



FORMULATION AND CHARACTERIZATION OF HERBAL TABLETS FOR THE MANAGEMENT OF DENGUE

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ABSTRACT

Tablets are used as formulation and are prepared by using plant extracts i.e., *Carica papaya* and *Embelica officinalis*. These tablets were prepared by using wet granulation method. In this article the extract of leaves of *Carica papaya* and fruits of *Embelica officinalis* were used for making herbal tablets. Extracts of leaves of *Carica papaya* was obtained by cold extraction and through maceration method and the extract of fruits of *Embelica officinalis* was obtained by maceration process. Both extracts were dried and mixed. These extracts were then impregnated with the excipients like diluents, binding agents, super disintegrating agent, lubricants, etc. to make granules. These granules were then evaluated by using various parameters like Angle of repose, tapped density, bulk density, Carr's Index, Hausner's Ratio and void volume. These granules were then used for the making of tablets of desired size and shape by punching in the machine. After preparation of the tablets their evaluation parameters were studied like physical appearance, weight variation, friability, disintegration time, hardness test and thickness. Also the parameters for the acceptance of the tablets is also done like flavor and sweetness. Recent studies have shown that herbal extract of leaves of papaya has beneficial effect as an anti-inflammatory agent, for its wound healing properties, anti-tumor as well as Immunomodulatory effects and as an antioxidant. Amla fruit is a rich natural source of vitamin C (Ascorbic acid) and contains 600-750 mg/100 g of the fresh pulp. Also it is rich in minerals matters like phosphorus, iron and calcium. Amla is used as an Immunomodulatory agent and hence enhance the immunity of the patient. Aim of the study is to design develop and optimize the dosage form to cure dengue and is based on the use of natural plant ingredients to intermingle with chemical as well as synthetic ingredients to develop an effective unit dosage forms for better patient compliance.

KEYWORDS: Papaya, Amla, Extracts, Herbal tablet, Dengue, Immunomodulatory, Platelets.



1. INTRODUCTION

Medicinal plants are widely distributed throughout the world but most abundantly in tropical countries. It is a mosquito-borne disease affected by infection of any anti-genically distinct dengue virus serotypes, belonging from *Flavivirus* genus as well as *Flaviviridae* family, contain with single positive stranded RNA viruses. It is estimated that about 25% of all modern medicines are directly or indirectly derived from higher plants. Thus, herbal medicine has led to the discovery of a number of new drugs, and non-drug substances. To achieve the desired benefit from herbal preparations, an individual must take the required dose over a certain length of time. Although it is generally believed that most herbal preparations are safe for consumption, some herbs like most biologically active substances could be toxic with undesirable side effects.¹

2. DRUG FORMULATION

2.1 Papaya: *Carica papaya* belongs to the fruits and vegetables class of family Caricaceae. The fruit are popularly used as desert or processed into Jam, puree or wine, while the green fruits are cooked as vegetable.² *Carica papaya* leaf (CPL) is used as food or as medication in folk medicine. Traditionally, the leaf extract was used as a tonic for the heart, analgesia and treatment for stomach ache. The extract is also known to have antioxidant properties but there are no scientific data reported on the protective effect of this extract on alcohol induced acute gastric damage.³



