five common types according to their role in tablet production or physiological dissolution. Some excipients may play more than one role, depending on their physical properties

Diluents are essentially fillers used to balance the required volume of the tablet. This is particularly important for very low-dose active ingredients, which would result in a very small-volume tablet that may have poor pharmacokinetic/physiological properties. Typically, inert ingredients include lactose, spray-dried lactose, microcrystalline cellulose (MCC) (Avicel 101 and 102), sorbitol, dibasic calcium phosphate dehydrate, calcium sulfate dehydrate.

Wet granulation	Dry granulation	Direct compression
Dispensing/Weighting	Dispensing, weighting	Dispensing/weighting
Sieving/Milling	Sieving/Milling	Sieving/Milling
Dry powder mixing	Dry powder mixing/Lubrication	Dry powder mixing/Lubrication
Wet massing with granulating fluid	Roller compaction /slugging	Compression
Wet screening	Milling/Crushing	
Drying	Compression	
Dry screening after checking LOD		
Lubrication		
Compression		

Figure3*: Steps required for each type of tablet processing method*

Binders are used to form a cohesive tablet consisting of all the different types of powdered and granular excipients with different particle shapes and sizes. Binders can be added in both dry and wet forms to form granules that can be compressed more effectively than powders. Examples include gelatin, glucose, lactose, starch, cellulose derivatives - methylcellulose, ethyl cellulose, hydroxy propyl methyl cellulose, hydroxy propyl cellulose, starch, poly vinyl pyrrolidone (povidone) and acacia.

Lubricants are used in cases where the powders or granules developed for tablet compression gum up the tablet die and punch, preventing smooth operation of the machine by interfering with the smooth ejection of tablets from the die cavity. Lubricants include soluble tartaric acid, magnesium stearate, calcium stearate, talc and kerosene. Alternatively, soluble components such as sodium lauryl sulfate, sodium benzoate or polyethylene glycol polymers (PEG) can be used

Lubricants help produce a better flowing granule or powder for use in mixers and in the cavity. Low friction is important to ensure that the die cavity is completely filled before tablets are pressed and ejected. Excipients used to minimize friction between particles to improve powder flow include colloidal silica, starch and talc. Super disintegrants are ingredients that alter the disintegration of the tablet when in contact with water. They can be adjusted so that the tablet disintegrates in the oral cavity, at a log pH in the gastrointestinal tract, or at a neutral pH in the intestine. Examples include croscarmellose sodium, crospovidone and starch.

2.Ingredient mixing and Granulation
Ingredients are selected by statistical design or trial and error to find a suitable tablet formulation. How these ingredients are combined and processed is of great importance.

Three different techniques can be used to prepare A mix before compressing the formulation into a tablet. The most common method involves the formation of moist granules (by the addition of a solvent such as water or isopropyl alcohol), which are then dried, sieved, and ground to ensure a suitable granule size and flow characteristics for compression. The many processing steps associated with this method are its major limitation. The process can also be carried out under completely dry conditions, with a somewhat reduced number of steps, known as dry granulation. The third and increasingly popular alternative is direct compression. In this process, a pre-constituted excipient is combined with the active ingredient and mixed before compression. Pretreatment of the powder mixture by a wet or dry granulation process is not required, so labor costs are low. However, the cost of pre-formulated excipients is higher.

In order for the tablet press to produce high quality tablets, it is essential that the mixture of ingredients entering the press be dry and of uniform particle size. If this cannot be achieved simply by mixing them appropriately, the ingredients must undergo an additional granulation step prior to the press operation to ensure uniform distribution of the active ingredient in the finished tablet.

2.1 Particle properties
Effective mixing of the solid ingredients (powder and granules) is critical in tablet production to ensure consistent and uniform distribution of the ingredients and physical properties of the tablet
It is common practice to start the initial mixing process by sieving the raw materials separately and then mixing them in a suitable mixer. Further processing, such as grinding (to reduce particle size) or further screening (to further control particle size distribution), may be desirable after additional processing steps to prevent the formation

of agglomerates (uneven clumps of material) Agglomeration occurs again at each processing step. Therefore, mixing and sieving may be required after each step to ensure effective distribution of the active ingredient and ingredients in the mixture. [1]

-Particle size and size distribution
Control of the particle sizes of the active ingredient and excipients is critical to control the strength and release profile of the tablet produced. In general, a desirable powder blend (or granule) must have good flow properties, compressibility, binding, ability to form tablets with good hardness and friability within limits, while meeting drug release requirements. [1]

Engineers and scientists have developed a wide range of equipment to measure the flowability of powders in order to understand the effects of powder behavior on tablet properties. Traditional tests include.

1. Bulk Density (Da)
2. Tapped Density (Dc)
3. Angle of Repose (α)
4. Inter-particle Porosity (Ie)
5. Carr Index (IC)
6. Hausner Ratio (IH)
7. Angle of repose
8. Loss on Drying (%HR)
9. Hygroscopicity (%H)
10. Particle Size (%Pf)

Incidence	Parameter	Symbol	Unit	Equation
Dimension	Bulk Density	Da	g/mL	Da = M/Va
	Tapped Density	Dc	g/mL	Dc = M/Vc
Compressibility	Inter-particle Porosity	Ie	-	Ie = (Dc-Da)/(DcxDa)
	Carr Index	IC	%	IC = (Dc-Da)/Dcx100
"Flowability"/Powder flow	Hausner Index ratio	IH	-	IH = Dc/Da
	Angle of Repose	(α)	°	Tgα = h/r
Lubricity/Stability	Loss on Drying	%HR	%	Experimental
	Hygroscopicity	%H	%	Experimental
Lubricity/Dosage	Particles <50 µm	%Pf	%	Experimental

Figure4: *The parameter and incidence used in determining quality of tablets*

The density of a powder can be determined by measuring the mass of a given volume of powder. The tapped density, i.e. the density after mechanical tapping of a container containing the powder sample, is an indicator of the amount of free space between the powder samples and of the powder's flowability. [1]

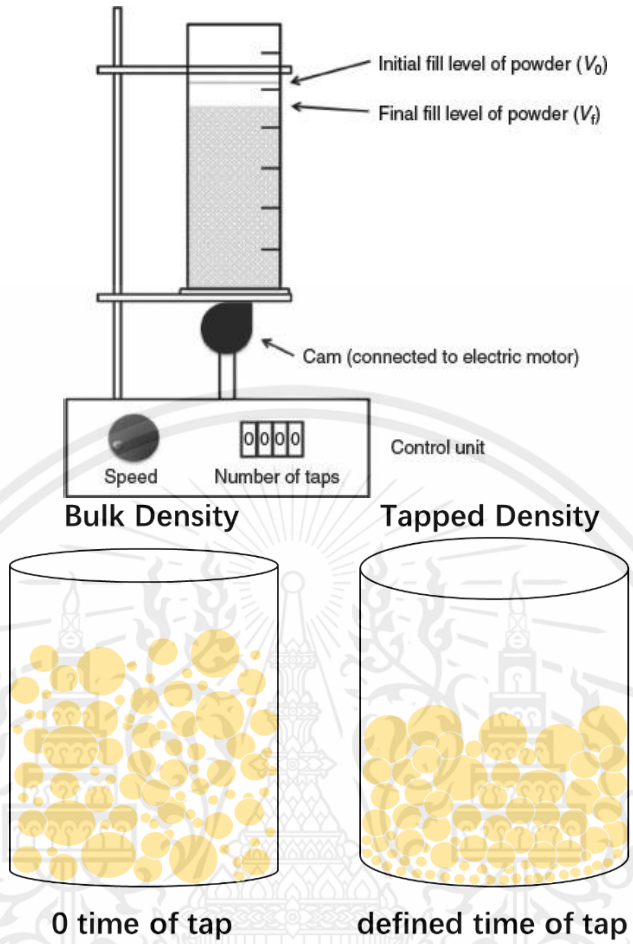
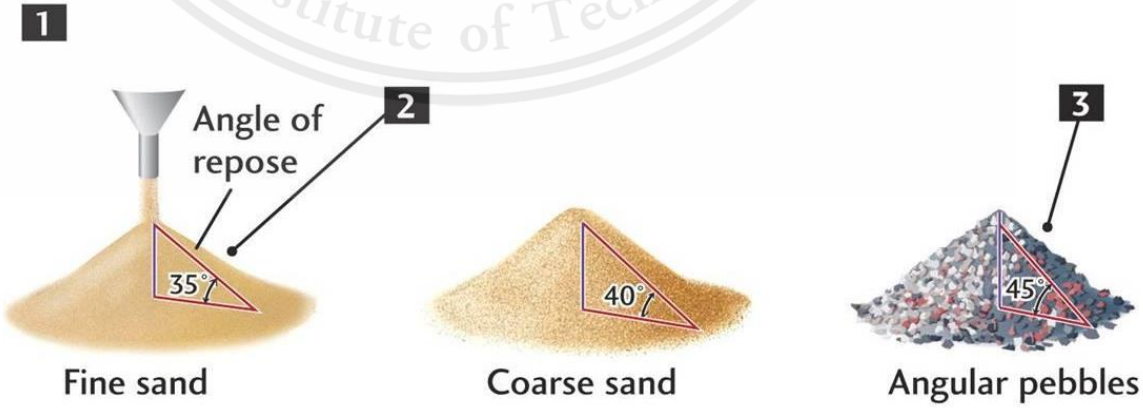


