



**FORMULATION AND EVALUATION OF SUSPENSION FOR TREATMENT OF
INTESTINAL PARASITIC WORMS AND MALNUTRITION USING CARICA PAPAYA
EXTRACTS**

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ABSTRACT

Soil Transmitted Helminthes (STH) is one of the world's most underappreciated tropical illnesses. Morbidity from STHs is highest in school-aged children, who have the highest infection. In 2001, the World Health Organisation (WHO) approved a resolution for large-scale mass drug administration (MDA), i.e. albendazole suspension, to deworm vulnerable children through school-based programmes. Because of the presence of Benzyl isothiocyanate, the seeds and fruits of *Carica papaya* have anthelmintic qualities. Due to the harsh taste of *Carica papaya* seed, it is necessary to convert it into an appropriate dosage form, such as seed suspension, which enhances patient compliance with dosage form. For formulation of suspension *Carica papaya* seed powder is used as an active agent and Carboxymethylcellulose sodium is used as suspending agent to varying its concentration (0.5%, 1%, and 1.5%) this may effect on its viscosity and stability of suspension. By performing *In-Vitro* Anthelmintic study it is found that *Carica papaya* seeds have ability to treatment of helminthic infection and by increasing the concentration of Carboxymethylcellulose sodium the viscosity and stability of suspension is increases. All the evaluation parameters of suspension are found to be satisfactory and *In-Vitro* Anthelmintic study shows the helminthic property of suspension. The stability studies are performed for the one month no significant changes are observed during stability. Hence our suspension has advantage over the helminths.

KEYWORDS: *Carica papaya*, Helminthes, Benzyl isothiocyanate, Suspension, Stability.

INTRODUCTION

One of the forgotten tropical diseases in the globe is soil-transmitted helminths (STH). Children in school age have the highest morbidity from STHs since they often have the largest infection burden. A resolution for the (MDA) of albendazole suspension to deworm vulnerable children through school-based programmes was adopted by WHO in 2001. The high frequency of dose and the enormous number of youngsters in the population could make the program's sustainability difficult. Additionally, the MDA places an increasing amount of medication pressure on the parent population, which is likely to create a genotype of parasite that can withstand chemotherapy.

Furthermore, the present MDA policy does not view child malnutrition as a pervasive issue in underdeveloped, poor countries. Therefore, a therapeutic alternative that is both economical and sustainable with little likelihood of developing resistance, such as suspending papaya seeds and fruits, must be developed.^[1]

Scientific research has shown that the seeds and fruits of the *Carica papaya* (Paw Paw) contain anthelmintic and antiamoebic activities. Fruits and seeds were found to contain benzyl isothiocyanate, which is a bio-active anthelmintic component, according to phytochemical research.^[2]

Papaya seeds from *Carica* are bitter and disgusting. Fruits have a distinctive aroma. Children and individuals of other ages do not readily accept them as a result. Therefore, in order to increase the acceptability of the preparation, it is necessary to produce a required dosage form, such as a suspension of seeds and fruits.

MATERIALS AND METHODOLOGY

Materials

Carica papaya seed powder, Ethanol, Glycerin, Methyl paraben, orange oil, Propyl paraben, Carboxymethylcellulose sodium, Beaker, test tubes, funnel, stirrer, pipettes, measuring cylinder, petri dishes, transparent vials, muslin cloth, dropper, spatula, stop watch, mortar and pestle are used during the

experimental work, Electronic Balance, Lab Stirrer, Motic Microscope, Stability Chamber, Brookfield Viscometer, Hot Air Oven, Tray Dryer, pH Meter, Refrigerator.

METHODOLOGY

Preformulation studies of drug and excipients

Organoleptic Properties of Drug and Excipients

The crude sample of *Carica papaya* seed powder and Excipients was studied for the organoleptic properties such as colour, odour, and pH.^[3]

Solubility studies

The solubility studies for *Carica papaya* seed powder was determined by using the shake flask method using various solvents like (Ethanol, Ether, Water, Acetone, and Chloroform).^[4]

Stability studies

• Physical Stability

The Physical stability of the *Carica papaya* seed powder was determined by checking the parameters like (Appearance, Uniformity, and Suspendability).

• Chemical Stability

The chemical stability of the *Carica papaya* seed powder was determined by checking the parameters like (Effect of the temperature and Humidity).^[4]

Microscopy

Motic digital microscopy was used to measure particle size of *Carica papaya* seed powder. The particle size was determined using a triturated powder of *Carica papaya* seed. The particle size was determined in micrometres, and the particles were found to be amorphous.^[5]

Moisture Content

Carica papaya seed has 80% moisture when ripe. To prepare dry powder of *Carica papaya* seed, moisture must be removed using a tray dryer or a hot air oven.

Formulation and development of suspension

Table 1: Formulation Development of suspension.

Sr. No	Ingredients	Formulation Code		
		F1	F2	F3
		Quantity	Quantity	Quantity
1	<i>Carica Papaya</i> seed powder (gm.)	0.189	0.189	0.189
2	Ethanol (ml)	1	1	1
3	Glycerin (ml)	2	2	2
4	Methyl paraben (gm.)	0.04	0.04	0.04
5	Propyl paraben (gm.)	0.008	0.008	0.008
6	Carboxymethylcellulose Sodium (gm.)	0.1 (0.5%)	0.2 (1%)	0.3 (1.5%)
7	Saccharin sodium	0.12	0.12	0.12
8	Orange flavour (ml)	qs	qs	qs
9	Orange colour(food)	qs	qs	qs
10	<i>Carica Papaya</i> fruit pulp	½ tea spoon	½ tea spoon	½ tea spoon
11	Distilled water (ml)	Up to 20ml	Up to 20ml	Up to 20ml

• Tray Dryer

To remove moisture from the solids deposited in the tray, a tray drier employs forced convection heating, in which hot air is continuously circulated through wet material. Tray dryers can dry items at temperatures ranging from 40⁰ to 60⁰ degrees Celsius and at speeds ranging from 0.5 to 1.5 meters per second.^[6]

• Hot Air Oven

To remove extra moisture, dry air passes through the materials in a hot air oven. Drying removes moisture from items, sterilizes samples, and is environmentally friendly.^[7]

Drug –Excipients compatibility studies

Physical examination of drug and excipient materials was used in the drug excipient interaction investigation. The drug and each excipient (1:1) mixture is deposited on vials with hermetically sealed rubber closures and placed in the environmental test chamber (Stability chamber, 40⁰C at 75% Relative Humidity) for 15 days. During storage, samples were examined for any changes, such as caking, liquefaction, gas generation, colour changes, aroma changes, and so on.^[8]

FTIR Studies of *Carica papaya*

FTIR is a full form for "Fourier Transform Infrared Spectroscopy." This is an of spectroscopy works on the idea that infrared light passes through the sample and this sample absorbs the infrared radiation. It is a valuable analytical tool for confirming drug-excipient interactions in formulations.