Figure 1: Showing leaf of *Carica papaya*

Papaya is also known as the source of papain enzyme, a kind of enzyme that is utilized as meat tenderizer. Papaya leaf extracts have phenolic compounds, such as protocatechuic acid, p-coumaric acid, 5,7-dimethoxycoumarin, caffeic acid, kaempferol, quercetin, chlorogenic acid. These compounds have antimicrobial activity and have been proven to be able to inhibit the growth of microbes.⁴ The high level of natural self-defense compounds in the tree makes it highly resistant to insect and disease infestation.⁵ *Carica papaya* has crown shaped large palmate leaves emerging from the apex of the trunk of the tree. The soft, hollow, cylindrical trunk ranges from 30 cm in diameter at the base to about 5 cm in diameter at the crown. The leaves (especially fallen ones) are used variously for the treatment of fevers, pyrexia, diabetes, gonorrhea, syphilis, inflammation and as a dressing for septic wound.⁶ Recent studies have shown its beneficial effect as an anti-inflammatory agent, for its wound healing properties anti-tumor as well as immunomodulatory effects and as an antioxidant. A toxicity study (acute, sub-acute and chronic toxicity) conducted on Sprague Dawley rats administered with *C. papaya* leaves juice revealed that it was safe for oral consumption. Safety studies based on OECD (Organization of Economic Cooperation and Development) guidelines for acute, sub-acute and chronic toxicity conducted on *C. papaya* extract and showed that it was found to be safe for human consumption. The leaves of papaya have been showed to contain many active components that can increase total antioxidant activity in blood and reduce lipid peroxidation level, such as paper chymopapain, cystatin, tocopherol, ascorbic acid, flavonoids, cyanogenic-glycosides glucosinolates. The alkaloids, flavonoids, saponins, tannin, and glycosides are related with anti-inflammatory activity. *C. papaya* leaves extract also found to have anti-bacterial effect, anti-tumor, and immunomodulation activities. The leaf of *C. papaya* is categorized as nontoxic because it's LD50 >15 g/kg body weight. The leaves also contain cardiac glycosides, anthraquinones, carpaine, pseudocarpaine, phenolic compounds.⁷



Figure 2: Showing papaya leaf with extract

Little information exists on the antimicrobial property of *C. papaya* dried and fresh leaves. Recently, antifertility, antihelminthic and anti-inflammatory activity has been reported. Leaves have been poultice into nervous pains, elephantoid growths. Papaya leaves are made into tea as a treatment for malaria. Antimalarial and antiplasmodial activity has been noted in some preparations of the plant, the leaves of the papaya plants contain chemical compounds of karpain, Substance which kills microorganisms that often interfere with the digestive function. Antimicrobials of plant origin effective in the treatment of infectious diseases and simultaneously mitigating many of the side effects often associated with synthetic antimicrobial agents have been discovered.⁸

2.2 Amla: It is fresh as well as dried fruits of the plant *Embllica officinalis* or *Phyllanthus emblica* belonging to family Euphorbiaceae.

Colour: Green color changes to light yellow or brick red at maturity

Odour: Odourless

Taste: Sore and Astringent

Size: Average size is between 1.5 and 2.5 cm in diameter

Shape: Depressed and Globular

Fruits are fleshy obscurely 4 lobed with 6-trygonus seeds. They are very hard and smooth in appearance. Amla fruit is a rich natural source of vitamin C (Ascorbic acid) and Contains 600-750 mg/100 g of the fresh pulp. Also it is rich in minerals matters like phosphorus, iron and calcium. It contain appreciable amount of pectin. Fresh fruit contains about 75% moisture. It is found that the vitamin content of dried fruits is not lost considerably. It may be due to the presence of tannins, which retards oxidation of vitamin C. *Amla* fruits are largely used in Indian medicine. It is used as an acrid, diuretics, refrigerant, laxative, diarrheas and dysentery. It is a popular ingredient of '*Triphala*' and '*Chyawanprash*'.⁹ The anti-inflammatory response of *E. Officinalis* extract has been well established and predicted mechanism for anti-inflammation is based on its function to reduce lymphocyte proliferation and histopathological severity of synovial hyperplasia.¹⁰



Figure 3: Showing leaves and fruit of Amla (*Embllica Officinalis*)



Description

Macroscopic

Drug consists of curled pieces of pericarp of dried fruit occurring either as separated single segment, 1-2 cm long or united as 3 or 4 segments, bulk colour grey to black, pieces showing a broad, highly shrivelled and wrinkled external convex surface to somewhat concave, transversely wrinkled lateral surface, external surface shows a few whitish specks, occasionally some pieces show a portion of stony testa (which should be removed before processing); texture rough, cartilaginous and tough.

Microscopic

Transverse section of fruit shows epicarp consisting of a single layered epidermis cell appearing tabular and polygonal in surface view; cuticle present; mesocarp cells tangentially elongated parenchymatous and crushed differentiated roughly into peripheral 8 or 9 layers of tangentially elongated smaller cells, rest consisting of mostly isodiametric larger cells with walls showing irregular thickenings; ramified vascular elements occasionally present; stone cells present either isolated or in small groups towards endocarp; pitted vascular fibers, walls appearing serrated due to the pit canals, leading into lumen.

