Popping balls papaya extract: Preparation of pediatric dosages in therapeutic formulations for therapeutic usage in dengue and malaria

Hrutuja Wagh1*, Avinash Bhosale2, Vishal Girbane1, Shravanee Bhosale1, Manish Bhise3, Mahesh Deshpande4, Piyush Chandra5 and Rakesh Ranjan5

1TMV’s Lokmanya Tilak Institute of Pharmaceutical Sciences, Pune, Affiliated to Dr. Babasaheb Ambedkar Technological University, Lonere, Raigad, Maharashtra, India; 2Satara College of Pharmacy, Satara, Affiliated to Dr. Babasaheb Ambedkar Technological University, Lonere, Raigad, Maharashtra, India; 3Shri Gurudatta Shikshan Prasarak Sanstha’s Institute of Pharmacy, Akola, Affiliated to Sant Gadge Baba Amravati University, Maharashtra, India; 4Amrutvahini College of Pharmacy, Sangamner, Affiliated to Savitribai Phule Pune University, Pune, Maharashtra, India; 5Government Pharmacy College, Nalanda, Affiliated to Bihar University of Health Sciences, Bihar, India

E-mail/Orcid Id:
H.W. hrutuja3196@gmail.com, https://orcid.org/0009-0000-4698-5827; A.B. bhosalea1@gmail.com, https://orcid.org/0009-0002-7813-248X; V.G. girbanevishal09@gmail.com, https://orcid.org/0009-0002-0712-4420; S.B. shravaneebhosale193@gmail.com, https://orcid.org/0009-0003-3159-4358; M.B. manishbhise.patiil1@gmail.com, https://orcid.org/0009-0002-3848-2549; M.D. maheshdeshpande83@gmail.com, https://orcid.org/0009-0003-4367-2192; P.C. piyushchandra001@gmail.com, https://orcid.org/0009-0005-2651-9913; R.R. rakesh7979@yahoo.com, https://orcid.org/0009-0009-0105-8531

Abstract: Spherification is a cutting-edge molecular gastronomy method that has just emerged in the realm of food science and technology, and it may be used to produce foods with superior sensory qualities and a high level of consumer acceptance and satisfaction. This method is excellent for making semi-solid spheres with a membrane coating so thin that it is barely discernible when placed in the mouth. This experiment used a simple spherification method to turn papaya extract into popping balls with sodium alginate. Intraventricular haemorrhage is a potentially fatal consequence of thrombocytopenia in the newborn period. Extracts from papaya leaves show promise as a treatment for refractory cases of newborn thrombocytopenia. This research aims to learn how to make popping balls out of papaya extract that are both safe to eat and tasty by adding jaggery as a sweetener. Physical parameters such as pH, viscosity, and stability of the prepared balls were studied in vitro, 30-day time frame. The findings revealed that papaya-popping balls are homogeneous and have a low viscosity. The expected drug release was 91%. Papaya popping balls were subjected to a three-month stability study. According to the results, there was no variation in colour, pH, or viscosity during the study. All the particles in the formulation were round so that it may be given to kids as an alternative to oral solid dose forms.

Keywords: Spherification, Sodium alginate, Calcium chloride, Popping balls, Papaya c., extract, Physical properties, Viscosity, Stability studies, In–vitro release

Introduction

The study of the physical and chemical changes that occur in food during preparation and cooking including the methods used to create popping boba—falls under molecular gastronomy. In other words, molecular gastronomy concerns the molecular changes in the foods we eat. Selecting, preparing, and enjoying delicious food is the subject of gastronomy. Food spheres are created using a molecular gastronomy technique called spherification, which perfectly fits the process (Gaikwad et al., 2019). Pop-ups are round candies with a gelatinous exterior and a liquid core. Molecular gastronomy is a subfield of food science that studies the physical and chemical processes involved in cooking and other forms of food preparation. Molecular gastronomy is the study of molecules that make up our food and how they change,
while gastronomy is the study of choosing, preparing, and consuming excellent food. Spheration to mould food into spheres is considered part of molecular gastronomy (Teixeira-Lemos et al., 2021).