Figure5: *Showing automated tapped density device and the difference between bulk and tapped density. (https://basicmedicalkey.com/powder-properties/)*

The angle of repose of a powdered or granular material is the greatest angle with respect to the horizontal plane at which the material can be piled without collapsing. The smaller the angle of repose, the lower the forces between the particles and the greater the fluidity of the material [1]



Compressibility index (%)	Angle of repose (°)	Flow character
≤10	25-30	Excellent
11-15	31-35	Good
16-20	36-40	Fair
21-25	41-45	Passable
26-31	46-55	Poor
32-37	56-65	Very poor
>38	>66	Very, very poor

Figure6: *Difference angle of repose in terms of particle size and table of flowability calculated from angle repose (https://www.researchgate.net)*

A powder with an angle of repose of 65° would be classified as extremely poor flowing, while a powder with an angle of 25°-30° would be classified as "free flowing" [2]

2.2 Material processing

Grinding and sieving are important processes performed on powders and granules at various stages of production. This is because the most important physical parameter of a particulate drug is undoubtedly its particle size. Particle size can be determined by laser diffraction, optical microscopy or by using sieves with different mesh sizes.[3]

Screens and mills are used to break down solids. This serves two purposes: first, the surface area of the particles is increased, which increases the dissolution rate. Second, differences between particle sizes are equalized to ensure homogeneous mixing. The goal of grinding is not necessarily to produce the smallest possible particle sizes, but rather to ensure uniformity. Indeed, the cohesive properties between very small particles can make them less effective in the compression phase.[4]

Ball milling or hammer milling can be expensive and time consuming. In the former, ceramic balls are used in a drum to grind the products. After a batch is ground, the mill and hundreds of ceramic balls in it must be cleaned.[5]

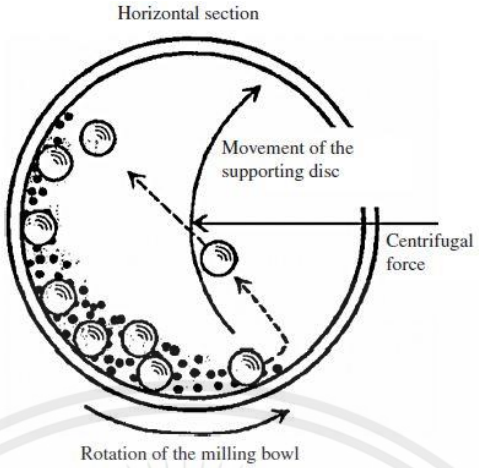


Figure7: *Ball milling process(https://www.understandingnano.com)*

Dry powder mixing

Proper mixing of solid particulate ingredients is of great importance to ensure uniformity of content. Mixing of the active ingredient and excipients in tablet form is almost always accompanied by a sieving process. The main purpose of sieving is to eliminate or reduce agglomerates. [6]

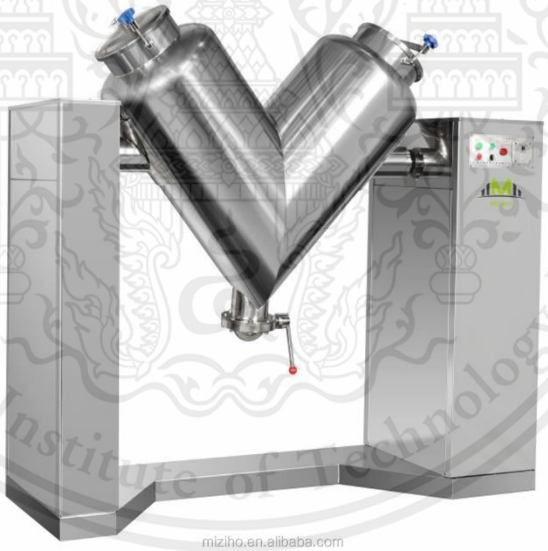


Figure8: *V-shape powder mixer(https://welldone-machinery.en.made-in-china.com)*

Granulation

Granulation, the process of particle enlargement by controlled agglomeration. That is, it is the use of a binder to produce granules of excipient and active ingredient with a uniform distribution that have better compression properties than the smaller particles that make up the granules. [7]

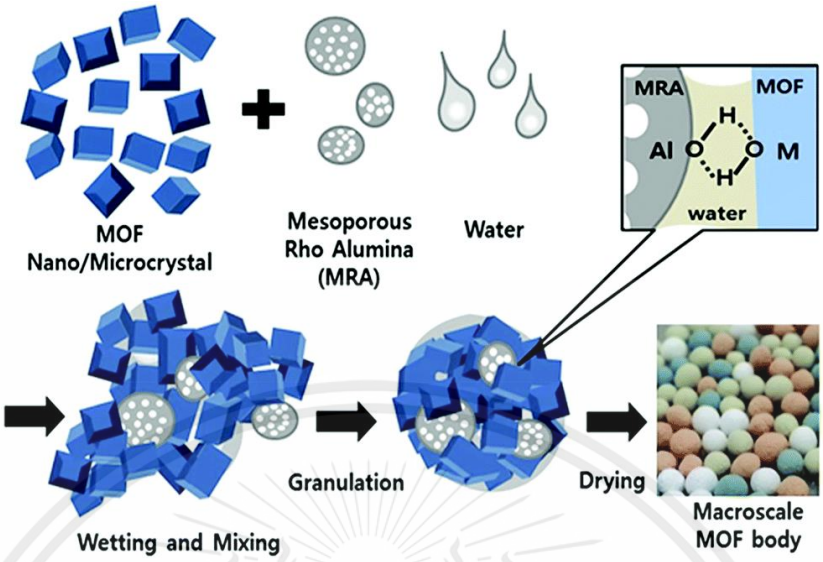


Figure9: *Granulation process. (https://pubs.rsc.org)*

The granulation process transforms fine powders into free-flowing, dust-free granules that are easy to process and can be used either wet or dry. While wet granulation is by far the most popular, not all APIs are compatible. [7][8]

Among the two techniques, wet granulation is the most widely used, although it involves many additional steps such as wet mixing, drying, and sieving, which are complex, time-consuming, and expensive, requiring a lot of space and multiple pieces of equipment.

Tablet compression

Tablet compression is the final step in the tablet manufacturing process. Compression is largely influenced by powder properties and machine parameters (die size, mechanism, speed, etc.) [9]

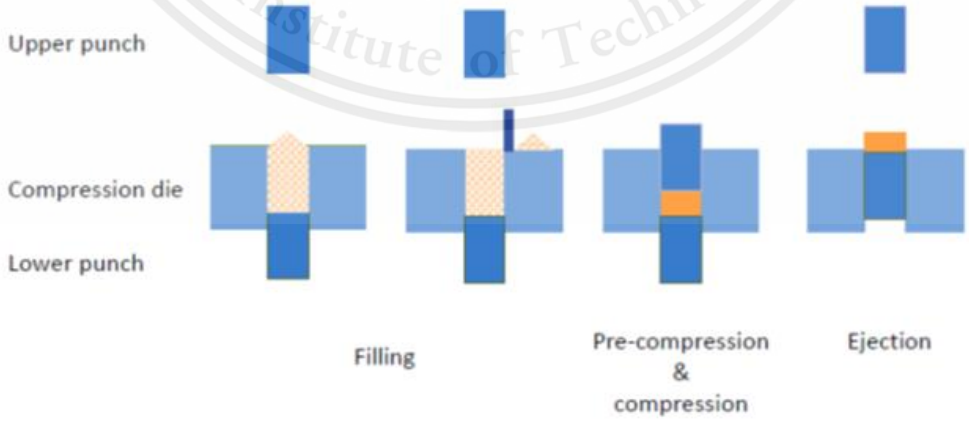


Figure10: *Tablet compression process (https://pharma-trends.com)*

The volume of the open cavity determines the weight of the tablet. This can be adjusted as needed during production. The distance between the upper and lower punches determines the thickness and hardness of the tablet: If the punches are close together, a thin and hard tablet is produced. If the punches are further apart, the tablet will be softer and thicker. This depends on the force applied by the automatic or manual press. These parameters can be carefully controlled to obtain the desired tablet specifications.