Powder

Fine powder shows epidermis with uniformly thickened straight walled isodiametric parenchyma cells with irregular thickened walls, occasionally short fibers and tracheids.¹¹

Causative Organism for Dengue

Viruses essentially consist of genetic material (nucleic acids, DNA strand) and a capsular envelope made up of proteins, often with a coat of a phospholipids (PL) bilayer with embedded proteins. They lack a metabolic system but depend on the infected cell for their growth and replication. Targeted therapeutic suppression of viral replication requires selective inhibition of those metabolic processes that specifically serve viral replication in infected cells. To date, this can be achieved only to a limited extent.¹²

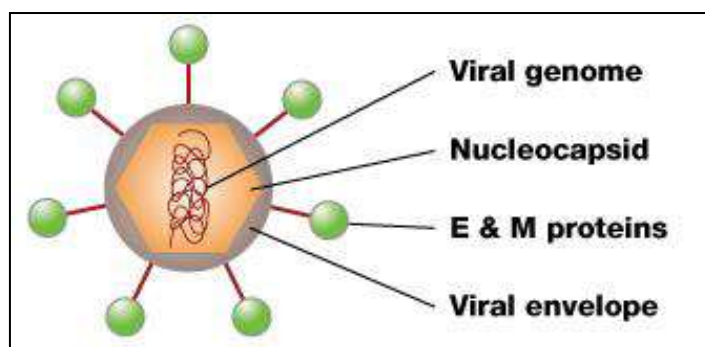


Figure 4: Showing Structure of Dengue Virus

Positive stranded encapsulated RNA virus, 3 structural protein genes: C, M, E & 7 NS protein genes
Dengue is an arthropod-borne viral disease carried by *Aedes aegypti* as the vector, caused by 4 possible viral serotypes, namely, serotype 1, 2, 3, and 4 of the Flaviviridae family. There is no specific antiviral drug available for the treatment of dengue infection. Each episode of infection is known to induce a life-long protective immunity to the homologous serotype but confers only partial and transient protection against subsequent infection by the other serotypes. Secondary infection is a major risk factor for Dengue Haemorrhagic Fever (DHF) possibly due to antibody-dependent enhancement. A patient with dengue fever presents typically with fever, headache, and rash known as the dengue triad. There are many other nonspecific signs and symptoms associated with DF and patient can progress to DHF and typically manifests as abdominal pain, bleeding, and even circulatory collapse. The clinical course of dengue has an abrupt onset followed by three phases, namely, the febrile phase, the critical phase and the recovery phase. It is during the critical phase that thrombocytopenia, characterized by a decrease in platelet count below 1,00,000/mm³ from the baseline and haemoconcentration, characterized by an increase of haematocrit by 20% or more, is detectable before the subsidence of fever and the onset of shock. Safety studies based on OECD guidelines for acute, subacute, and chronic toxicity were conducted on *C. papaya* extract and showed that it was found to be safe for human consumption. The present study was conducted to determine and investigate the traditional claim that CPLJ increases the platelet count in patients with DF and DHF.¹³



3. MATERIALS AND METHODS

3.1 Material used

Plants used are locally cultivated Papaya (*Carica papaya*) and Amla (*Emblica officinalis*) and authenticated in own laboratory. Lactose, Starch, Magnesium Stearate, Talc, Methyl Parabens, Mannitol, Sucrose, Sodium Starch Glycolate, Ethanol were procured from sigma Aldrich. Vanillin, Calcium Carbonate, Sodium Carbonate and Sodium Saccharin were procured by CDH, chemicals. All other ingredients are of analytical grade.

3.2 Methodology

3.2.1 Preparation of extracts of *Carica papaya*

3.2.1.1 Cold extraction

The collected green *Carica papaya* leaves were washed with distilled water from which 50 grams of the leaves were crushed and grounded in a blender using 200 ml of distilled water in order to obtain the juice from the fresh leaves.