Spheration works by combining two critical chemicals (alginate and calcium salt) to create a gelatinous substance that may encase liquid droplets into miniature liquid-filled pop-ups in a controlled gelification reaction. Spheration can be either primary, in which sodium alginate-containing liquid is immersed in calcium-containing water, or reverse, in which calcium-containing liquid is poured into sodium alginate-containing liquid. Chefs frequently utilise the gelation technique known as spheration to form liquid into tiny edible spheres in calcium-alginate capsules. Spheration combines two critical chemicals (alginate and calcium salt) to create a gelatinous substance that may encase liquid droplets into miniature liquid-filled pop-ups in a controlled gelification reaction. Spheration can be either primary, in which sodium alginate-containing liquid is immersed in calcium-containing water, or reverse, in which calcium-containing liquid is poured into sodium alginate-containing liquid. Chefs frequently utilise the gelation technique known as spheration to form liquid into tiny edible spheres in calcium-alginate capsules (Thomas Liji, 2019).

Sodium alginate and calcium chloride react in this way. Polysaccharide alginate and positively charged sodium ions that bond to the alginate molecules make up sodium alginate obtained from seaweed. When dissolved, sodium alginate turns into a liquid because the sodium ions escape from alginate molecules. Calcium alginate is produced when sodium alginate is added to a calcium chloride solution. The solution thickens and becomes gelatinous because calcium ions, with their two charges, can attach to two alginate molecules at once (Gadhwal et al., 2016).

**General reaction**

\[ 2\text{NaC}_6\text{H}_7\text{O}_6\text{+CaCl}_2 \rightarrow 2\text{NaCl}+\text{C}_1\text{2H}_{14}\text{CaO}_{12} \]

![Figure 1. Reaction between sodium alginate and calcium chloride](image)

The popping balls technique can be a better alternative in preparations of herbal juice. Pop-ups for treating dengue and malaria, especially in paediatric patients. The herbal juice used to prepare Popping balls is the leaf extract of the papaya plant.

Papaya (*Carica papaya* Linn.), a member of the Caricaceae family, is widely consumed due to its medicinal and nutritional benefits. Various papaya plant parts have been utilised medicinally from prehistoric times. In this work, we attempted to create a novel dosage from the papaya tree leaves. Therapeutic potential in *C. papaya* may stem from the plant’s alkaloids, glycosides, tannins, saponins, flavonoids, or glycosides. Carpaine, methyl gallate, rutin, loliolide, clitorin, isouquerentin, nicotiflorin, kaempferol-3-O-neohesperidoside, and isorhamnetin-3-O-β-D-glucopyranoside are some of the several chemical compounds involved [3,4]. The papaya (*Carica papaya*), sometimes known as pawpaw, is a popular tropical fruit thanks to the widespread belief that it has positive health effects. One of the most promising of these claims is that papaya leaf extract can help return platelet counts to normal in dengue fever (Das et al., 2020).

In dengue patients, a low platelet count is a warning sign, but it also predicts illness severity, indicates liver damage and mortality, and is a marker for vascular protein leakage. Papaya leaf extracts have been the subject of extensive research into their potential impact on platelet counts. A systematic evaluation found that the increase in platelet count in the extract group was statistically significantly higher than in the control group.

**Mechanism**

Whether it's created from dried or fresh crushed leaves, papaya leaf extract is full of valuable substances, such as alkaloids like carpaine and anthraquinone, saponins that cleanse the skin, and cardiac glycosides like carposide and tannins that strengthen the heart. As a result, it can protect the red blood cell membrane and has high antioxidant and free radical scavenging activity. Therefore, it may play a preventative role against hemolysis in high-stress situations (Kong et al., 2021).

By decreasing the amount of circulating interleukin, which is produced by activated immune cells, the dengue virus can cause a low platelet count. Viruses seek mononuclear and macrophage cells, as well as endothelial cells, to feed on.

According to one study, papaya leaf extract can effectively neutralise dengue virus in plasma and considerably decrease platelet aggregation (Dotto and Abihudi, 2021; Milind and Guruditta, 2011).