In the ejection phase of tablet compression, the tablet is removed from the lower punch die station. In this phase, the upper punch retracts from the cavity of the die. The lower punch then rises above the punch surface to eject the newly formed tablet, which is automatically pushed away from the compression area.

In this experiment, you will make 10 tablets of each type according to the instructions on the following pages. The ingredients used will be tested for flowability and the tablets produced will be evaluated against a number of general parameters.

These properties include:
(a) tablet weight
(b) tablet dimensions
(c) tablet friability
(d) tablet hardness
(e) tablet disintegration time
(d) tablet dissolution time

Experiment details
When developing a new or generic tablet, it may be desirable to find out which excipients have been used for related active ingredients. This can minimize the time required to profile the properties of different tablet formulations.
In this experiment, we will make ascorbic acid (vitamin C) tablets. The tablets will consist of 50 mg of active ingredient and another250 mg of excipients. The goal of the project is to produce tablets with a total weight of 300 mg, a diameter of 10 mm and a width of 5 mm. The tablet thickness should be ~5 kg, the friability < 1% and the dissolution time < 5 minutes.
The tablets are prepared by the method of direct compression with 3 different diluents. The first diluent is PROSOLV® MCC with a particle size of 90 mM, MCC-102 with a particle size of 100 mM, and tapioca starch, which has a particle size of 10 mm. Both are composed of glucose subunits, but the type of binding between these units significantly affects the properties of the tablets produced. The reasons for the differences in the properties of starch and cellulose are explained on the following.

Microcrystalline Cellulose & Starch
Starch and Microcrystalline Cellulose Starch is produced from alpha glucose, whereas cellulose is produced from beta glucose (typically derived from wood pulp).

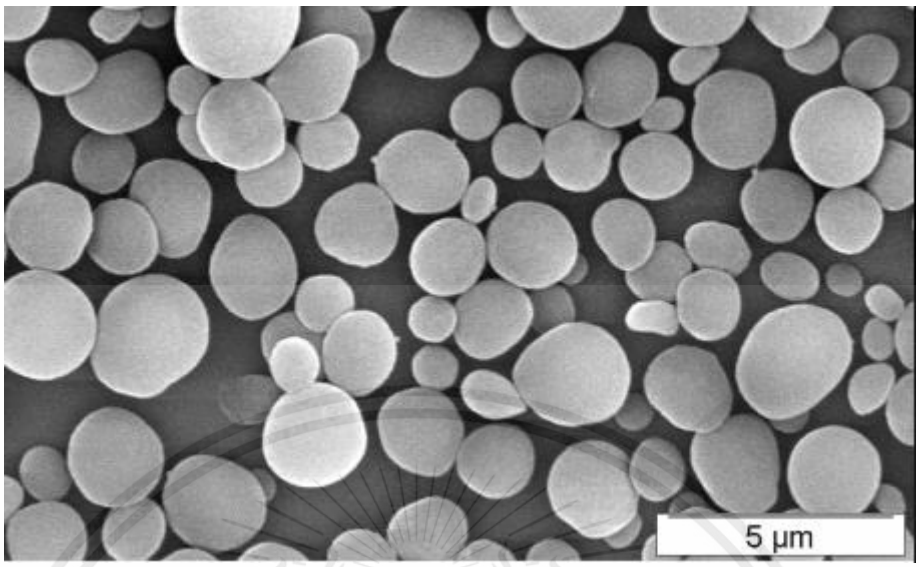


Figure11: *image of starch particles(https://www.researchgate.net)*

Amylose, which is composed of -D-glucose units linked together by -(1-4) glycosidic bonds, makes up starch. It makes up around 20–30% of starch, one of the two components. Amylose is more difficult to digest because of its closely packed helical shape. Plants contain amylopectin, a highly branched polymer of -glucose units that is water soluble. [10]

A linear chain of several hundred to many thousands of (14) connected D-glucose units make up the polysaccharide known as cellulose. In contrast to that for the (14)-glycosidic bonds found in starch, this linkage motif. A polymer with a straight chain is cellulose. As opposed to starch, the molecule adopts an extended and somewhat stiff rod-like shape, helped by the equatorial conformation of the glucose residues. No coiling or branching takes place. In order to lock the chains tightly together side by side, the numerous hydroxyl groups on the glucose from one chain establish hydrogen bonds with oxygen atoms on the same or on a neighboring chain. [11]

When compared to starch, the particle sizes found in MCC are often bigger and more crystalline. Due to their improved flowability and compaction characteristics, they are therefore suitable for use in direct compression tests. [12]

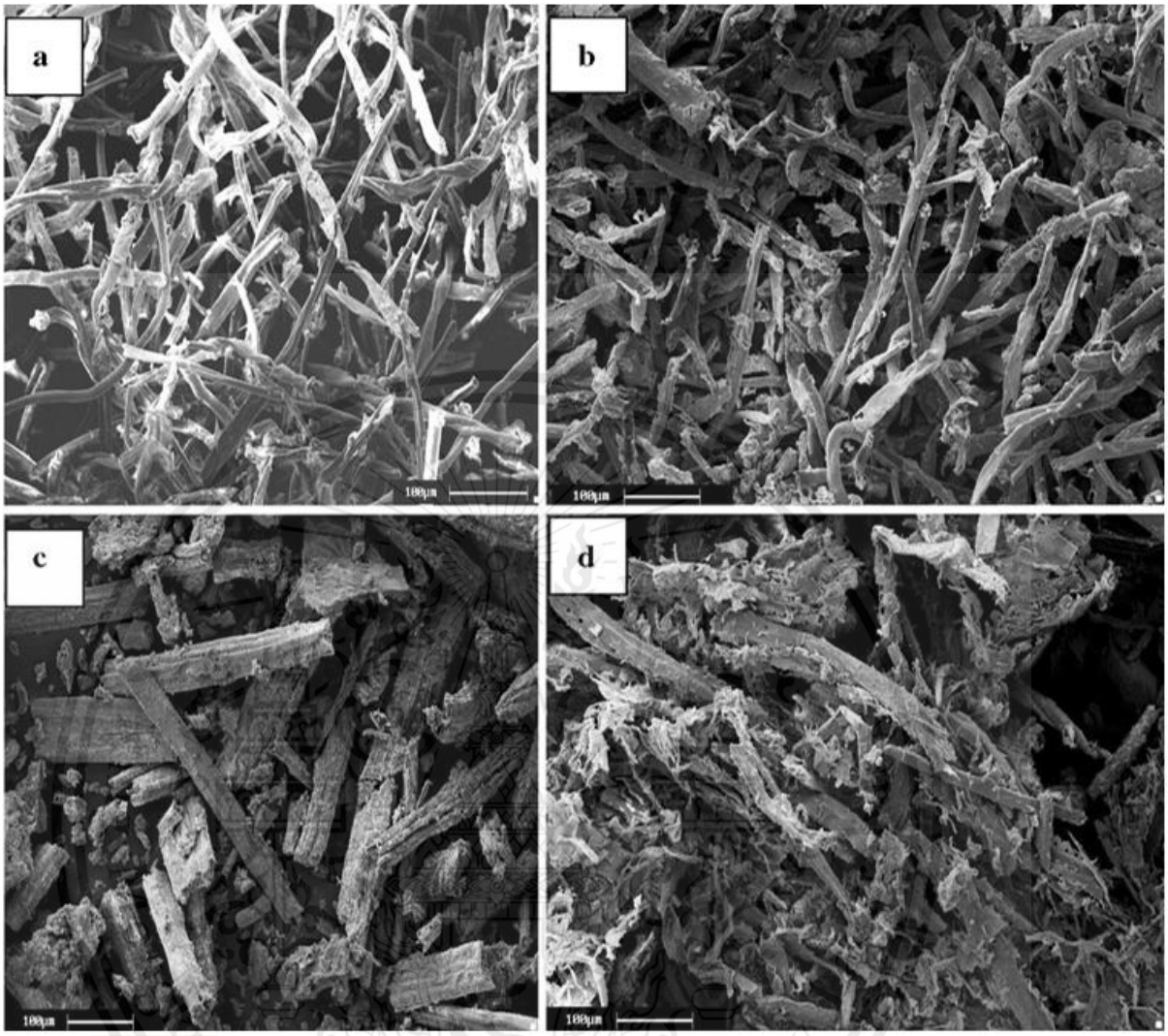


***Figure12**: micro crystalline cellulose particles (https://www.researchgate.net)*

Microcrystalline cellulose (MCC) and colloidal silicon dioxide are combined in a special way to create PROSOLV® SMCC (CSD). It has a high level of inherent functionality and is a multifunctional excipient, all of which require less complex processing and transfer that functionality to the drug formulation. Compared to other kinds of MCC or starch binders, this excipient produces higher-quality, more reliable tablets. This is partially attributable to the MCC component's higher surface area and more spherical form, which enable more efficient packing during compaction.

