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Halal Science Centre
University of Cyberjaya

Synthesis and Characterization of Capsule Formulation Using Kappa Carrageenan As Alternative Halal Binder

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Assalamualaikum
Salam Malaysia Madani

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INTRODUCTION – HALAL PHARMACEUTICALS

- The halal market is **expanding rapidly**, encompassing not only food and beverages but also cosmetics, pharmaceuticals, and personal care products. This growth is driven by the increasing Muslim population worldwide, which is expected to reach nearly 30% of the global population by 2050.
- As a result, the halal industry is estimated to be worth trillions of dollars, attracting significant attention from multinational companies aiming to cater to this substantial market segment.
- Recently, more consumers both Muslim and non-Muslim **prefer to purchase halal pharmaceutical product** instead of non-halal.
- The intention to purchase halal pharmaceutical products is positively affected by attitude, religiosity, knowledge of halal products and perceived behavioural control (RA Kasri,. 2021).

INTRODUCTION - BINDERS

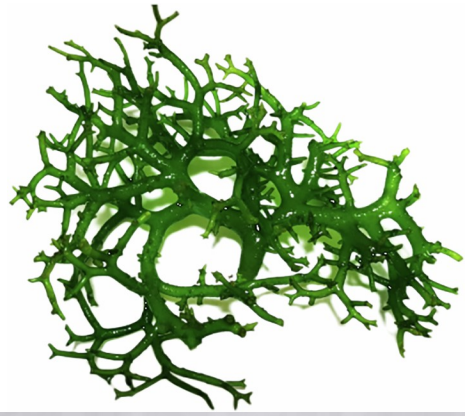
- Drug **binders**, also known as granulating agents or adhesives, are crucial components in pharmaceutical formulations.
- **Binders** traditionally serve the important function of **facilitating the processing of active pharmaceutical ingredients into appropriate dosage forms** that can effectively deliver the drug to its targeted site of action upon administration. Consequently, the inclusion of a binder in a formulation impacts the manufacturability, stability, bioavailability, and overall efficacy of the drug (Apeji., 2019).
- The **binder** holds the powdered drug and other excipients together, ensuring that the **tablet keeps its integrity** during manufacturing, packaging, and storage.
- The excipient or binder provide specific structure and form to the formulation, enhance stability, mask unpleasant tastes, improve palatability, add volume to formulations with potent active ingredients, enable convenient and precise dosing, facilitate handling of the active substance, and streamline the manufacturing process (Adepu., 2021).

INTRODUCTION – HALAL CAPSULE

- The word '**capsule'** is derived from the Latin word *capsula* which means a small box or container.
- A drug capsule is a solid dosage form consisting **of a shell that encapsulates a drug formulation** and is typically made of gelatin.
- Capsules consist of **gelatin** either **hard** or **soft** and **non-gelatin shells**, typically derived from the hydrolysis of collagen that achieved through acid, alkaline, enzymatic, or thermal hydrolysis sourced from animals, or they can be cellulose-based (A Prakash,. 2017).
- The **halal status of gelatin-based products in pharmaceuticals is a concern**, and alternative sources is essential (N Azira., 2023).

INTRODUCTION – KAPPA CARRAGEENAN

- **Kappa carrageenan** is a polysaccharide derived from red seaweeds commonly from *Kappaphycus alvarezii*. Due to its **remarkable gelling properties,** it is widely used in the pharmaceutical and food industry as a stabilizer, thickener, gelling agent, and emulsifier (He et al., 2017).
- Its gelling properties make it suitable **to act as binder** in capsule formulation as **alternative to gelatin.** Binders act as adhesives **to promote cohesion and bonding in formulation.**
- The **primary role of binders** is to ensure that the solid particle in the capsule are compacted and held together forming capsule, tablet or granule (E Hamed., 2005).
- Kappa carrageenan exhibits shear-thinning behavior, where its viscosity decreases with increasing shear rate. It possesses excellent suspending and stabilizing properties.



SIGNIFICANCE OF STUDY

- **Gelatin** is a crucial excipient utilized in the manufacture of hard and soft-shell capsules, providing an effective means of safeguarding contents against light, oxygen, contaminants, and microbial growth while masking taste and odor.
- However, due to concerns over **non-halal gelatin**, researchers are investigating alternative sources, **including Kappa carrageenan**.
- Therefore, this study's importance lies in enhancing the pharmaceutical industry by **introducing more options for halal** and **plant-based capsules** that can benefit both the Muslim and vegetarian populations.