DOI: https://doi.org/10.52756/ijerr.2023.v32.016
A 15-fold rise in ALOX12 has been documented after supplementation with papaya leaf extract. By stimulating the growth and maturation of megakaryocytes, this enzyme stimulates the synthesis of platelets.

• Compared to controls, the extract causes a 13.5-fold increase in the platelet-specific platelet-activating factor receptor (PTAFR) gene.

• The flavonoid quercetin in papaya leaves blocks the activity of the serine proteases NS2B and NS3, which are essential for replicating the dengue virus. Thus, the extract blocks the viral assembly process. When given orally, papaya leaf extract has been linked to an increase in platelet count as fast as 24 hours. The sum of WBCs increased dramatically (Shetty et al., 2019).

Newborns frequently experience thrombocytopenia. Intraventricular haemorrhage is a potentially fatal consequence of thrombocytopenia in the newborn period. Extracts from papaya leaves show promise as a treatment for refractory cases of newborn thrombocytopenia. Our baby’s platelet count, which had been low due to recurrent thrombocytopenia, rose significantly after taking an extract of papaya leaves (Kugo et al., 2018).

Dose for Children (Pothapregada et al., 2015)
• For children: 275mg (5ml) 3 times /day for 5 days (1 year and less than 5 years)
• For children: 550mg (10ml) 3 times/day for 5 days (5 years and less than 18 years)
• For children: 1100mg tablet 3 times/ day for five days (weighing more than 40kg)

Objective:
The objectives of the present research are as follows-
1. Mask the bitter taste of herbal juices
2. Accuracy of dosage form
3. Easy to use in pediatric patients

Material and methods
Material used
The materials used for the preparation of pop-ups are:

1. Papaya leaves extract
2. Sodium alginate
3. Sodium benzoate
4. Calcium chloride
5. Sodium citrate
6. Distilled water
7. Jaggery
8. Flavouring agents

Sample collection
Leaves of C. papaya were collected from Tilak Maharashtra Vidyapeeth Campus & authenticated at Yashwantrao Chavan College of Science, Satara.

Preparation of C. papaya leaf extract
The gathered plants were rinsed in consecutively tap water to remove dirt or debris and dried in the shade for about 15 days. The dried leaves were broken up and ground into a powder using a mortar and pestle. The powder was then soaked in organic solvents such as hexane, ethyl acetate, methanol, and ethanol before being put through a Soxhlet device for solvent extraction. The collected material was then frozen at 4 degrees Celsius for later analysis (Verhagen and de Groot, 2014; Hussain et al., 2021).

Phytochemical investigation
Fresh floral extract from C. papaya in various solvents is tested for alkaloids, flavonoids, saponins, steroids, tannins, phlorotannins and glycosides (Khan et al., 2021).

Method of preparation of popping bulls
1. Take 250ml of herbal juice + 2gm of sodium alginate 1gm sodium benzoate 3gm of jaggery, and grind the mixture until a thick solution is obtained.
2. Freeze the solution overnight to remove the air bubble.
3. Make the calcium chloride solution (300ml water+ 2gm of calcium chloride)
4. Add a drop of sodium alginate solution to the calcium chloride solution.
5. Transfer the measured papaya extract of your sodium alginate to a clean cup or small basin. You shouldn’t pick up too much foam. Refrigerating sodium alginate and food solution for at least an hour, preferably overnight, is advised for defoaming. If too many bubbles are in the solution, ball formation in the succeeding phases may be impeded.
6. Have a second-hand clock, stopwatch, or timer available. To determine the pH of the papaya extract solution, compare the colour of a pH test strip dipped into the solution to the colour chart on the box. Make a note of it in the spreadsheet. Ingest a tiny amount of the papaya extract solution using the syringe or a medication dropper. If the foam is on top of the solution, you can...
remove it by dipping the needle under it and then sucking it. Wipe any foam or surplus solution from the syringe’s sides on the container’s rim to prevent contamination.

7. The time of the drop’s immersion in the solution is crucial; therefore, let it sit for 60 seconds (sec). After 60 seconds, carefully remove the ball from the solution using a clean spoon, carefully removing as little of the solution as possible to avoid injuring the ball.