Tablet testing

Among the characteristics that tablets must possess are those that allow rapid and efficient processing by pharmaceutical machines and that ensure effective, controlled release of the required dose in the body.

Pharmaceutical engineering is the branch of engineering that deals with drug discovery, formulation, and manufacturing, as well as analytical and quality control procedures. In this project, we will analyze the properties of a particular type of tablet manufactured

in a Food and Drug Administration (FDA)-approved good manufacturing practice (GMP) environment.

In order to guarantee product quality and uniformity, tablets manufactured in the industry are prepared in accordance with strict guidelines. This is accomplished by thorough quality control (QC) procedures that need constant observation of the identity and quality of the ingredients, the machine processing, and the characteristics of the final tablets. The following characteristics are strictly controlled:

a. Tablet weight
b. Tablet dimension
c. Tablet friability
d. Tablet hardness
e. Tablet disintegration time
f. Tablet dissolution time

Test for quality control
To guarantee that the amount of active medicine being administered is at least 5% of the anticipated dose, it is critical that tablets be made with a consistent weight. As a result, tablets are constantly checked for weight.

The production process, which involves processing tablets on massive industrial machinery, conveyer belts, and packaging systems, places a premium on a tablet's dimensions. Therefore, it's crucial to provide constant dimensions. Using a Vernier caliper, dimensions can be measured

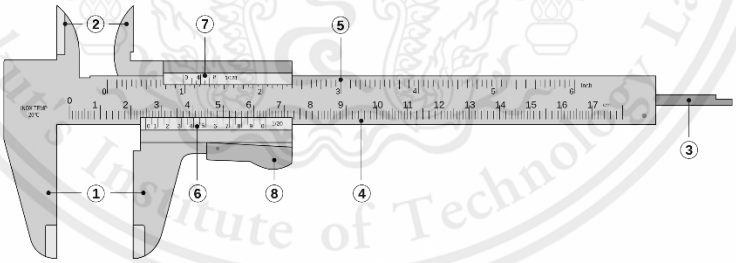


Figure13: *Vernier caliper (https://th.m.wikipedia.org)*

Tablets must pass through numerous processing stages during the pharmaceutical production process, each of which has the potential to abrade the tablet. In order to prevent considerable sample loss, it is imperative to guarantee that tablets have suitably resistant surface qualities. In a friability testing equipment, a tablet's capacity to prevent sample loss due to abrasion can be evaluated. Prior to inserting the samples into the cylindrical device, 5 to 10 samples are weighed. The tablet is then turned for 5 minutes at a rate of 4 revolutions per minute (RPM). Then, the tablets are weighed once more, and the total sample loss due to abrasion is represented as a %.

Figure14: *Tablet friability tester (https://westtune.en.made-in-china.com)*

Although similar in principle to friability, tablet hardness is a more crucial factor in predicting dissolution and disintegration. Hard substances are less likely to be harmed during transport and more likely to maintain their integrity when taken orally. This is crucial for acid-sensitive medications since they must get beyond the stomach's acidic environment before dissolving in the intestine, where the bulk of medicines are absorbed.

In order to achieve the regulated release of the active component during the optimization of tablet dose formulations, this parameter may be crucial.

A variety of instruments can be used to gauge the hardness of tablets. Each device works on the fundamental tenet that a force must be applied until the tablet breaks. Each of the distinct planes can be used to evaluate asymmetric tablets. Tablets often need to demonstrate mechanical strengths greater than 5 kg.

Figure15: *Tablet hardness testers(https://www.erweka.com/tablet-hardness-testers.html)*

Before a tablet to be absorbed, it must first have the ability to break up into tiny pieces. By raising and lowering tubes containing a 1 mm (18 mesh) sieve into water at roughly 37° C, tablet disintegration is observed (buffered at a specified pH according to the required pharmaceutical monograph according to the local FDA). It is observed how long it takes for every tablet to break up and fall through the bottom of the tube, which is generally expected to take no longer than 30 minutes.

Figure16: *Tablet disintegration test (https://www.tradeindia.com)*

Disintegration of the tablet does not necessarily mean that the entire active component has been dissolved in solution. The amount of time it takes for a tablet to completely dissolve in a particular solution is a similar test. In this instance, a table is positioned in a beaker that has a spinning component that stirs the fluid. The amount of time needed for the sample to completely dissolve, as calculated by UV absorbance. By comparing the sample's UV absorbance to that of a known standard with a known concentration, it is possible to calculate the UV absorbance threshold at which the entire compound is completely absorbed. The length of time needed for the sample to fully dissolve is documented; once again, this period should normally not exceed 30 minutes.

Statistical analysis

The sample average (x) and standard deviation (SD) for this experiment must be determined (equation 2). Averages do not provide information about a sample's variation.

$$\bar{x} = \frac{\sum_{i=1}^{n} x_i}{n}$$ equation 1

$$SD = \sqrt{\frac{\sum (x - \bar{x})^2}{n - 1}}$$ equation 2

The data in samples can be tightly clustered around the mean, making them very uniform, or they can be widely dispersed. The term "standard deviation" refers to a statistic that measures this range of values. The broader the range of results, the larger the standard deviation. 68% of the data for data with a normal distribution are within one standard deviation of the mean, 95% are within two standard deviations, and 99% are within three standard deviations.

Mechanic of Gaviscon antacid
Gaviscon works quite differently from a simple antacid. It contains an ingredient, sodium alginate, which forms a gel that floats to the top of the stomach contents. This acts as a barrier to stop acid refluxing into the esophagus while leaving the acidity of the stomach relatively unchanged.

The main ingredients of Gaviscon are:
- sodium alginate
- sodium bicarbonate
- calcium carbonate.

With the sodium alginate as main ingredient, making alginate raft that floats on top of stomach content [13]

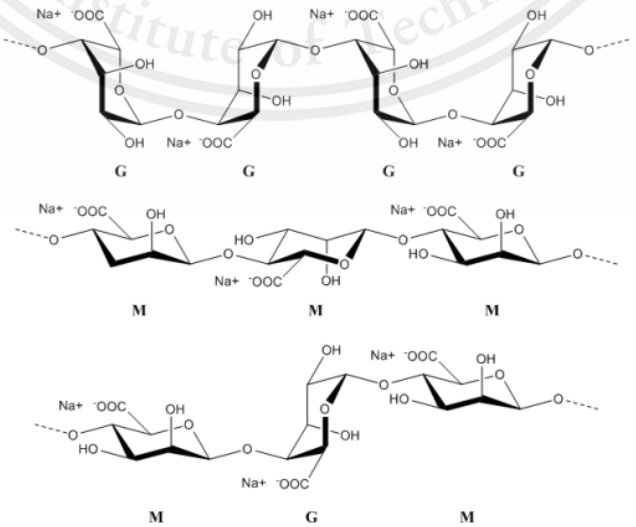


Figure17: *raft structure (https://www.researchgate.net)*

Sodium Alginate is a linear polymer made from two sugar-like monomers (which we shall call ‘G’ and ‘M’) each of which has a −COO− group. For each −COO− group there is a Na+ ion to balance the charges. G stands for (1 → 4) α-L-guluronate and M for (1 → 4) β-D-mannuronate. These are both sugars, so sodium alginate is a polysaccharide. You will not know (or be expected to know) any of the chemistry of sodium alginate, but you can make some predictions based on what you know about more familiar compounds. [14]

CHAPTER 3
METHODOLOGY

Introduction

This chapter describes the material and approach in which are used in this research study. This chapter will be divided into three parts; Ingredients and formula developing, Tablet making process, and Quality testing.

Material and methods

The methodology consisted of two main parts which are the processing of tablet and the quality checking. The processing part is consisting of three main steps, which are Ingredient and formula developing, Tablet manufacturing, and Tablet quality testing. These steps provided a comparison in compatibility and effectiveness of each ingredients, by trial and error, the more effective and potent ingredient would be chosen for the tablet manufacturing. As there are limited in ingredients supply and many possible results, so these methods are to eliminate as much failure factors as possible in limited span of time.