DSC Studies of *Carica papaya*

Thermoanalytical methods determine the amount of heat required to elevate a sample's temperature. For the DSC investigation, a 2–5 mg sample was needed, and a Differential Scanning Calorimetry apparatus was used to calculate the DSC of pure medication. On an aluminium pan, the test sample is heated to a nitrogen flow pressure of 2 bar at a rate of 100°C/min.

Preparation method of suspension

In a china dish, heat the needed amount of glycerine to a temperature of 70⁰ degrees Celsius, and then add the required amount of Methyl paraben and Propyl paraben. Allow the mixture to cool to room temperature before filtering through a 200-mesh nylon cloth. Then, in another beaker, place half of the distilled water, Transferred the leftover Glycerin, which was filtered through a 200-mesh nylon cloth, to half of the water in the methyl and propyl paraben water beaker. Mix the Carboxymethyl Cellulose sodium into the Glycerin well. This solution should be filtered using a 100-mesh stainless steel screen. Transfer this solution to a separate beaker, mix thoroughly, and set aside overnight. Mix Ethanol into the solution well. In Step V, add *Carica papaya* seed powder in little amounts while constantly stirring. Check the pH after thoroughly mixing. Allow this solution to de-aerate for 1 hour. This solution was transferred to a 100-mesh stainless steel screen and well mixed. In 5ml of water, dissolve the needed amount of Saccharin Sodium. Using a 200-mesh nylon cloth, filter the solution. Add flavour; combine the solutions from Steps VI, VII, and VIII. Make up the volume with distilled water to 20ml. Fill amber-colored bottles half with the suspension.

Evaluation of suspension

Physical Test

Suspension formulation was tested physically at the surrounding temperature (25°C). The suspension sample was examined for physical tests utilising factors such as Nature, Colour, Odour, and Texture.^[3, 16, 17]

pH

The pH of the suspension was determined using a pocket-sized pH metre. The pH of the suspension phases also adds to the stability and characteristics of formulations.^[3, 16, 17]

Sedimentation volume

The sedimentation volume is defined as the ratio of the sediment's final height (Hu) to the suspension's beginning height (Ho). By measuring the volume of suspension in a graduated cylinder, the volume of sedimentation was estimated³.

Sedimentation volume= Hu/HO

Flow rate

The time taken for a suspension sample to flow through a pipette is defined as the flow rate of the suspension³.

Flow rate = Volume of suspension in pipette (ml)/Flow time.

Determination of viscosity

The viscosity of a suspension displays its stability behaviour; as the viscosity grows, so does the stability of the suspension, because viscosity prevents particles from settling at the bottom of the container.^[17, 18]

Viscosity of the suspension can be measured by two ways.

- **Using Brookfield Viscometer**

At room temperature, the viscosity of the suspension was evaluated using a Brookfield digital viscometer and the needed amount of sample. This machine tests viscosity at 50 RPM with spindle number S63.^[9]

- **Using Ostwald viscometer^[10]**

At room temperature (25°C), the viscosity of the suspension was evaluated using an Ostwald viscometer. Viscosity of liquid by Ostwald Viscometer (η_2) = $\rho_2 t_2 / \rho_1 t_1 \times \eta_1$

Where,

ρ_1 = Density of water gm/ml

ρ_2 =Density of sample gm/ml

η_1 = Viscosity of water centipoise

η_2 = Viscosity of Test sample centipoise

t_1 = Time flow A to B

t_2 =Mean time test A to B

Density

The density of a suspension is determined using the density bottle method. Density bottles are mostly used to determine the density of pharmaceutical solutions. Although these density bottles are not volumetric instruments, they have been calibrated.^[15]

Particle Size of suspension

The zeta seizer is mostly used for measuring particle size in suspensions; it is a nano range instrument that detects particle size in liquid mediums. In liquid media, the Zeta seizer measures three parameters: particle size, zeta potential, and molecular weight. The zeta seizer can perform titrations, which are used to determine the melting point of proteins. NIBS technology is used by Zetasizer to determine particle size.

Stability Testing

- **Crystal growth**

The development of crystals during long-term storage reduces the stability of the solution. Crystal formulation experiments were conducted at 4°C, Room temperature (RT), and 47°C.^[11, 19]

- **Stability testing as per ICH guidelines**

The aim of stability testing is to determine a rechecking period for the drug substance or a shelf life for the drug product, as well as suggested storage conditions, by demonstrating how the quality of a drug substance or drug changes over time due to environmental factors such as temperature, humidity, and light. The average kinetic temperature in every region may be calculated using climate data, and the world can be divided into four climatic zones, I through IV. This advice is applicable to climatic zones I and II. It was resolved that stability information generated in each of the three EC regions—Japan and the US—would be mutually acceptable to the other two regions, provided the information is confirmed by this guideline and the labelling complies with national/regional norms. The

International Conference on Harmonization (ICH) developed a guideline for "Stability testing of novel drug substances and products Q1A (R2)" that was used for stability studies [ICH, 1993].^[12, 20]

Accelerated Stability Testing

For one month, the suspension is held in accelerated conditions of 40°C 20°C and 75%RH 5%RH.^[13, 21]

In- vitro Anthelmintic Assay

This study was carried out to determine the anthelmintic effect of *Carica papaya* seeds, which can be utilised to determine the anthelmintic effect of suspension prepared from *Carica papaya* seeds. During the test, an adult earthworm (Pheritimidæ) is used to evaluate the anthelmintic effect.^[14, 22, 23]

RESULT AND DISCUSSION

➤ Pre- formulation studies

Characterization of drug

Organoleptic Properties of drug

The organoleptic features of *Carica papaya* seed powder, such as colour, odour, and pH, were investigated in a crude sample.