3.2.1.2 Maceration

An aqueous extract of *Carica Papaya* was prepared with 100% distilled water by adding 50g of fresh cut leaves in to 200 ml of distilled water. The mixture was kept in the room temperature for two days. At the end of the first day the water containing the extract was filtered and collected, then it was resuspended with 200ml fresh distilled water and the maceration was continued again for the next day. Finally both extracts were combined.



Figure 5: Showing *Carica papaya* Extract

3.2.1.3 Concentration of Extract

The mixture was heated at 50-60° C for 48 hours. The procedure involves simple decoction process of the aqueous extract from which the soluble compounds further heated at a higher temperature 70-75°C for 3 hours until the solvent gets evaporated completely. Temperature was maintained to avoid the charring of the product. The obtained dry product was weighed and the yield was noted.

3.2.2 Preparation of extracts of *Emblica officinalis*:-

Procured plant materials Amla pericarp was dried and then coarsely powdered in a blender. The coarse powder 1 kg was subjected to maceration for 72 hours, followed by exhaustive maceration for 48 hours by using solvents 60% ethanol. The solvents was decanted and filtered with filter paper and recovered by distillation with help of rotary vacuum evaporator at 750°C to 800°C. The extracts were dried under desiccator and stored in airtight container at room temperature.



Figure 6: Showing Amla Extract

3.2.3 Preparation of tablets

3.2.3.1 Wet granulation method

The concentrated extract of Carica papaya and Amla was mixed with the excipients such as Sodium starch glycolate, Methyl paraben, Starch, Sodium saccharin, Vallinin, Calcium carbonate and Mannitol in order to increase its bulkiness and to convert in to a powder mass with passable flow property and compressibility. It was passed through sieve no. 8 & 12 in order to break the lumps to get uniform granules in which Talc and Magnesium stearate were added finally. The total weight of the granules was noted and evaluated.



Figure 1: Showing batch F1 Tablets



Figure 2: Showing batch F2 Tablets

3.2.3.2 Procedures of Evaluation Parameters of Granules

3.2.3.2.1 Angle of Repose

Powder is poured from a funnel onto a horizontal surface; it will form a cone due to gravitational forces. The angle between the sides of the cone and the horizontal is referred to as the angle of repose. The angle of repose is a relatively simple technique for estimation of the flow property of powder. Powders with low angle of repose are free flowing and those with a high angle of repose are poorly flowing powders. 10gm of granules were passed through funnel and the pile was formed. The angle of repose was calculated by using the formula:

$$\text{Angle of Repose } (\theta) = \tan^{-1} \frac{\text{Height (h)}}{\text{Radius (r)}}$$

3.2.3.2.2 Bulk Density

This is obtained to know the exact volume of the granules that is being placed in the cylinder. Initials are used in the formula. Bulk density is also known as the fluff and poured density and is calculated by using formula:

$$\text{Bulk Density} = \frac{\text{Mass (M)}}{\text{Volume (V)}}$$

**3.2.3.2.3 Tapped Density**

It is obtained with the help of tap density apparatus, in which the powder is filled in the cylinders and the tapping is done. After few times of intervals the volume of the cylinder is noted done and the tapped density of the granules is calculated using following formula:

$$\text{Tapped density} = \frac{\text{Weight of granules (W)}}{\text{Volume of granules after 50 taps (V}_{50})}$$

3.2.3.2.4 Carr's Index

After obtaining the tapped and fluff density, the Carr's Index is being calculated by using 100ml measuring cylinder and calculated by following formula:

$$\% \text{age Compressibility} = \frac{\text{Tapped density} - \text{Fluff density}}{\text{Tapped density}} * 100$$

3.2.3.2.5 Hausner's Ratio (H.R.)

This ratio is obtained after the tapped density is calculated by using following formula:

$$\text{H.R.} = \frac{\text{Tapped density}}{\text{Poured density}}$$

3.2.3.2.6 Void Volume

This volume of the granules is obtained by using the values of bulk volume and tapped density. This will indicates the air volumes that is being created in the granules during tapping and is calculated by using formula:

$$\text{Void Volume} = \text{Bulk Volume} - \text{Tapped Volume}$$

3.2.3.3 Procedures of Evaluation Parameters of Granules**3.2.3.3.1 Weight Variation**

10 tablets were selected randomly and weight individually. The average of tablets is calculated using formula and the Standard deviation is calculated by using following formula:

$$\text{Standard Deviation (S.D.)} = \sqrt{\frac{\text{Deviation}^2 (D^2)}{\text{No. of tablets (N)}}}$$

3.2.3.3.2 Hardness test

This test is done using the Monsanto and Pfizer apparatus. In this the tablet is kept in its place in the apparatus and the pressure is applied to it. The pressure is noted down which have been recorded by the pressure gauge and average hardness is calculated.