3.1 Ingredients and Formula developing

Each ingredient has different duty in making tablets, and even under the same ingredient has different sub-properties when purchased from different manufacturer. Proper testing is required to compares those properties and choose the one that give most desirable result.

Based off of 2003 Gaviscon (WO 03/ 068246 A2); The formula that contains ingredients that are viable in Thailand and have most potential to success were chosen. (Example 8)

Ingredient	Example	
	Comparative 2	8
	mg/tablet	mg/tablet
Sodium alginate LPR5/60	250.00	250.00
Sodium bicarbonate	133.50	133.50
Calcium carbonate	80.00	80.00
Mannitol	607.75	432.75
Polyethylene Glycol 20000	0.00	175.00
Flavour 1	5.50	5.50
Flavour 2	1.10	1.10
Sweetener 1	5.50	5.50
Sweetener 2	1.65	1.65
Magnesium stearate	15.00	15.00
Tablet weight	1100mg	1100mg

Example	Toothpacking	Mouthfeel	Taste	After taste	Overall
Example 8	Very slight	Drier, crisper. Tablet broke up quickly.	Pleasant, mint	None	OK - acceptable
Compara-tive 2	Worst of all batches	Drying, cloying pasty, chewy & sticky	Pleasant, mint	None	Poor - unacceptable

Figure 18: *Example 8 of 2003 Gaviscon (WO 03/ 068246 A2)*

The ingredient used in the mentioned formula are purchased from multiple manufacturer and compared via property testing before choosing suitable sample to use. Then further modified the non-active ingredients proportions accordingly to result of tablet produced in previous experiment. For example, increasing amount of PEG2000 and decreasing amount of Mannitol to help the tablet dissolve faster, since the tablet in previous experiment took longer than thirty minutes. [12][13]

3.2 Tablet making Process

There are 5 individual steps in tablet making process. Each step has its own importance which will be listed below.

- mixing

The mixing process is conducted to make sure that the dosage of final product is effective enough for the patience and distribute evenly among all tablet in every batch. In this project, mixing was done by rotating ingredient in mixing container. Resulting in slow mixing process and throughout mixed ingredient.

- granulation

Granulation can be divided into two parts, powder wetting and nucleation. Granulation is an important step of making sure the ingredients could stick together by coating granule with binder before compression. In this project, granulation was done by mixing ingredient with small amount of water in a mortar.

- drying

Granule need to be dried before compress to ensure the strength of the tablet. When water particle stuck in the tablet, after the water evaporate out it will leave a gap between particles which reduce tablet strength and friability. To know how long the granule, need to be dried, weight the granule every 5-10 minutes until the weight is constant.

- sieving

The particle should be passed through sieve before and after drying process, to control the preferable particle size. If the granules are too big, the tablet will be crumbly; if the granules are too small, the tablet will be too compact. In this project we've experience about the range of these particle using sieve of sized: 1mm, 0.6mm, and 0.45mm.

- compression

In this project, the tablet was compressed by hand-compressed machine because of the lack in resource. Resulting in inconsistent final product from human error.

3.3 Tablet quality testing

To see if the tablet is marketable or not, 2 sets of quality testing must be performed, physical property testing, and therapeutic properties.

- Physical property testing can be divided into 5 small tests

1 Size/weight: Is necessary in controlling dosage of tablet, especially in mass production. Measuring with Vernier caliper and 3-4decimals scale.

2 dissolving time: Dissolving tablet in water with the help of magnetic stir bar, the tablet should be all dissolved within 30 minutes

3 Hardness: Measure by tablet hardness tester. The tablet should not be too hard since it is a chewable tablet. The reference Gaviscon tablets has the strength of 14.

4 Friability: Measure by let tablets rotate inside friability tester for 5-10 minutes to simulate shipping circumstance. The tablet shouldn't lose more than 0.1% of original weight after 5 minutes of rotation.

-Therapeutic properties testing for this tablet can be divided into two parts

1 raft testing: Since the main property of the tablet is to forms a raft on top of stomach content, the raft needs to be uniform and has enough strength. Test would be performed by put 800g tablet into a flask of 50ml of 0.1M HCl, observe and measure the thickness of the raft.

2 basicity: By reverse titration against 0.01M HCl, one tablet of Gaviscon can hold 74.1ml before reaching neutral state.

CHAPTER 4
EXPERIMENTAL RESULT

4.1 Introduction

This chapter presents the results from our conducted experiment throughout the semester and progress in between.

4.2 Progression map

Steps:

- testing initial patent and gather data: preparing reference and other necessary data
- Physical properties of tablet: Hardness, solubility, friability
- Medical properties: ensure neutralizing properties of bases inside the tablet
- Raft formation: the raft forming fast and strong enough to prevent acid reflux