Table 2: Organoleptic Properties of drug.

Sr. No	Parameter	Observation
1	Colour	Brown
2	Odour	Pungent
3	pH	7.4-7.6

➤ Solubility studies

The solubility of *Carica papaya* seed powder in various solvents was investigated.

Table 3: Solubility Studies of drug.

Sr. No	Parameter	Observation
1	Ethanol	Soluble
2	Ether	Sparingly Soluble
3	Water	Very Slightly Soluble
5	Acetone	Sparingly Soluble
6	Chloroform	Sparingly Soluble

➤ Stability Studies

A. Physical Stability

Table 4: Physical Stability of drug.

Sr. No	Parameter	Observation
1	Appearance	Amorphous
2	Uniformity	Non-Uniform

Suspendability

Table 5: Suspendability of drug.

Sr. No	Suspendability	Observation
1	Ethanol	Partially Suspended
2	Ether	No Suspended
3	Water	Suspend
4	Acetone	No Suspend
5	Chloroform	Suspend

B. Chemical Stability

Effect of temperature

Table 6: Effect of temperature on drug.

Sr. No	Weight	Temperature	Observation
1	0.1gm	4°C	No change
2	0.1gm	RT	No change
3	0.1gm	47°C	No change

Effect of Humidity

Table 7: Effect of Humidity on drug.

Sr. No	Weight	%RH	Observation
1	0.1gm	0	No change
2	0.1gm	35%	No change
3	0.1gm	53%	No change
4	0.1gm	75%	No change

➤ Microscopy

Table 8: Particle size of drug.

Sr. No	Drug	Particle size
1	<i>Carica Papaya</i> seed powder	0.05-1mm

Characterization of excipients

➤ Organoleptic properties of excipients

Table 9: Organoleptic Properties of Excipients.

Sr. No	Name of Excipient	State	Colour	Odour	pH
1	Ethanol	Liquid	Colourless	Pungent	6.2-6.4
2	Glycerin	Liquid	Colourless	Odourless	4.5-5.0
3	Methyl paraben	Solid	White	Faint odour	3-8
4	Propyl paraben	Solid	White	Aromatic	6.4-7.5
5	Carboxymethylcellulose Sodium	Solid	White	Odourless	7.0-7.5
6	Saccharin sodium	Solid	White	Sweet	6.2-7.2
7	Orange Flavor	Liquid	Yellowish	Pleasant	3.5-4.5

➤ Drug- Excipient compatibility Studies

Table.10: Drug- Excipient compatibility Studies.

Sr. No	Composition	Caking	Liquefaction	Discoloration	Odour/gas formation	Conclusion
1	<i>Carica papaya</i> seed powder + Methyl paraben	No	No	No	No	Compatible
2	<i>Carica papaya</i> seed powder + Propyl paraben	No	No	No	No	Compatible
3	<i>Carica papaya</i> seed powder + Carboxymethylcellulose Sodium	No	No	No	No	Compatible
4	<i>Carica papaya</i> seed powder + Saccharin Sodium	No	No	No	No	Compatible

➤ FTIR spectra of *Carica Papaya*

The peak and several wave values (cm⁻¹) in the FTIR spectra of *Carica Papaya* seed powder indicate the presence of functional groups in the sample.

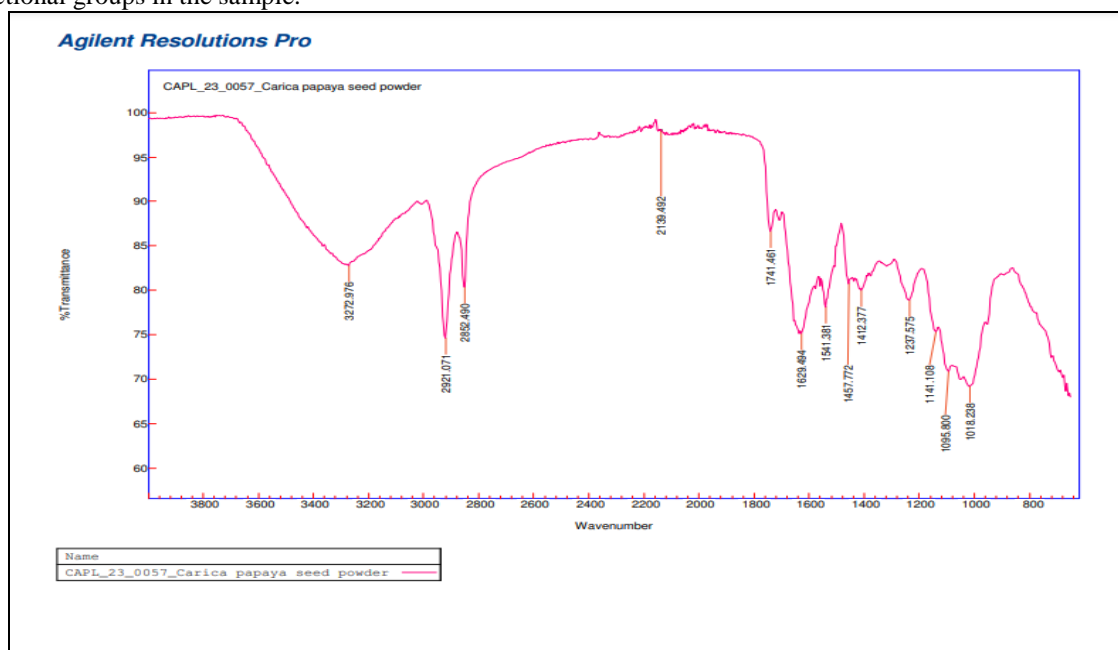


Figure.1: FTIR Spectra of *Carica papaya*.

FTIR Spectra of drug and Excipients

Figure 8.1 depicts the FTIR spectrum of *Carica papaya* seed powder, while Figure 8.2 depicts the FTIR spectrum of a drug-excipient physical mixture. FTIR studies were performed to ensure interactions between *Carica Papaya* seed powder and excipients included in the formulation. The drug's stability was demonstrated by the presence of

the same peaks in the formulation. Peak variations are minor in all physical combinations of *Carica Papaya* and other excipients. Identical peaks with minor changes in formulation were discovered, proving the drug's stability. There was no change in the drug's peak, demonstrating that the drug and excipients did not interact, indicating that they are helpful in suspension formulation.