3.2.3.3.3 Friability test

This test is carried out by using Friability apparatus. The weighted tablets are placed in the apparatus and it is rotated at 25 rpm for 5 minutes. After sometimes tablets are removed out from apparatus and again they are weight. The friability is calculated by using following formula:

$$\text{Friability} = \frac{\text{Initial weight (Wi)} - \text{Final weight (Wf)}}{\text{Initial weight (Wi)}} * 100$$



3.2.3.3.4 Acceptability test

In this test the acceptability of the tablets is checked, whether the tablets are suitable to eat or not. The sweetness & odour of tablets are tested by 5 volunteers and the acceptance is noted down in the table with the remarks given by each volunteer regarding the tablets.

3.2.3.3.5 Disintegration test

3 tablets are taken for the evaluation of the disintegration time. The tablets are placed in the disintegration apparatus and the time is observed till the tablet gets totally disintegrated. The temperature of the apparatus is maintained at 37° C.

4 RESULTS AND DISCUSSION

4.1 Results

Formulation of tablets with Plant extracts: Two batches of tablets were prepared using calcium carbonate, lactose, SSG, starch, mannitol, vallinin, sodium saccharin, magnesium stearate, talc, sodium carbonate, Papaya leaves and Amla fruit extract is used in the preparation of tablets. These are the main ingredients that are used for the manufacturing of Trial batch as well as F1 & F2 batch and are showed in the Table No. 1

4.1.1 Formulations table

Table No. 1

Sr. No.	Ingredients Used	Trial Formulation	Formulation (F1)	Formulation (F2)
1.	Sodium starch glycolate	5 gm	2.5 gm	3.5 gm
2.	Lactose	50 gm	20 gm	--
3.	Starch	1.5%	1.5%	1.5%
4.	Methyl paraben	1 gm	100 mg	100 mg
5.	Mannitol	5 gm	1.5 gm	1.5 gm
6.	Sodium saccharin	--	1 gm	1 gm
7.	Magnesium stearate	1.5 gm	1.5 gm	1.5 gm
8.	Talc	2 gm	1 gm	1 gm
9.	Vallinin	1 gm	200 mg	200 mg
10.	Papaya extract	--	2 gm	2 gm
11.	Amla extract	--	1.75 gm	1.75 gm
12.	Calcium carbonate	---	2 gm	2 gm
13.	Sodium Carbonate	--	5 gm	--

These are some ingredients that are used in preparation of tablets which are useful in the treatment of dengue.

4.1.2 Evaluations of Granules

The evaluation parameters angle of repose, tapped density, bulk density, Carr's Index, Hausner's Ratio and Void volume were carried out for the granules of F1 & F2 and are showed in the Table No. 2.

Table No. 2 Showing different Evaluation parameters of Granules of F1 & F2

Sr. No.	Evaluation parameters	Formulation (F1)	Formulation (F2)
1.	Angle of Repose (°)	0.537	0.500
2.	Tapped density (g/ml)	0.85	0.745
3.	Bulk density (g/ml)	0.689	0.617
4.	Carr's Index	18.9	17.2
5.	Hausner's Ratio	1.234	1.207
6.	Void Volume (ml)	7	6

These are some evaluation parameters that are carried out for the granules used to manufacture dengue tablets.



4.1.3 Evaluations of tablets

The evaluation parameters like Physical appearance, acceptability test, weight variation, friability, hardness, thickness and disintegration test were carried for the F1 & F2 and are shown in Table No.3.