OBJECTIVES

To develop an alternative plant-based capsule production by using Kappa carrageenan as binder through dipping method

1. To investigate **antimicrobial properties** of synthetic Kappa carrageenan

2. To **formulate** hard shell capsule using synthetic Kappa carrageenan by using various formulation

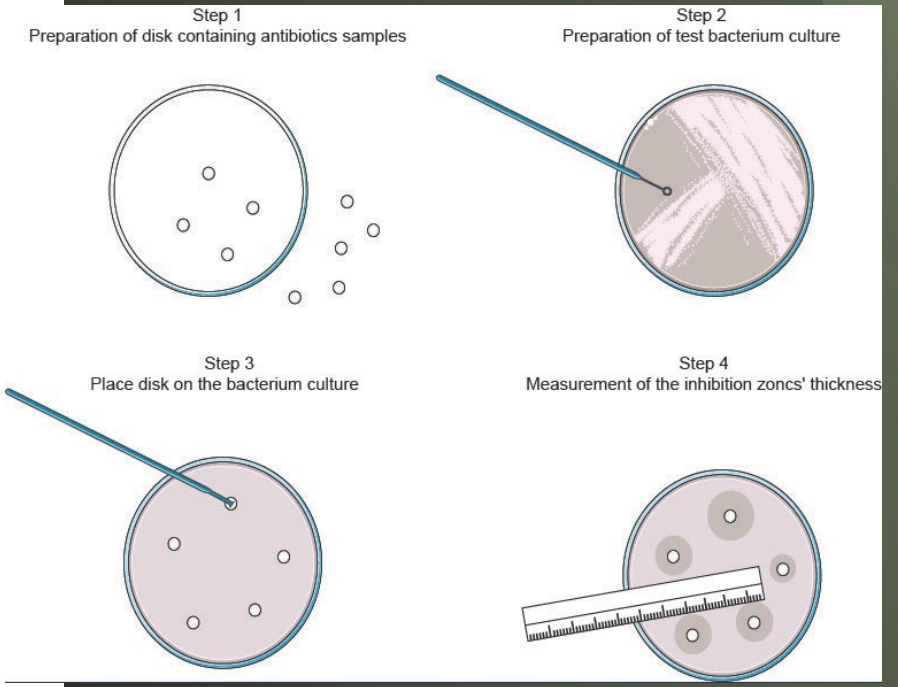
3. To **evaluate** the capsule formulated using various test

METHODOLOGY

1. Antimicrobial properties of synthetic *Kappa carrageenan (KC)*

- Microbes used in the test
  - *Staphylococcus aureus* (Gram + bacteria)
  - *Escherichia coli* (Gram - bacteria)
- Positive control
  - Gentamicin
- Negative control
  - Distilled water

- KC concentration
  - 1g, 1.5g, 3g diluted in 10ml of distilled water



METHODOLOGY

2. Formulation Process

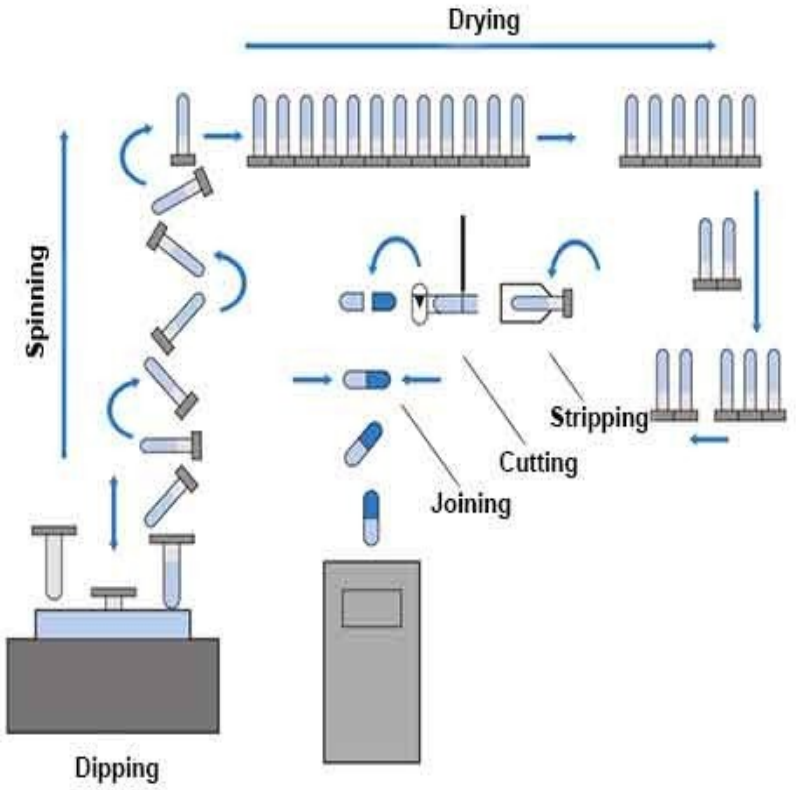
Sorbitol solution is added to a heated **kappa carrageenan** solution at 80 degrees Celsius until thoroughly combined.