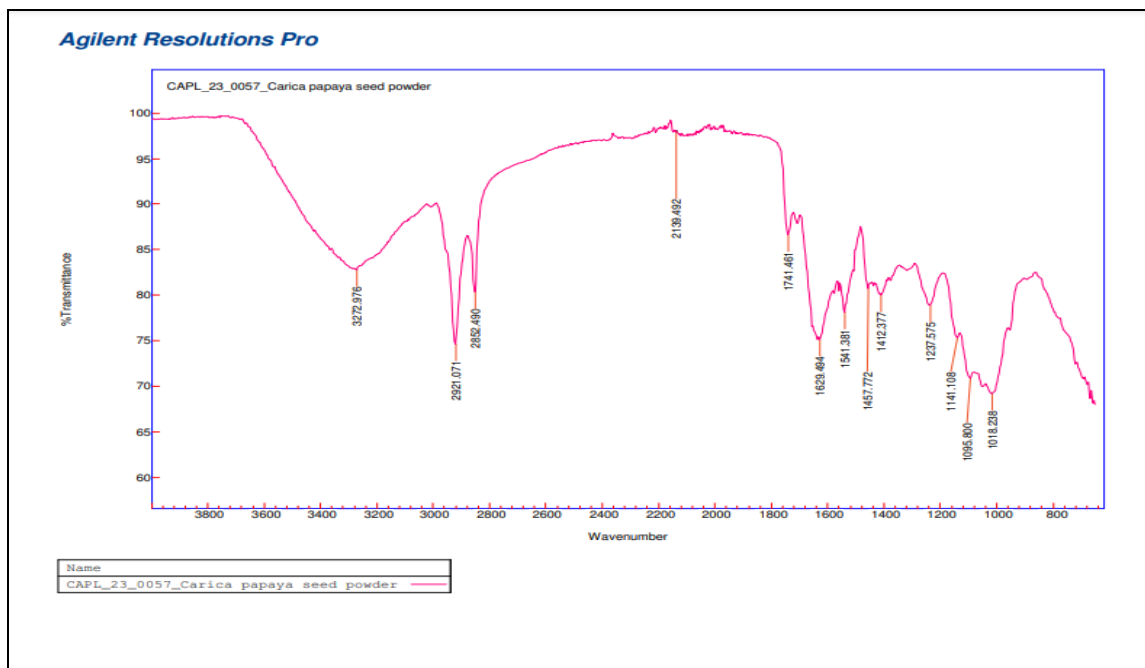


Figure.2: FTIR spectra of *Carica Papaya* seed powder + Excipients.

➤ **Differential Scanning Calorimetry of *Carica Papaya* seed powder**

DSC is used to do thermal analysis on *Carica papaya* seed powder. *Carica Papaya* seed powder DSC curve

displays a significant exothermic peak at 82.45°C. Figure 8.3 shows the DSC thermogram.

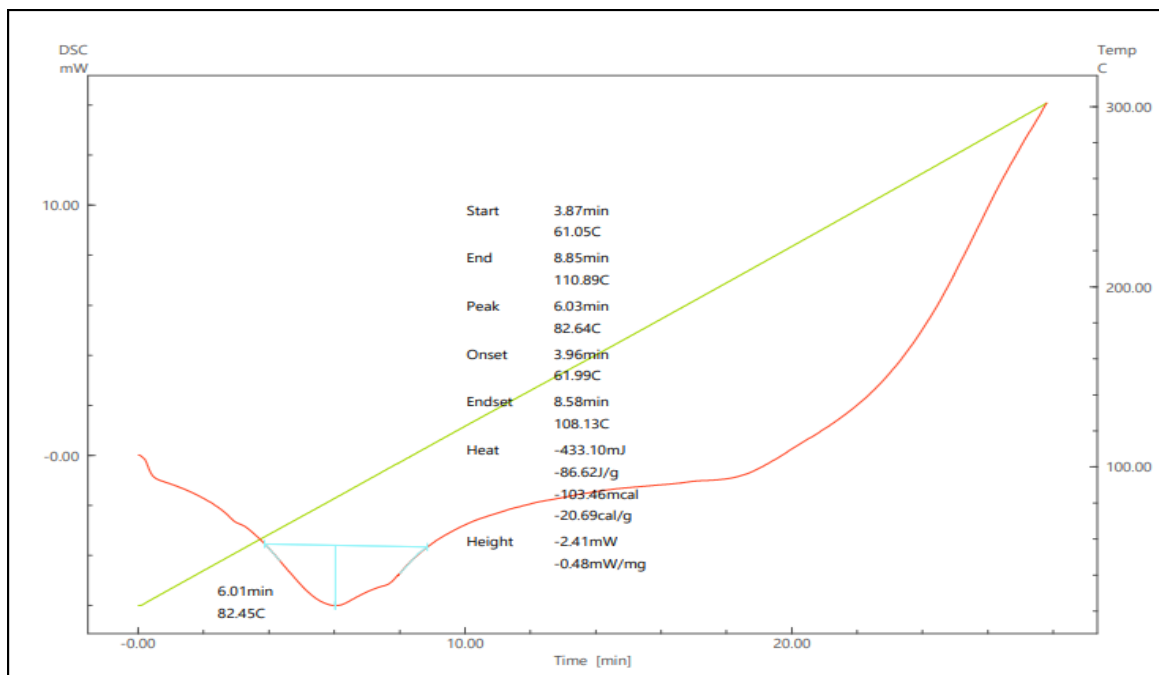


Figure.3: DSC *Carica Papaya* seed thermogram of powder.