Tablet No. 4: Showing different Evaluation parameters of Granules of F1 & F2

Sr. no.	Evaluation parameters		Formulation (F1)		Formulation (F2)		
1.	Physical Appearance	Color	Brownish-black		Brownish		
		Odour	Sweetish		Sweetish		
		Taste	Sweet		Sweet		
		Shape	Round		Round		
		Flavor	Vanilla		Vanilla		
		Size	Diameter (cm)	1		1	
			Width (cm)	0.5		0.5	
2.	Acceptance Test	Volunteers	Flavor	Sweetness	Flavor	Sweetness	
		Brisha	+++	+++	+++	+++	
		Shikha	+++	+++	+++	+++	
		Poonam	++	++	---	++	
		Anu	---	+++	++	+++	
		Shivani	+++	+++	+++	+++	
3.	Weight Variation (gm)		0.028		0.084		
4.	Friability (%)		0.32		1.66		
5.	Hardness Test (kg/cm ²)		4.25		4.00		
6.	Thickness Test (mm)		0.00633		0.00633		
7.	Disintegration Time (minutes)		7:30		6:50		
			7:35		7:00		
			7:36		7:15		

These are some evaluation parameters that are carried out for the tablets that are manufactured for dengue.

4.2 Discussion

The preparation, evaluation and submission of the tables were done successfully. Three batches were prepared that is, one is trial batch and others are drug containing batch F1 and F2. There were many differences that are seen in the both of the formula of formulation F1 and F2. As in formula of both the batches to increase their bulkiness different diluents are used. In F1, Lactose is used while in F2, Calcium Carbonate is used. In formula also there is difference between the super disintegrating agent i.e., Sodium Starch Glycolate (SSG) in both formulations, the amount of SSG is increased in F2. In F1, the use of Sodium Bicarbonate is done that will decrease the tablet disintegration time. Papaya leaves extract is used to prepare the formulation because due to Dengue the Platelet count in patient is decreased, it will increase the count. Amla fruit extract is used to increase the immunity of the patient. The sweetening agents are also used to mask the bad taste. Also the flavoring agent is used which will mask the bad odour too. The difference between the evaluation parameters of Granules is also seen. Every evaluation parameter of F1 is Greater than the F2. The evaluation parameters of the tablets also have difference in both F1 and F2. As in physical appearance, tablets of F1 is having brownish-black colour and in F2, tablets are having brownish color. Acceptability test of both formulations indicates that they can be easily taken by patients. Weight variation and friability of F1 is lesser than F2. Thicknesses of the tablets of both formulations are same. Hardness and disintegration time of the F2 is lesser than as that of F1.

5 CONCLUSION

From all the results obtained and discussion observed, the conclusion is obtained that the tablets were prepared for the Dengue was successful and that can be used for the treatment of the disease. In the present study the extract of leaves of *Carica papaya* was used and fruits of *Embelica officinalis* were used for making tablets. Extracts of leaves of *Carica papaya* was obtained by cold extraction and through maceration. Extract of fruits of *Embelica officinalis* was obtained by maceration process. These extracts were impregnated with the excipients like diluents, binding agents, lubricants to make granules. These granules were used for making tablets of desired size and shape. Recent studies have



shown in the present study herbal extract of leaves of papaya has beneficial effect as an anti-inflammatory agent, for its wound healing properties anti-tumor as well as immunomodulatory effects and as an antioxidant. Amla fruit is a rich natural source of vitamin C (Ascorbic acid) and Contains 600-750 mg per 100 g of the fresh pulp. Also it is rich in minerals matters like phosphorus, iron and calcium. It contain appreciable amount of pectin. It is found that the vitamin content of dried fruits is not lost considerably. The two plants extract that have been used for the preparation the tablets are said to be useful in the treatment of the disease. As, one extract i.e., Papaya leaves extract is used to increase the platelet count in body and the other i.e., Amla fruit extract is used to increase the immunity of the patient.

Present study may be used for as a novel approach for the treatment of Dengue infections. Tablets were prepared successfully from the plant extract of *Carica papaya* and *Embelica officinalis* with appropriate ingredients. Tablets were evaluated for different parameters showed satisfactory results. Results showed that F1 formulation showed better Disintegration time as compared to F2 formulation with other satisfactory parameters.

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