8. Place the ball on the plastic wrap on top of graph paper, then count the number of lines it crosses to determine the ball’s longest and shortest dimension (or its diameter and height). Make sure to write down your results in the table. Figure 6 shows how to align the plastic wrap so the ball's edge is parallel to one of the lines. The diameter in millimeters can be determined by counting the number of lines the ball crosses. The number of lines the ball crosses will be multiplied by two if the lines on your graph paper are 2 mm apart. Graph paper with lines spaced 2 mm apart is a good illustration; if a ball occupies around 2.5 lines, its diameter is 5 mm (2.5 times 2 mm = 5 mm).

Figure 3. (a) Uniform solution of food and sodium alginate (b) Addition of food solution in calcium chloride solution (c) Prepared papaya popping balls

Figure 4. (a, b & c). Measurement of dimension of balls by graph paper
9. Repeat steps 1–9 twice to get 3 popping balls from the papaya extract and calcium chloride solution.

Please remember that the objects we refer to as "balls" need not be perfectly round to be included in the "measured balls" tally.

10. Mix 0.5 grams of sodium citrate into the papaya extract and sodium alginate solution. Using a clean spoon, include the sodium citrate, and then wait 60 seconds to let any air bubbles created during mixing escape.

11. Remember that if the balls didn't form spheres before you added sodium citrate, they might start to increase the chemical, but they might stop again if you add too much. When the balls are no longer round (because they have flattened out and no longer retain their round shape), proceed to step 8 again.

The pop-ups should be dried before being packed (Khan et al., 2021; Halford, 2014).

2.6 Characterization
2.6.1 Phytochemical evaluation

Characterization of papaya leaf gel

<table>
<thead>
<tr>
<th>Phytochemicals</th>
<th>Observations</th>
<th>Inferences</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alkaloids</td>
<td>Mayer’s test</td>
<td>No colour change</td>
</tr>
<tr>
<td></td>
<td>Wanger’s test</td>
<td>No colour change</td>
</tr>
<tr>
<td>Saponins</td>
<td>Frothing of extract, which persisted for 15 min</td>
<td>+</td>
</tr>
<tr>
<td>Flavoids</td>
<td>Flavonoids</td>
<td>The transition from orange to light red colour</td>
</tr>
<tr>
<td></td>
<td>Flavones</td>
<td>The transition from light red to deep crimson</td>
</tr>
<tr>
<td>Steroids</td>
<td>Yellowish with green fluorescence</td>
<td>+</td>
</tr>
<tr>
<td>Tannins</td>
<td>Formation of a green precipitate</td>
<td>+</td>
</tr>
<tr>
<td>Phlobatannins</td>
<td>Deposition of red precipitation</td>
<td>+</td>
</tr>
<tr>
<td>Glycosides</td>
<td>Absence of brick red precipitate</td>
<td>+</td>
</tr>
<tr>
<td>Reducing Sugar</td>
<td>Fehling’s Test</td>
<td>Presence of Brick Red precipitate</td>
</tr>
<tr>
<td></td>
<td>Benedict’s Test</td>
<td>Presence of Green Colour</td>
</tr>
</tbody>
</table>

Stability studies

To conduct stability experiments on finished popping balls, they were kept in two different environments: at room temperature and accelerated temperature (40°C ± 5°C, 75%±5% RH), all of which adhere to the ICH criteria. For three months, the formulation is monitored for changes in physical parameters.

Viscosity

The Brookfield viscometer’s spindle DV-E-64 was used to determine the popping balls' viscosity. Viscosity was tested at room temperature (25°C± 5°C) for a set period of 2 minutes at a rotational speed of 1.5 RPM. Three independent viscosity measurements were performed, each time utilising a new sample.

In vitro drug release

USP dissolution type II (paddle type) was used for the In vitro drug release investigation of popping balls. The 900 ml of 0.1 N HCl solution was used in the dissolving test, which was run at 37± 0.5°C and 100 RPM. At 5, 10, 15, 20, and 30 minutes, an equal volume of the solution was removed from the dissolving device and replaced with a fresh dissolution medium. After filtering through a 0.5 µm membrane, the samples were analysed at 263 nm in a UV-Vis Spectrophotometer. The steps were repeated three times for accuracy.

