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Original Research Article

Formulation and evaluation of guava leaf extract gel for mouth ulcer management

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ABSTRACT

Background: The highlight of this study was preparation of microparticles using the extract of guava leaves which led to novel drug delivery of the herbal extract.
Aim: The aim of the study was to formulate a microparticles loaded gel for management of mouth ulcer.
Materials and Methods: The microparticles were prepared by solvent evaporation method using the polymer, oil and liquid phase. Then the preparation of gel base was done with incorporation of microparticles. The evaluation of the microparticles and the gel was done.
Results and Discussion: This study is an effort to develop a herbal gel for mouth ulcers offering better compatibility and lesser discomfort. We used Psidium guajava leaf extract microparticles for the preparation of gel. The gel formulations prepared were transparent and homogeneous within the pH range of 6 to 6.8. The formulation showed acceptable spreadability, extrudability and rheological properties. The formulation showed antibacterial effect against Staphylococcus aureus and E coli. Therefore, developed formulations have the potential to treat mouth ulcers.
Conclusion: The Psidium gujava leaf extract microparticles loaded gel is a good mucoadhesive gel for mouth ulcer management. Therefore, herbal ingredients can be used for novel drug delivery and make it safe for administration with lesser risk of adverse reactions.

1. Introduction

Mouth ulcers are yellowish or white depression with red margination in the mucus lining of the mouth cavity, characterized by inflammation and pain.[1] Synthetic and semi-synthetic medicaments are suggested to treat mouth ulcers like antibiotics and antiseptics, local anesthetics, local analgesics, steroidal and non-steroidal anti-inflammatory drugs. Topical steroids are the most frequently used treatments but they have some serious adverse effects on the continuous application like adrenal insufficiency, immunosuppression, osteoporosis, hyperglycemia, gastrointestinal disturbance, etc.[2] The use of plant-based medications is gaining huge popularity due to better patient compliance and because of the side effects and the adverse effects of synthetic chemicals. Several studies have reported, the use of plant parts or extracts such rhizome of *Curcuma longa* **,** leaves of *Psidium guajava,* leaves of Piper betel, *Zingiber Officinale,* in the form of mouth wash, paste, or mucoadhesive gels for the treatment of oral ulcers.[3]

Psidium guajava is an evergreen shrub that belongs to the Myrtaceae family.[4] Alkaloids, carotenoids, phenols, Flavonoids are found in this plant especially quercetin is found as the major component. It demonstrated several activities including antibacterial, anti-diarrhoeal, anti-ulcer properties.[5] Guava leaves contain essential oils such as

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isopropyl alcohol, menthol, α-pinene, terphenyl acetate, limonene, β-pinene, caryophyllene, and β-bisabolene. Oleanolic acid is also found in the guava leaves.[6] Leaves have a high content of limonene about 42.1% and caryophyllene, about 21.3%. Leaves of guava have a lot of volatile compounds.[7] The present investigation deals with the gel formulation using ethanolic extract of guava leaves for the treatment of mouth ulcer.

2. Materials and Methods

2.1. Materials

The raw materials including the polymers, excipients and chemicals required for the present work were procured from different sources.

2.2. Preparation of psidium guajava leaves extract

The soxhlet extractor was set up to obtain the ethanolic extract of *Psidium guajava* leaves.

100gm of coarsely powdered *Psidium guajava* leaves were loaded into the thimble and the thimble was placed into the main chamber of soxhlet extractor. 500ml of ethanol was added to round bottom flask and placed onto a heating mantle. The soxhlet extractor was attached to the round bottom flask. A reflux condenser was attached above the extractor, with a cold water inlet attached at the lower end and the outlet above. The solvent was heated to reflux and extract, till the extract coming out was colorless.

2.3. Preparation of microparticles

Psidium guajava leaf extract microparticles were prepared by emulsion solvent diffusion evaporation technique. Accurately weighed quantity of *Psidium guajava* leaf extract, Ethylcellulose, HPMC were taken and acetone was added with stirring to avoid aggregation. The organic phase was transferred slowly into the oil phase containing coconut oil, castor oil and Span 80 while continuous magnetic stirring at 1000 rpm for 60 min to remove the organic solvent. Subsequently, samples were filtered and microparticles were dried.