Workflow flowchart

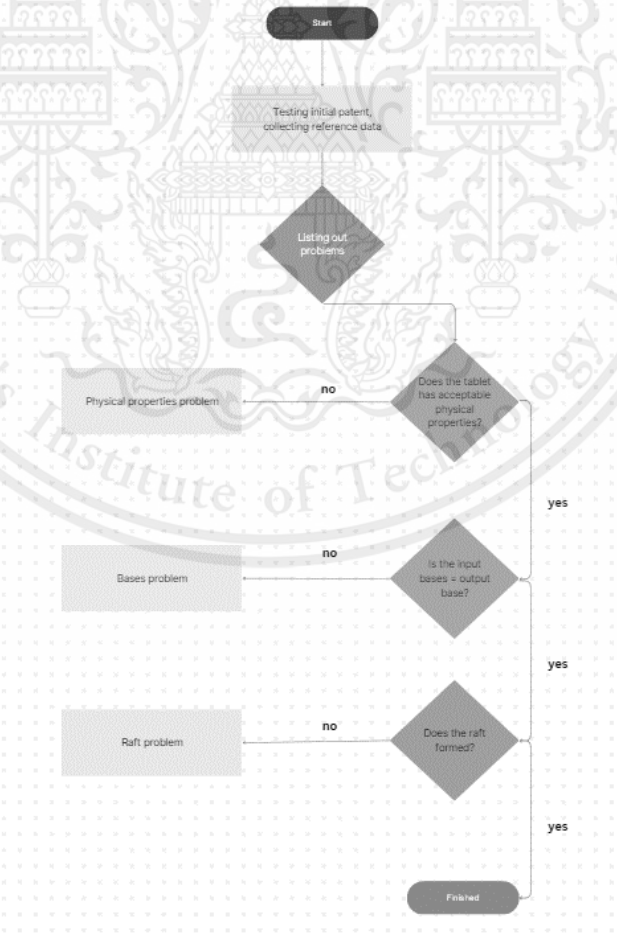


Figure19: *Flowchart of project workflow*

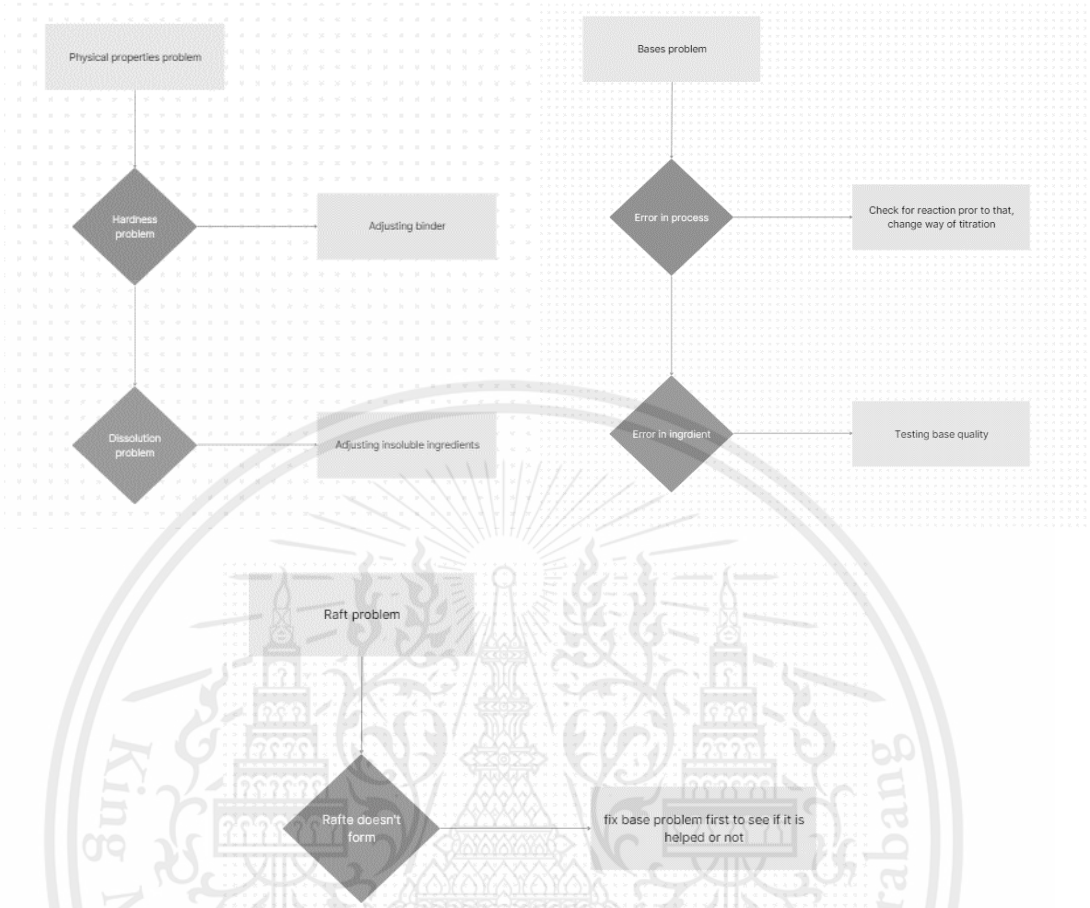


***Figure20**: Flowchart of workflow of each category of evaluation*

4.3 Experiment

4.3.1 Preparation

Due to the requirement of accurate mole of acid use to have accurate result in each experiment, the titration experiment is required in making reference acid (HCl), and reference base (NaOH) by using KHP as standardize. [14]

NaOH table (Titration with KHP)

Diluted from 1 to	Volume of NaOH used (ml)	mole contained	Molarirty
0.07	17.7	0.001	0.807
0.07	17.8	0.001	0.802
0.07	17.7	0.001	0.807

HCl table

Dilute from 1 to	Mole contained	Volume of HCl(L)	Molarity
0.1	0.0034	0.05	0.068
0.1	0.0034	0.05	0.068
0.1	0.0034	0.05	0.068

***Figure 21**: The titration result from preparing HCl and NaOH*

The result of titration; 0.68M HCl, and 0.8M NaOH.

To get a result similar to our reference tablet, Gaviscon, titration needed to be done to determine an accurate amount of base per one portion.

Gaviscon	mole of bases
Flask 1	0.001504
Flask 2	0.001478
Flask 3	0.001491
Average	0.001491

***Figure22:** The mole of bases in 3 Gaviscon tablets, from titration.*

Average mole per 1 tablet in Gaviscon is 0.001491mole of bases, which is lower than calculated mole of bases in one tablet (0.0033mole)

4.4.2 Experiment log

Choosing starting formula

To get general idea of desired formula, patent itself must be studied. The initial formula was chosen from 2003 Gaviscon patent [WO03/068246 A2]; Example 8, page 13.

Ingredient	Example	
	Comparative 2	8
	mg/tablet	mg/tablet
Sodium alginate LFR5/60	250.00	250.00
Sodium bicarbonate	133.50	133.50
Calcium carbonate	80.00	80.00
Mannitol	607.75	432.75
Polyethylene Glycol 20000	0.00	175.00
Flavour 1	5.50	5.50
Flavour 2	1.10	1.10
Sweetener 1	5.50	5.50
Sweetener 2	1.65	1.65
Magnesium stearate	15.00	15.00
Tablet weight	1100mg	1100mg

Example	Toothpacking	Mouthfeel	Taste	After taste	Overall
Example 8	Very slight	Drier, crisper. Tablet broke up quickly.	Pleasant, mint	None	OK - acceptable
Compara-tive 2	Worst of all batches	Drying, cloying pasty, chewy & sticky	Pleasant, mint	None	Poor - unacceptable

Figure 23: *Example 8 of 2003 Gaviscon (WO 03/ 068246 A2)*

The test was conducted to see the property of our formula and the way to perform granulation.

We have made 4 batches of granulated samples with 4 different formulas, following this table. The change of Copovidone and Mannitol is to see if the amount of these two

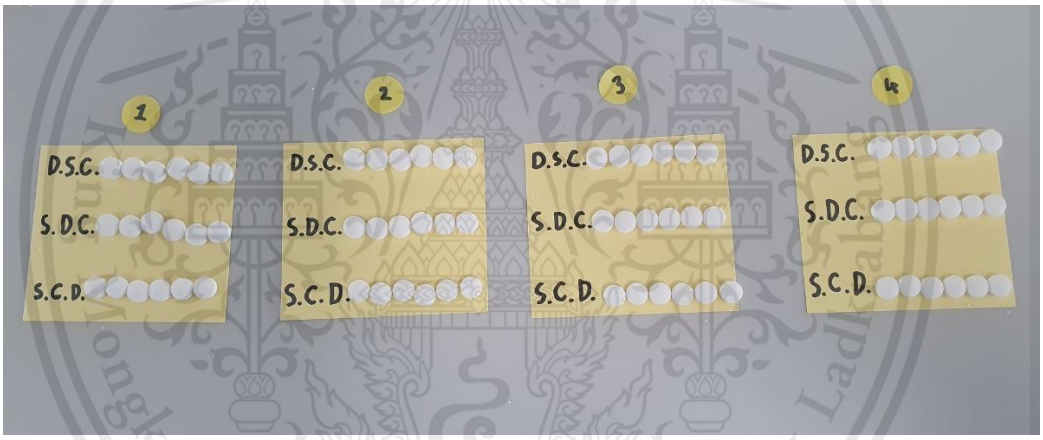
ingredients have effect on dispersing rate, due to Mannitol being left as residue and Copovidone working as super disintegrant.

Sample no.	Sodium alginate	Sodium bicarbonate	Calcium carbonate	PEG 20000	Copovidone	Mannitol
1	2.5g	1.335g	0.8g	0.3g	0.2g	6.145g
2	2.5g	1.335g	0.8g	0.3g	0.3g	6.045g
3	2.5g	1.335g	0.8g	0.3g	0.4g	5.945g
4	2.5g	1.335g	0.8g	0.3g	0.5g	5.845g

***Figure24**: weight of each ingredients of each batch number*

Then divide each sample into 3 processing orders which often used in tablet making from wet granulation

1. D.S.C. (Dry --> Sieve --> Compress)
2. S.D.C. (Sieve --> Dry --> Compress)
3. S.C.D. (sieve --> Compress --> Dry)



	Sample 1	Sample 2	Sample 3	Sample 4	results
D.S.C.	rigid	Very rigid	rigid	rigid	D.S.C. is the most promising method out of 3 methods.
S.D.C.	Very brittle	Very brittle	Very brittle	Very brittle	
S.C.D.	brittle	brittle	brittle	rigid	
results	The formulation of samples one and two are closer to ideal.				

***Figure25:** The table showing qualitative data of tablet that has been measured out in figure20 after being produced differently.*

Examine difference in properties for each granule size

This experiment was conducted to further analyze previous experiment, to control the range of particle used in experiments afterward. The size of the sieve was referenced from the patent itself. [17]

In this experiment, we found that the decreasing particle size of tablet gives more toughness of the tablets. But due to the limitation of not being able to control the smallest size of particles in that range, 0.45mm-0.6mm particles has been utilized

Samples	>1mm	1mm-0.6mm	0.6mm-0.45mm	<0.45mm
Hardness 1	Brittle	More brittle	Brittle	Rigid
Hardness 2	Brittle	-	Brittle	Rigid
Flakiness 1	The flakiest	Flaky	Flaky	The least flaky
Flakiness 2	The flakiest	-	Flaky	The least flaky

Figure26: *The table showing quantitative data of hardness of tablets made from granule in 4 particle ranges*

	Gaviscon	<0.45mm	0.45-0.6mm	0.6-1mm
mole of bases per tablet	0.00743	0.005	0.0057	0.0058

Figure27: *The table showing moles of bases in tablets made from granule in 3particle ranges*

A batch of ingredient has been processed using data result from experiment 1 & 2, this batch will be throughoutly check for quality of the tablet itself and medical properties in order to see where should be improved.

The results was not up to standard, it lacks in hardness and solubility in terms of physical properties, as for the medical propeties, the raft and the bases seems to be lack as well.

Decreasing disintegration time

From previous experiment, my hypothesis is that the reason why the properties are poor is because the tablet doesn't disperse fast enough, for the reason of when comparing to gaviscon tablet, the difference in time used to dissolve the whole tablet between the two was stark.