Then, **starch** solution is added into the mixture and blended again until well-mixed.

Chopstick was **dipped** into the mixture and **rotated** using palm to ensure even distribution.

The mixture-coated chopstick is then placed in an incubator for **drying** at 40 degrees Celsius for 12 hours to ensure proper hardening.

After drying, the capsule is **removed** from the chopstick, and **trimmed** to a length of 1 cm



Dipping Method

Dipping	Stripping
Spinning	Cutting
Drying	Joining

METHODOLOGY

2. Formulation Process

Material	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10	F11	F12	F13	F14	F15
Kappa carrageenan (g)	3	5	7	10	25	30	5	3	10	25	30	5	6	7	10
Sorbitol (g)	5	5	5	10	10	10	25	25	30	30	30	40	40	40	40
Starch (g)	0	0	0	0	0	0	7.5	9	10	10	10	6	6	6	0
Distilled water (ml)	100	100	100	100	100	100	100	100	200	200	200	100	100	100	100

METHODOLOGY

3. Evaluation of capsule formulated

Weight Variation Test	• 3 capsule shells from each formulation **with weight variation was weighed**.
Swelling Degree Test	• Capsule was immersed in 100 mL of water at a temperature of 30°C for a period of 1 hour, without stirring. • After removal from the water, the **capsules were dried using filter paper to remove excess moisture** before their mass is measured.
Disintegration Test	• The capsules are positioned in the basket-rack assembly, which is then lowered into a **fluid-filled thermostatically controlled bath**. • The assembly was lowered and raised 30 times per minute, and the bath is maintained at a temperature of 37 ± 2 °C.

METHODOLOGY

3. Evaluation of capsule formulated

Dissolution Test

- Capsules were dispersed in three different pH levels
  - 1.2 (HCl) representing the acidic environment of the stomach, 4.5 (citrate buffer) representing the pH of the gastrointestinal tract, and 6.8 (phosphate buffer) representing the pH of the intestine.
- **The dissolution test** was conducted for each capsule over a duration of 3 hours, utilizing the paddle method at a speed of 100 rpm.

Swelling Degree Test

- Immerse the capsules in a known volume.
- Incubate for **1 hour** to simulate gastric residence.
- Reweigh again

Water content Analysis

- The sample was placed into the **evaporating dish** and subjected to an oven set at a temperature range of 102-105 °C for a duration of 5-6 hours.
- The evaporating dish is then placed in the desiccator, allowed to cool for 30 minutes, and weighed.

RESULTS & DISCUSSION

- **Antimicrobial Screening**

Bacteria	Zone of inhibition (mm)				Positive Control (Gentamicin disc)	Negative Control (Distilled water)
	Blank	1g	1.5g	3g		
Gram Positive S. Aereus	0	0	0	0	Presence of antimicrobial activity	Absence of activity
Gram Negative E. Coli	0	0	0	0	Presence of antimicrobial activity	Absence of activity

- No **antimicrobial activity** shown for all concentration.
- Might be due to **low concentration of kappa carrageenan**.

- Kappa carrageenan suppress the growth of both Gram-positive and Gram-negative bacteria.
- The oxidized κ-carrageenan possessed broad-spectrum antibacterial activity (M. Zhu et. al., 2017).

FORMULATION OF HARD GELL CAPSULE

- **Selection of optimum formulation**

Formulation	Ingredient Ratio (K:S:St:W)	Apperance
F13	6 : 40 : 6 : 48	
F14	7 : 40 : 6 : 47	
F15	10 : 40 : 0 : 50	

- Was determined via appearance and stability of the capsule.
- F13-15 was chosen for next test.