DSC thermogram of Drug and Excipients

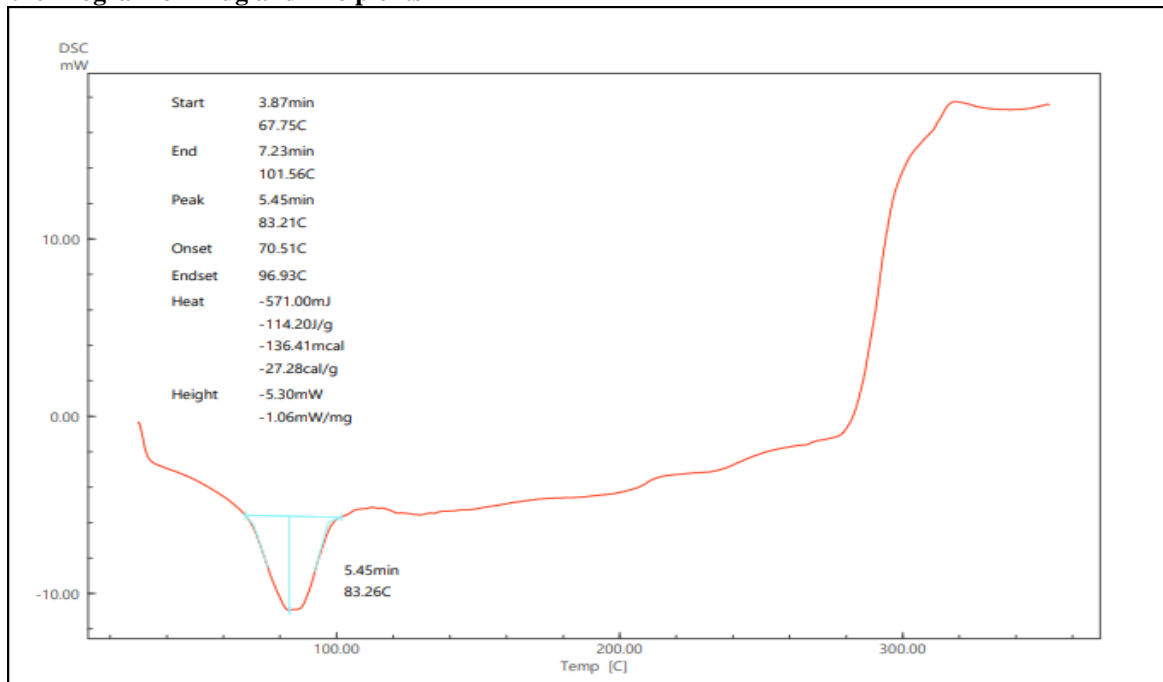


Figure 4: DSC thermogram of *Carica Papaya* seed powder + Excipients.

Evaluation of suspension

➤ Physical Test

Table.11: Physical Test of Suspension.

Sr. No	Parameter	Batch		
		F1	F2	F3
1	Nature	Liquid	Liquid	Liquid
2	Colour	Orange	Orange	Orange
3	Odour	Pleasant	Pleasant	Pleasant
4	Texture	Suspension	Suspension	Suspension

➤ pH

Table.12: pH of Suspension.

Sr. No	Parameter	Batch		
		F1	F2	F3
1	pH	7.6	7.6	7.6

➤ Redispersibility

Table.13: Redispersibility of Suspension.

Sr. No	Parameter	Batch		
		F1	F2	F3
1	Redispersibility	1 Inversion	1 Inversion	1 Inversion

➤ Sedimentation Volume

Table.14: Sedimentation Volume of Suspension.

Sr. No	Parameter	Time (Min)	Batch		
			F1	F2	F3
1	Sedimentation Volume	50	0.96	0.98	0.99
2	Sedimentation Volume	100	0.94	0.95	0.98
3	Sedimentation Volume	150	0.93	0.92	0.96
4	Sedimentation Volume	200	0.9	0.88	0.9

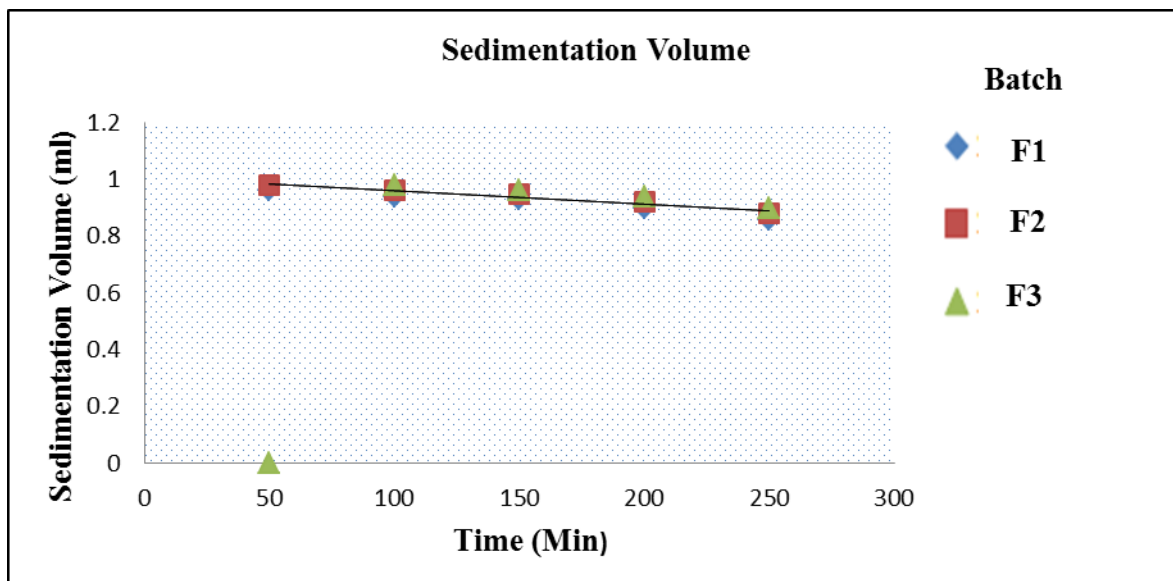


Figure 5: Sedimentation Volume V/S Time.

Table.15: Mean Sedimentation Volume of Suspension.