In an attempt to fix the dissolution problem, the proportions between superdisintegrant(Copovidone) per Mannitol has been increased, and also changing the brand of Sodium alginate to see the differences.

The amount of Copovidone is increased by 10% each, to narrow down the amount necessary for ideal properties. Change in brand of Alginate helps improving rate of disintegration.

Brand: Sigma Aldrich	5%Binder 40% PEG 20K		5%Binder 30%PEG 20K		4%Binder 50%PEG 20K	
	Hardness	Disintegration time	Hardness	Disintegration time	Hardness	Disintegration time
Mean value	14.5	28.13 minutes	15.2	27.07 minutes	19	33.22 minutes
Brand: Panreac	5%Binder 40% PEG 20K		5%Binder 30%PEG 20K		4%Binder 50%PEG 20K	
	Hardness	Disintegration time	Hardness	Disintegration time	Hardness	Disintegration time
Mean value	12	>55 minutes	13.5	52.12 minutes	14.2	50.32 minutes

Figure28: *The table showing hardness value and Disintegration time of 6 tablet formula from 2 different brand of Sodium alginate.*

From this experiment, the conclusion is that, Alginate from Sigma Aldrich are relatively easier to dissolve in water than alginate from Panreac, and the amount of PEG 20K in tablets should not exceed 4% Binder and 50% PEG20K due to tablet becoming unchewable. (Hardness: For reference, gaviscon tablet have hardness of 14)

Effectiveness of bases

After strenghten the tablet hardness and fixing disintegration problem, the next problem to look on is base loses. In experiment 2, the result was shown that raft does not form at all, and the base output is also less than base input.

Two active bases in our formula are Calcium carbonate and Sodium bicarbonate. Both of them release carbondioxide that then function to lift up the Alginate raft, as shown in equations below. [14]

$$CaCO_3 + 2HCl \rightarrow CaCl_2 + CO_2 + H_2O$$

$$HCl + NaHCO_3 \rightarrow NaCl + CO_2 + H_2O$$

Our hypothesis is that the raft couldn't form because there is not enough bases reactions to create CO_2 to lift the raft, which could be form the granulation process or from other non-active ingredient interfering the reaction.

Said hypothesis have been put to test by titrating only active ingredient in the amount of one tablet, which resulting in the same problem; output bases is less than input bases. So we tried testing the neutralizing quality of our base ingredients.

Flask number	Mole of HCl	Mole base (approx)	Volume NaOH	Mole of NaOH	Mole bases
1	0.004	0.0033	13.3	0.0017	0.0023
2	0.004	0.0032	14.1	0.0018	0.0022
3	0.004	0.0032	15.3	0.002	0.002

Figure29: *The table showing the titration results of 3 controlled factor for future reference*

The result is that the amount of base mole is still lack, there're two hypothesis to this problem; either the base has reacted in container, or there is a problem in titration methods.

We change the testing method from direct titration to indirect titration based on suspition that weak bases should be titrate indirectly for more accurate result.

This experiment, the amout per tablet of each bases were measured out, seperately.

Flask	$CaCO_3$ weight (g)	$NaHCO_3$ weight (g)
1	0.138	0.085
2	0.135	0.082
3	0.134	0.08

Figure30: *The table showing weight of $CaCO_3$ and $NaHCO_3$*

Flask number	Mole base, from calculation	Mole base, from titration
1	0.0033	0.0023
2	0.0032	0.0022
3	0.0032	0.002

Figure31: *The table comparing mole of bases from calculation and from titration*

The bases output is around 69.7% of the intended input. With this information, we proceed with adding the ingredient for raft, Sodium alginate.

Flask	CaCO3 weight (g)	NaHCO3 weight (g)	Sodium Alginate weight (g)
1	0.133	0.081	0.252
2	0.134	0.08	0.251
3	0.135	0.082	0.253

Figure32: *The table showing weight of ingredients in each flasks*

Flask	Mole base, from calculation	Mole base, from titration
1	0.0032	0.0028
2	0.0032	0.0027
3	0.0032	0.0028

Figure33: *The table* comparing mole from calculation and titration

The bases output is 87.5% of the intended input when including Sodium Alginate. With 87.5% of bases and decent raft formation during this experiment.

Effectiveness of mixing process

Since previous experiments has provide enough information to conclude that active ingredients are effective, this experiment will be about the other possibility that makes raft unable to form in final product; the tablet processing process.

The first process of making tablets is mixing ingredient, the problem could be formed from not mixing throughly. To test this hypothesis, the sieved granule has been devided by granule size then performing titration on each group to see if the amount of base are equal or not.

Batches	Average mole
Active ingredient (calculated)	0.0032
>1mm	0.0026
1mm-0.6mm	0.0026
0.6mm-0.45mm	0.0023
<0.45mm	0.0025

Figure34*: The table shows moles per tablet of each particle range*

The titration result shown that the base distributed equally among the group of difference particle size, which means the mixing process is not the problem.

Effectiveness of granulating and drying process

In previous experiments, it has proven that mixing process is effective enough as the base is evenly distribute among the all group of particle size. The next possibilty of error is wet granulation nd drying process, which could leads to acid-base reaction prior to the main reaction.

To do that is to compare the titration result and raft formation of raw ingredient to granule after wet granulation and drying.
The amount of mole per tablet for each groups are rather close to each other with the particle of size smaller than 0.45mm containing least bases.

Batches	Average mole of bases
Active ingredient (calculated)	0.0032
Unprocessed ingrediant	0.0027
Wet granule	0.0028

>1mm	0.0026
1mm-0.6mm	0.0025
0.6mm-0.45mm	0.0023
<0.45mm	0.0016
Grinded granule	0.0023

***Figure35**: The table shows moles per tablet for each particle range*

The result of raft formation was noted in two catagories; qualitative properties and raft forming speed. The granule smaller than 0.45 is the closest to reference.

Time used to form raft	Flask 1	Flask 2	Flask 3
Active ingredient	Forming upon contact	Forming upon contact	Forming upon contact
Wet granule	Forming upon contact	Forming upon contact	Forming upon contact
>1mm	Doesn't form	Doesn't form	Doesn't form
1mm-0.6mm	Doesn't form	Doesn't form	Doesn't form
0.6mm-0.45mm	Doesn't form	Doesn't form	Doesn't form
<0.45mm	Forming upon contact	Forming upon contact	Forming upon contact
Grinded granule	Forming upon stir	Forming upon stir	Forming upon stir

***Figure36**: The table shows speed of raft formation of each particle batch*

Quality of the raft	Flask 1	Flask 2	Flask 3
Active ingredient	Gel like, a bitelastic	Gel like, a bit elastic	Gel like, a bit elastic
Wet granule	Gel like, lesselastic than referene	Gel like, less elastic than reference	Gel like, less elastic than reference
>1mm	The raft didn't form	The raft didn't form	The raft didn't form
1mm-0.6mm	The raft didn't form	The raft didn't form	The raft didn't form
0.6mm-0.45mm	The raft didn't form	The raft didn't form	The raft didn't form
<0.45mm	Gel like, a bit elastic, very similar to reference	Gel like, a bit elastic, very similar to reference	Gel like, a bit elastic, very similar to reference
Grinded granule	Thin gel layer, not elastic	Thin gel layer, not elastic	Thin gel layer, not elastic

***Figure37**: The table shows quantitative quality of raft by each particle range*

***Figure38**: The photo showing raft from each particle batches (from left to right: active ingredients, >1mm, 1mm-0.6mm, 0.6mm-0.45mm, <0.45mm)*

Batches	Thickness of the raft(mm) (diameter 72.5mm)
Active ingredient	11
>1mm	2
1mm-0.6mm	2
0.6mm-0.45mm	4
<0.45mm	12

***Figure39**: The table shows thickness of raft from each particle range*

From this experiment, the particle smaller than 0.45mm has the best raaft formation but also the only range that seems to contain less base than other.

4.4 Limitation

- The tablet compressor is too small to make the desired weight
- The oven that used to dry the granule are not controllable in terms of specific heat and humidity
- The amount of ingredient per batch are not enough to be processed through mixing machine
- The compression process cannot be done properly due to human error in force applied

CHAPTER 5
CONCLUSION

5.1 Conclusion

Our objective was to recreate the medical properties of Gaviscon with ingredient that is accessible in Thailand to make the treatment more accessible to our currency rate.