RESULTS & DISCUSSION

• Weight Variation Test

Formulation	Weight (g) (Mean ± SD)	p-value	No. of capsule deviated by 10%
F13	0.2268 ± 0.0413	< 0.001	None
F14	0.1980 ± 0.0294		None
F15	0.3045 ± 0.0429		None
Commercial	0.0379 ± 0.0011		None

- Weight of **F15 is higher** compared to other formulation.
- High concentration of KC is used in F15 and the capsule shell appear to be thicker than other formulation.
- The commercial capsule size is 2 with diameter of 0.6cm while the formulation size is probably 0 with diameter of 0.7cm referring to the diameter of the

• Disintegration Test

Formulation	Time (mins) (Mean ± SD)	p-value
F13	11.0333 ± 0.4168	< 0.001
F14	21.2333 ± 0.4168	
F15	27.3300 ± 0.9169	
Commercial	6.7733 ± 0.4801	

- Disintegration time should not exceed 30 minutes according to USP.
- KC capsule contain more water than commercial capsules, making it difficult to dissolve under normal conditions (Fauzi et. al., 2020).
- Thickness, size and weig**All formulation meet the requirement of disintegration time**ht of capsule may affect the disintegration

RESULTS & DISCUSSION

- **Dissolution Test (Citrate Buffer pH 4.5)**

Formulation	Time of sampling (mins)	Absorbance at 243nm	Percentage of drug release (%)
F13	10	0.007	98.5
	30	0.002	99.4
	45	0.001	99.8
F14	10	0.001	99.7
	30	0.001	99.7
	45	0.000	100
Commercial	10	0.006	98.6
	30	0.002	99.5
	45	0.000	100

- Only F13 and F14 are used in this test due to its better appearance, shape and texture compared to F15.
- The capsule cannot be joined and sealed together tightly because of its size and hardness.

RESULTS & DISCUSSION

- **Dissolution Test (Phosphate Buffer : pH 6.8)**

Formulation	Time of sampling (mins)	Absorbance at 243nm	Percentage of drug release (%)
F13	10	0.007	98.5
	30	0.002	99.4
	45	0.001	100
F14	10	0.001	99.7
	30	0.001	99.7
	45	0.000	100
Commercial	10	0.006	98.6
	30	0.002	99.5
	45	0.000	100

- The capsule cannot be joined and sealed together tightly because of its size and hardness.
- **At 45th min**, paracetamol is completely released for both formulation.
- Paracetamol is more rapidly dissolved at pH 4.5 than at pH 6.8.
- It is therefore easier to dissolve in a weakly acidic medium than in strongly acidic or neutral media. (Fauzi et. el., 2020)

RESULTS & DISCUSSION

• Swelling Degree Test

Formulation	Swelling Degree (%) (Mean ± SD)	p-value
F13	274.993 ± 22.635	< 0.001
F14	336.997 ± 30.422	
F15	458.630 ± 38.057	
Commercial	436.793 ± 31.974	

- There is no standard for SD in the production of hard capsules (Fauzi et al., 2021).
- Possible reason for the high degree of swelling of KC capsules is the gel forming ability of KC.
- High swelling degree will help the material to withstand disintegration and dissolution longer than gelatin (Fauzi et al., 2020).
- **F15 has highest reading.** Most amount of KC is used in F15 compared to other formula.

RESULTS & DISCUSSION

• Water Content Analysis

Formulation	Water Content (Mean ± SD)	p-value
F13	12.883 ± 0.830	< 0.001
F14	20.850 ± 0.691	
F15	23.433 ± 0.681	
Commercial	7.3767 ± 0.031	

- According to USP , water content for hard capsules usually consists of **10-15%**.
- Capsule containing more than **20%** of water content may **cause the growth of mold or fungi.**
- Low water levels cause capsule shells to be brittle and break easily. Requirement for the moisture content of hard-shell capsules is 13– 16% (Stegemann S., 2002).
- **F13** fulfilled the requirement while other formulation exceed 20% of water content.

CONCLUSION

Kappa carrageenan extracted from fresh seaweed source may have different antimicrobial activities than the synthetically made kappa carrageenan used in this research.

The **best formulation from this study is F13** due to its best characteristic in term of appearance, shape, weight variation, disintegration time, dissolution, water content and swelling degree.

Kappa Carrageenan shows to be a potentially useful excipient in controlled or extended-release capsule since the capsule took more than 15 mins to disintegrate.

Kappa carrageenan can be use as **alternative binder in hard-shell capsule production.**

PUBLICATIONS

Review | IRIS

Antioxidant Properties of Kappa Carrageenan and Its Formulation and Evaluation as Halal Binder in Paracetamol Tablets

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Formulation and Evaluation of Paracetamol Tablet Using Konjac Glucomannan as Natural Halal Binder

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Synthesis and Characterization of Capsule Shell Formulation Using Konjac Glucomannan as an Alternative Halal Binder

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