Sr. No	Parameter	Batch		
		F1	F2	F3
1	Mean sedimentation volume	0.918	0.938	0.954

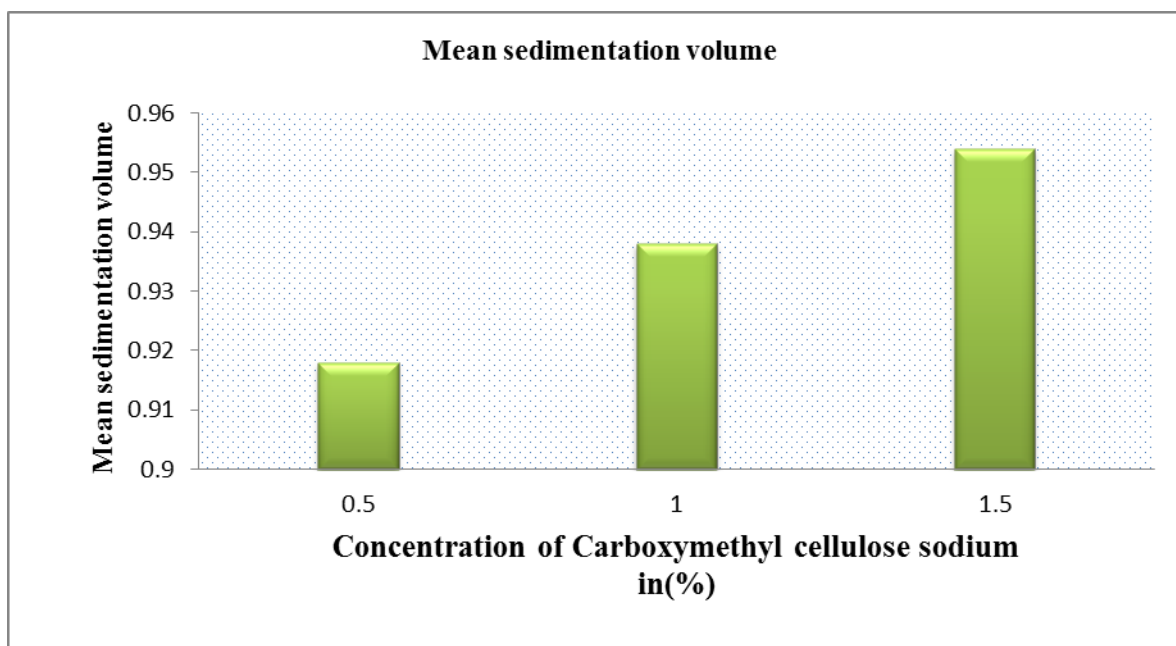


Figure.6: Mean Sedimentation Volume V/S Concentration of Carboxymethyl cellulose sodium in (%).

➤ Flow Rate

Table.16: Flow rate of Suspension.

Sr. No	Parameter	Batch		
		F1	F2	F3
1	Flow rate	5ml/10	5ml/12.56	5ml/15.35

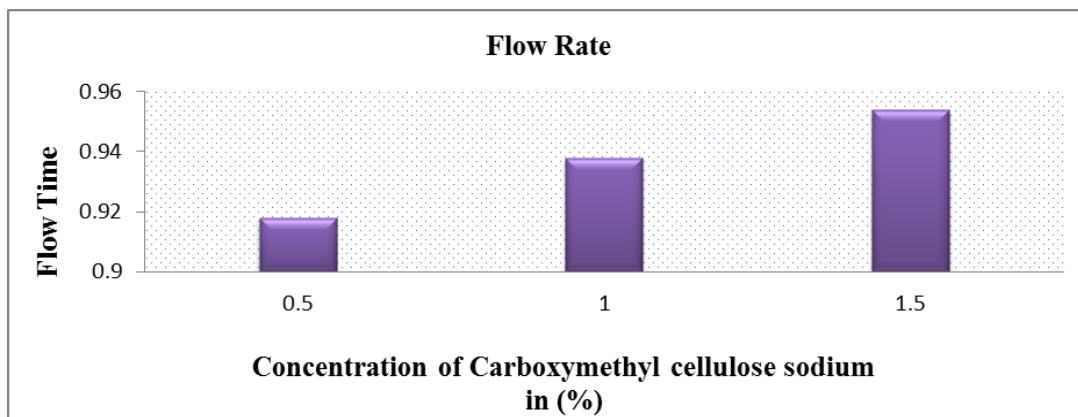


Figure.7: Flow rate V/S Concentration of Carboxymethyl cellulose sodium in (%).

➤ Viscosity

Table.17: Viscosity of Suspension.

Sr. No	Parameter	Batch		
		F1	F2	F3
1	Viscosity (cp)	37.85	42.61	66

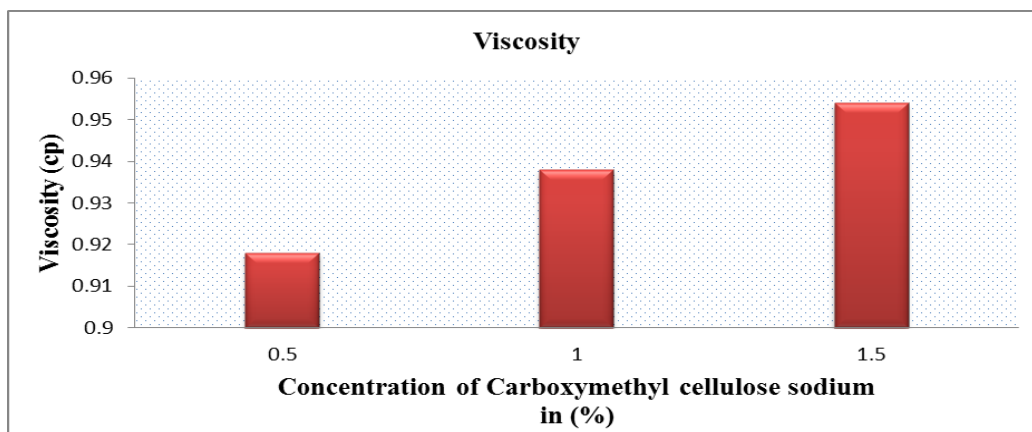


Figure.8: Viscosity V/S Concentration of Carboxymethyl cellulose sodium in (%).

➤ Density

Table.18: Density of Suspension.