Our theoretical framework to achieve that objective is to use the patent of Gaviscon as a reference material, then finding ways to improve the product. However there was several examples of patents published. Because there are varieties of example in patet published, we have picked out the most promising one according to our own personal judgment after reading the literature. The example we pick has offer the base and general idea of where we need to improve it, which can be divided into 3 catagories; Physical properties, Medical properties, and Raft formation.

5.1.1 Physical properties

For physical properties, two factor in which we decided to study and improve are hardness of the tablet and tablet disintegration time.

For hardness, the starting hardness was lower than our reference product. Using principle of each ingredient property, we tried to add more binder to add strength and cohesion between particles.

For disintegration time, the starting disintegration time was longer than our reference product. The disintegration time has been decreased by decreasing the amount of ingredient that are insoluble, add more disintegrant, and using a more soluble brand of alginate.

5.1.2 Medical properties

For medical properties, the anti ulcer tablet needed to have a properties of reducing acidity of stomach acid. We perform a study on that reaction and try to find a way to improve it.

In our starting formula, the amount of base that we put into the tablet has decresed when came into contact with acid. In an attempt to fix this problem, we have tried to process the tablet in multiple different way and changing titration methods.

5.1.3 Raft formation

As for raft formation, the starting formula we picked out from the patent seems to not have any raft at all. This problem was later improved by the increase in acid-base reactions, creating gas which help lifting the raft up to the top.

5.2 Discusssion

This study is proceeding to the setted objective but unable to complete some of it. Our study leads to tablet that has good physical properties, and gel-like raft with acid decreasing property. However, the result was not so consistant throughout the study, making the third objective of mass-production stays unachieved.

REFERENCES

1. Themes, U., & A. (2016, June 20). *Powder Properties*. Powder Properties | Basicmedical Key. https://basicmedicalkey.com/powder-properties/
2. *Practical: Determination of Angle of repose, Carre's Index & Hausner ratio of given powder*. (2017, July 9). Practical: Determination of Angle of Repose, Carre's Index & Hausner Ratio of Given Powder. https://knowledgeofpharma.blogspot.com/2017/07/practical-determination-of-angle-of.html
3. Mirhosseini, Hamed & tabatabaee amid, Bahareh. (2013). Effect of different drying techniques on flowability characteristics and chemical properties of natural carbohydrate-protein Gum from durian fruit seed. Chemistry Central journal. 7. 1. 10.1186/1752-153X-7-1.
4. Simek, Michal & Grünwaldová, Veronika & Kratochvíl, Bohumil. (2016). Comparison of Compression and Material Properties of Differently Shaped and Sized Paracetamols. Powder and particle. 2017. 10.14356/kona.2017003.
5. Themes, U., & A. (2016, June 20). *Powder Properties*. Powder Properties | Basicmedical Key. https://basicmedicalkey.com/powder-properties/
6. *High energy ball milling process for nanomaterial synthesis*. (n.d.). High Energy Ball Milling Process for Nanomaterial Synthesis. https://www.understandingnano.com/nanomaterial-synthesis-ball-milling.html
7. Valekar, A. H., Cho, K. H., Lee, U. H., Lee, J. S., Yoon, J. W., Hwang, Y. K., Lee, S. G., Cho, S. J., & Chang, J. S. (2017, December 8). *Shaping of porous metal–organic framework granules using mesoporous ρ-alumina as a binder*. Shaping of Porous Metal–organic Framework Granules Using Mesoporous P-alumina as a Binder - RSC Advances (RSC Publishing). https://doi.org/10.1039/C7RA11764G
8. Themes, U., & A. (2016, June 20). *Powder Properties*. Powder Properties | Basicmedical Key. https://basicmedicalkey.com/powder-properties/
9. *A Design of Experiments for Tablet Compression*. (2011, September 2). PharmTech. https://www.pharmtech.com/view/design-experiments-tablet-compression
10. *Genetic dissection of floridean starch synthesis in the cytosol of the model dinoflagellate Crypthecodinium cohnii - PubMed*. (2009, December 15). PubMed. https://doi.org/10.1073/pnas.0907424106
11. *K. Das, D. Ray, N. R. Bandyopadhyay and S. Sengupta, "Study of the Properties of Microcrystalline Cellulose Particles from Different Renewable Resources by XRD, FTIR, Nanoindentation, TGA and SEM," Journal of Polymers and the Environment, Vol. 18, No. 4, 2010, pp. 532-538. - References - Scientific Research Publishing*. (n.d.). K. Das, D. Ray, N. R. Bandyopadhyay and S. Sengupta, "Study of the Properties of Microcrystalline Cellulose Particles From Different Renewable Resources by XRD, FTIR, Nanoindentation, TGA and SEM," Journal of Polymers and the Environment, Vol. 18, No. 4, 2010, Pp. 532-538. - References - Scientific Research Publishing. https://www.scirp.org/(S(351jmbntvnsjt1aadkposzje))/reference/referencespapers.aspx?referenceid=1055410
12. *Tablet Compression Tooling >> Punches and Dies | Natoli Engineering*. (n.d.). Tablet Compression Tooling >> Punches and Dies | Natoli Engineering. https://natoli.com/products/tablet-compression-tooling/
13. Scandiffio, P., Mantilla, T., Amaral, F., França, F., Basting, R., & Turssi, C. (2018, August 1). *Anti-erosive effect of calcium carbonate suspensions*. PubMed Central (PMC). https://doi.org/10.4317/jced.54994

14. *Write the balanced chemical equation when Hydrochloric acid reacts with Sodium Bicarbonate?* (n.d.). Write the Balanced Chemical Equation When Hydrochloric Acid Reacts With Sodium Bicarbonate? https://byjus.com/question-answer/write-the-balanced-chemical-equation-when-hydrochloric-acid-reacts-with-sodium-bicarbonate/
15. P. (n.d.). *Concept Sodium Alginate*. Sodium Alginate - PubChem. https://pubchem.ncbi.nlm.nih.gov/compound/Sodium-Alginate
16. *Povidones, Copovidones, and Crospovidones for Pharmaceutical Products*. (n.d.). BASF Pharma. https://pharma.basf.com/chemistry/povidones-copovidones-crospovidones
17. Grathwohl, T. (2019, September 3). *Influence of the particle size of copovidone and crospovidone on tablet characteristics - Pharma Excipients*. Pharma Excipients. https://www.pharmaexcipients.com/petrochemicals/povidones/influence-crospovidone-tablet/
18. *Gaviscon Oral: Uses, Side Effects, Interactions, Pictures, Warnings & Dosing - WebMD*. (n.d.). Gaviscon Oral: Uses, Side Effects, Interactions, Pictures, Warnings & Dosing - WebMD. https://www.webmd.com/drugs/2/drug-18801-5123/gaviscon-oral/aluminum-magnesium-antacid-oral/details
19. Chauhan, P., & Chauhan, R. (2017, September 16). CONDUCIVE ENVIROMENT FOR FOSTERING INDIA SPECIFIC INNOVATION: NEW MEDICAL DEVICE RULES 2017. *International Journal of Drug Regulatory Affairs*, *5*(3), 20–26. https://doi.org/10.22270/ijdra.v5i3.203
20. UK governments settle legal case with Reckitt Benckiser over Gaviscon. (2014). *The Pharmaceutical Journal*. https://doi.org/10.1211/pj.2014.11138558
21. *US Patent Application for Chewable Formulation Comprising Alginate, Bicarbonate And Carbonate Patent Application (Application #20110287062 issued November 24, 2011) - Justia Patents Search*. (2009, July 15). US Patent Application for Chewable Formulation Comprising Alginate, Bicarbonate and Carbonate Patent Application (Application #20110287062 Issued November 24, 2011) - Justia Patents Search. https://patents.justia.com/patent/20110287062
22. *Mannitol: Uses, Interactions, Mechanism of Action | DrugBank Online*. (n.d.). Mannitol: Uses, Interactions, Mechanism of Action | DrugBank Online. https://go.drugbank.com/drugs/DB00742
23. *Compression Process in Pharmaceutical Industry*. (2021, December 16). Pharma Specialists. https://www.pharmaspecialists.com/2021/12/compression-process-in-pharmaceutical.html
24. *US9186409B2 - Solid pharmaceutical composition for neutralizing stomach acid - Google Patents*. (2010, April 23). US9186409B2 - Solid Pharmaceutical Composition for Neutralizing Stomach Acid - Google Patents. https://patents.google.com/patent/US9186409B2/en
25. *EP3184115A1 - Oral compositions for the treatment of gastroesophageal reflux disease - Google Patents*. (2015, December 22). EP3184115A1 - Oral Compositions for the Treatment of Gastroesophageal Reflux Disease - Google Patents. https://patents.google.com/patent/EP3184115A1/en