Stability studies of popping balls

To conduct stability experiments on the finished popping balls, they were kept in two different environments: at room temperature and accelerated temperature (40°C ± 5°C, 75%±5% RH), all of which adhere to the ICH criteria. The formulation is monitored over three months for changes in physical parameters such as colour, pH, jaggery crystallisation, stiffness, and viscosity as part of stability tests.
Results and Discussion

Papaya leaves were dried and soxhlated with different menstruum, including water, ethanol, methanol, and chloroform. The phytochemical content of the dried extract was analysed. Flavonoids, sugars, glycosides, saponins, steroids, and an absence of alkaloids were found in the early phytochemical screening. Table 1 displays the outcomes. Extracts of Papaya Caria were mixed with sodium alginate and calcium chloride to make the popping balls. Figure 1 shows the finalised papaya-popping ball formulation. A visual examination of the papaya-popping balls was performed. Sodium alginate and calcium chloride do not produce a firm, transparent papaya-popping ball (Gaikwad et al., 2019).

Using a digital pH meter, we found that the papaya popping ball had a pH between 6.9 and 7.2. All formulations' viscosities were measured with a Brookfield Viscometer. The findings revealed that papaya-popping balls are homogeneous and have a low viscosity. Table 2 displays the results. A dissolution device type-I was used to measure the drug release from the jellies. A paddle device assessed drug release in-vitro from the papaya-popping ball. The projected drug release rate based on estimates was 91%. Maximum drug release was observed with this formulation (Table 3). Studies of stability were carried out. Papaya popping balls underwent three months of stability testing in a temperature and humidity-controlled setting. Table 5 displays the collected data. The results showed that the optimised formulation had not changed in color, pH, or viscosity.

Conclusion

Using sodium alginate and calcium chloride, the papaya popping balls were successfully formulated in the present study. This composition was rigid and aesthetically pleasing. The optimised formulation has good stability and satisfactory physicochemical attributes. All the particles in the formulation are round, making it easy to dose kids with it instead of other solid oral medications. Furthermore, the use of natural extracts is in accordance with the increasing inclination towards holistic and integrative therapy. Nevertheless, it is crucial to emphasise the significance of thorough scientific investigation and clinical studies in order to substantiate the safety, effectiveness, and suitable dosage of Popping Balls papaya extract for its application in pediatric patients. The establishment of standardised criteria for inclusion into treatment regimens would need crucial collaboration among researchers, pharmaceutical specialists, and medical professionals. As the field of medical innovation progresses, there is an increasing interest in investigating botanical therapies such as

<table>
<thead>
<tr>
<th>Table 2. General Appearance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Papaya extract popping balls</td>
</tr>
<tr>
<td>physical appearance</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Table 3. In-vitro drug release of papaya extract popping balls</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dissolution parameter</td>
</tr>
<tr>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Table 4. Characterization of papaya extract popping balls</th>
</tr>
</thead>
<tbody>
<tr>
<td>Quantity of sodium citrate added in total</td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td>0</td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td>0.5 gm</td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Table 5. Stability study data of the Popping Bolls</th>
</tr>
</thead>
<tbody>
<tr>
<td>Papaya extract popping balls</td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td></td>
</tr>
</tbody>
</table>
Popping Balls papaya extract. This exploration offers prospective alternative therapy alternatives for illnesses that now have limited therapeutic choices, perhaps enhancing accessibility to these treatments. The successful progression from the first stages of research and formulation to the eventual attainment of regulatory approval and integration into clinical practise necessitates a collaborative and interdisciplinary approach. This endeavour demands a steadfast dedication to the welfare of patients and strict respect for ethical principles.

**Competing interests**

The authors declare that there is no conflict of interest.

**References**


https://doi.org/10.7759/cureus.14164


---

**How to cite this Article:**


DOI: https://doi.org/10.52756/ijerr.2023.v32.016

This work is licensed under a Creative Commons Attribution-NonCommercial-NoDerivatives 4.0 International License.

DOI: https://doi.org/10.52756/ijerr.2023.v32.016