Sr. No	Parameter	Batch		
		F1	F2	F3
1	Density (gm/ml)	1.2	1.36	1.64

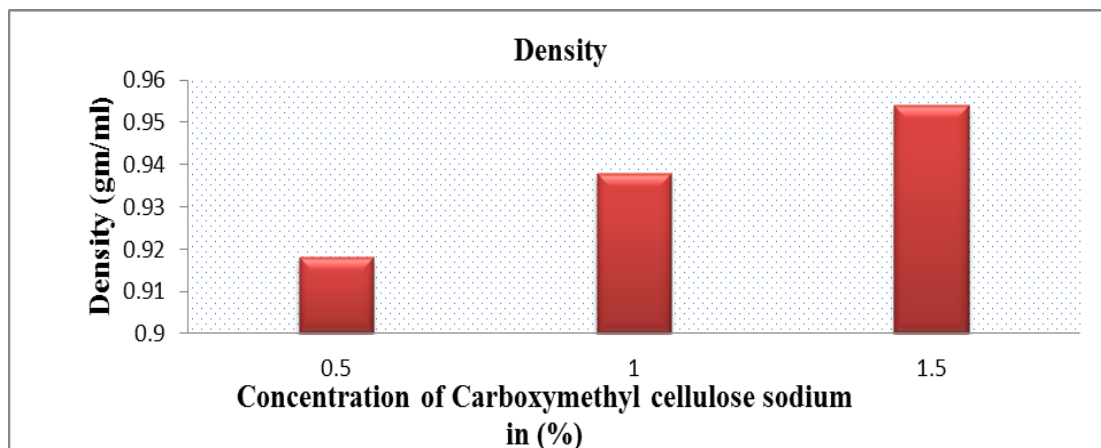


Figure.9: Density V/S Concentration of Carboxymethyl cellulose sodium in (%).

Particle size measurement by Zeta seizer.

Table.19: Particle size of suspension by Zeta seizer suspension.

Sr. No	Drug	Particle size
1	Particle size Measurement of Optimized batch	1022.7 nm

Table.20: Reports of Zetasizer.

Peak No.	S.P.Area Ratio	Mean	S. D.	Mode
1	1.00	245.2 nm	58.1 nm	232.0 nm
2	---	--- nm	--- nm	--- nm
3	---	--- nm	--- nm	--- nm
Total	1.00	245.2 nm	58.1 nm	232.0 nm

Figure10. Frequency (%) V/S Diameter (nm)

➤ Stability Testing

A. Crystal Growth

Table.21: Crystal formulation in of Suspension.

Sr. No	Sample Number	Sample in (ml.)	Time duration (Hr.)	Temperature (⁰ C.)	Crystal formation
1	F1	5	24	4 ⁰ C	No
2	F2	5	24	RT	No
3	F3	5	24	47 ⁰ C	No
1	F1	5	24	4 ⁰ C	No
2	F2	5	24	RT	No
3	F3	5	24	47 ⁰ C	No
1	F1	5	24	4 ⁰ C	No
2	F2	5	24	RT	No
3	F3	5	24	47 ⁰ C	No

B. Accelerated stability studies

Throughout the studies, it was discovered that the best optimised formulation of *Carica papaya* suspension is (F3), which was subjected to evaluate the physico-chemical parameters at one week intervals up to one

month. The results show that there was no more change in the physico-chemical properties of *Carica papaya* suspension. For 60 days, the optimised formulation (F3) was kept at room temperature (40⁰C). The additional research was completed in 30 days.

Table.18: Accelerated stability studies of Suspension.

Sr. No	Initial	Sample	Testing
		0 Month	1Month
1	pH	7.6	7.6 (±1)
2	Redispersibility	1 Inversion	1 Inversion
3	Sedimentation Volume	0.954	0.954 (±0.1)
4	Flow rate	13.35	13.35 (±0.1)
5	Viscosity (cp)	66	66 (±0.1)
6	Density (gm/ml)	1.64	1.64 (±0.1)

➤ In- Vitro Anthelmintic study

Observation table for Reference Suspension

Table.22: Time of paralysis of reference suspension.

Sr. No	Reference dilutions of Albendazole mg/ml	Time of paralysis in (min)
1	10	33.58
2	20	28.26
3	30	24.3
4	40	23.42
5	50	20

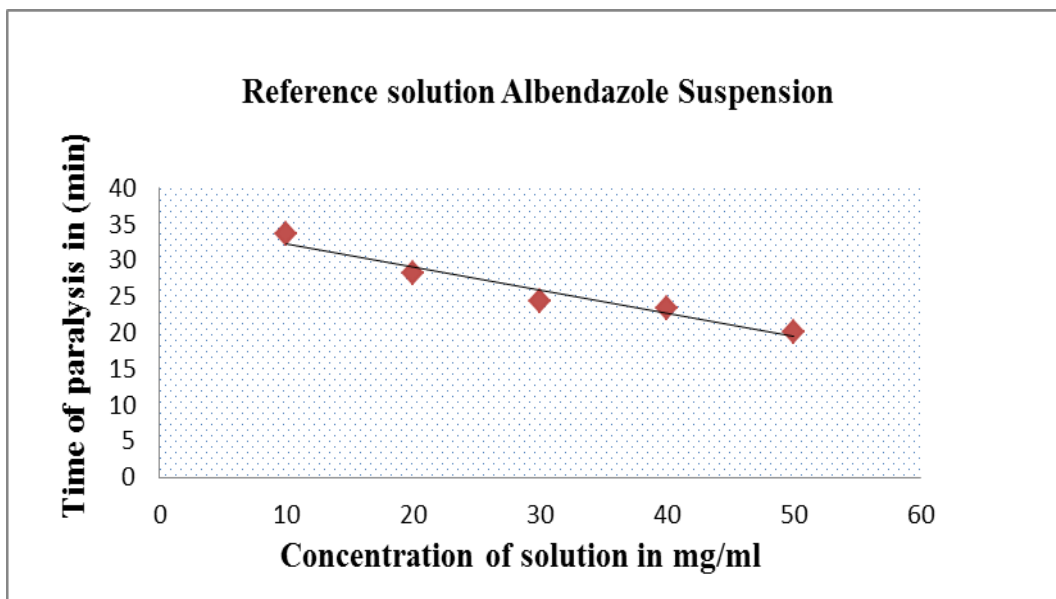


Figure.11: Concentration of solution V/S Time of paralysis.

Observation table for Test Suspension

Table.23: Time of paralysis of test suspension.

Sr. No	Test dilutions of <i>Carica papaya</i> suspension mg/ml	Time of paralysis in (min)
1	10	30.18
2	20	30.2
3	30	24.34
4	40	22.9
5	50	19.2

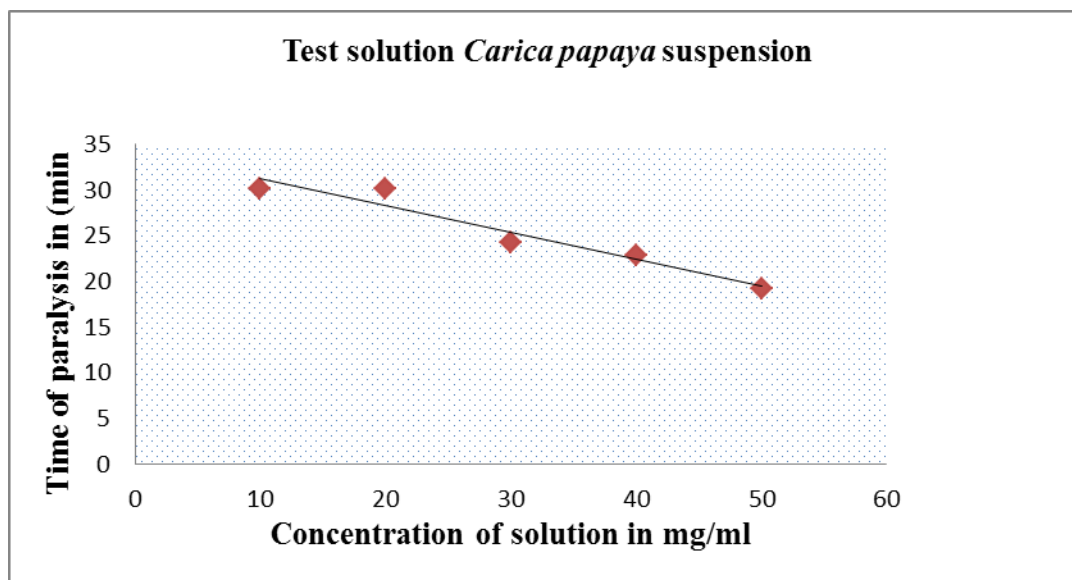


Figure.12: Concentration of solution V/S Time of paralysis.

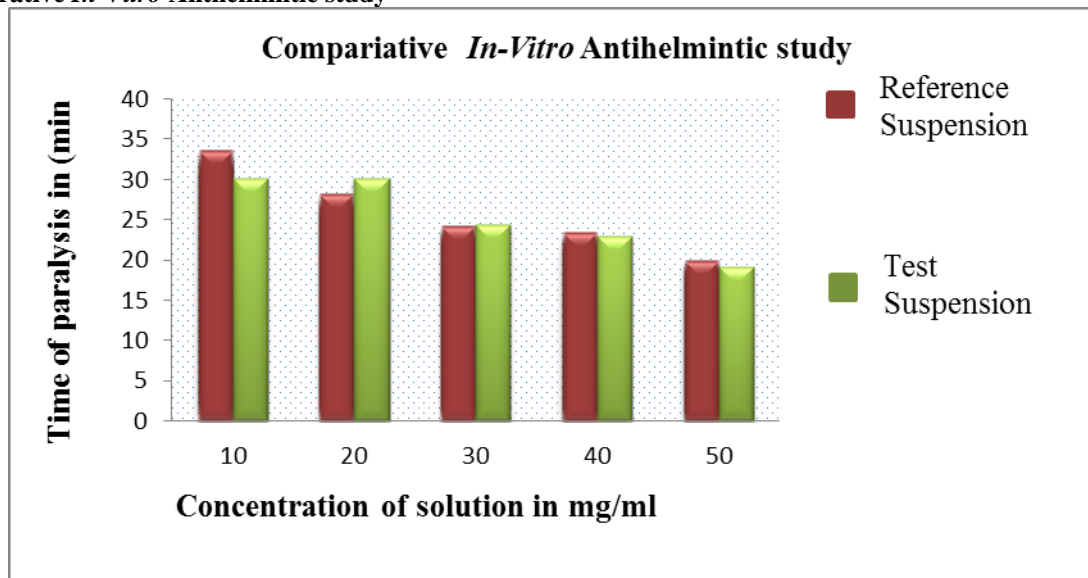
Comparative *In-Vitro* Anthelmintic study

Figure.13: Concentration of solution V/S Time of paralysis.

DISCUSSION

The current study aimed to develop a *Carica papaya* suspension for the treatment of helminthiasis.

Ethanol, Glycerin, Methyl paraben, Propyl paraben, Carboxymethylcellulose sodium, Saccharin sodium, and taste were used in the F1-F3 batch. The suspension was satisfactory; it redispersed easily when shaken, and the particles were consistent in size. The suspension exhibited anthelmintic activity in an in-vitro anthelmintic assay.

Carboxymethylcellulose sodium content is low in the F1 batch. As a result, the viscosity and stability of this batch are poor, and particles sink at a rapid rate.

The Carboxymethylcellulose sodium content in the F2 batch is medium. As a result, the viscosity and stability of this batch are slightly higher, but the sedimentation rate of the particles is slightly lower than in the previous F1 batch.

Carboxymethylcellulose sodium content is high in the F3 batch. As a result, the viscosity and stability of this batch are increased, and the particle sedimentation rate is extended.

Among these formulas, the F3 batch has the best viscosity and stability.

All suspension evaluation parameters were found to be satisfactory, and the In -Vitro anthelmintic investigation revealed the expected time of paralysis. The stability investigations took about a month to complete. There were no significant changes in pH, Redispersibility, sedimentation volume, flow rate, viscosity, or density. As a result, *Carica papaya* suspension has an edge against helminthiasis.

CONCLUSION

The current study sought to create a solution for the treatment of intestinal parasite infection in children.

In prior studies, albendazole suspension was utilised to treat helminthiasis. According to the World Health Organisation (WHO), as time passes, there is a risk of developing anthelmintic resistance, such as changing helminthic genetic material or mutation in their organelles, which can affect the potentiality of albendazole suspension.

As a result, an alternative treatment suitable for children or other age groups, such as suspension, is required. *Carica papaya* seed powder suspension anthelmintic study has the potential to treat helminthic infection, which is an alternate treatment to Albendazole suspension.

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