2.4. Preparation of microparticles loaded gel

Weighed quantity of Carbopol 930 and HPMC was dispersed in distilled water with continuous stirring. Methyl paraben, propyl paraben and *polyethylene glycol 400 were added* and mixed properly, then the volume was made upto 100 ml with distilled water. Finally ingredients, microparticles were mixed properly to the Carbopol 930 gel with continuous stirring and tri-ethanolamine was added drop wise to the formulation for adjustment of required pH (6.8-7) and to obtain the gel at required consistency. The Table 1 shows amount of ingredients added for different batches.

Table 1: Formulation of gel

Ingredients	**F1**	**F2**	**F3**	**F4**	**F5**	**F6**
Carbopol 930	0.1	0.15	0.2	0.25	0.25	-
HPMC	-	0.3	0.2	0.5	0.1	0.5
Methyl Paraben	0.0007	0.0007	0.0007	0.0007	0.0007	0.0007
Propyl Paraben	0.002	0.002	0.002	0.002	0.002	0.002
Triethanolamine	2.5	2.5	2.5	2.5	2.5	2.5
Microparticles	0.25	0.25	0.25	0.25	0.25	0.25
Ditlled water	QS	QS	QS	QS	QS	QS

2.5. Evaluation of microparticles loaded gel

2.5.1. Visual inspection

The prepared gel was observed for color, odor, and appearance.

2.5.2. PH

The pH meter was used to check the pH. About 0.5 gm of the gel was weighed and dissolved in 50.0 ml of distilled water and its pH was measured.[8]

2.5.3. Viscosity

The viscosity of gel was studied using Brookefield Viscometer. The sample (50 g) was placed in a beaker and was allowed to equilibrate for 5 min before measuring the digital reading using a spindle No. 63 at 50 rpm. At this speed, the corresponding reading on the viscometer was noted.[9]

2.5.4. Spreadability

Spreadability is expressed in terms of time in seconds taken by two slides to slip off from gel that is placed in between the slides under the direction of a certain load. Lesser the time taken to separate the slide better is the spreadability.[10] Spreadability is calculated by using the formula:

$S = M \times L / T$

Where M = weight tied to upper slide

L = length of glass slides

T = time taken to separate the slides

The spredability test showed that F4 batch showed good spreadability compared to other batches as mentioned in the Table 2.

Table 2: Spreadability test

FormulationM (gm)		L (cm)	T (Sec)	S = ML/T
F1	20	2	12.5	3.2
F2	20	1.7	10	3.4
F3	20	1.5	10	3
F4	20	2.6	10	5.2
F5	20	2.3	10	4.6
F6	20	1	10	2

2.5.5. Permeation studies procedure

A cellophane membrane, (soaked in glycerin 12 hours before use) was fixed to one end of the two side open ended cylinder (donor compartment). The sample was taken in a cellophane membrane and it was immersed in a beaker containing 100 ml of phosphate buffer pH 6.8 (receptor compartment). The entire surface of the cellophane membrane was in contact with the receptor compartment which was agitated using magnetic stirrer rotated at 100 rpm and a temperature of 37°C±2°C was maintained. 1 ml of sample from the receptor compartment was taken at every 5 minutes interval for 30 minutes, then at 45 and 60 min. and then every 30 minutes interval up to 6 hrs. Same amount of pH 6.8 phosphate buffer was replaced. The samples were diluted with pH 6.8 phosphate buffer. The absorbance of the resulting solution was then measured at 216 nm against phosphate buffer solution pH 6.8 as blank using Systronics 2201 UV double beam spectrophotometer.

2.5.6. Agar well diffusion method

Nutrient agar medium was prepared and sterilized by autoclaving at 121°C for 15 minutes. The two agar plates were prepared and labeled. The nutrient agar after sterilization was poured into the two plates and allowed to solidify. After solidification the culture of *Staphylococcus aureus* and *Escherichia coli* were applied on each plate. Then the wells were prepared using cork borer. Then the samples were poured in respective wells using micropipette. The plates were incubated at 37°C for 24 hours.

3. Results

3.1. Physical evaluation of formulated gel

The physical evaluation of colour, odour, texture and appearance of the prepared gel was shown in Table 3. The color of all the batches was yellowish to pale yellow due to the guava leaf extract microparticles as the extract contains tannins. The odour was characteristic and the texture of the gel was smooth.

3.2. Viscosity and pH

Viscosities of the formulations were measured by Brookfield viscometer. The viscosity of gel are shown in Table 4. The formulation F1, F4, F5 batches showed viscocity between 2100- 2300cp, F2, F3, F6 show 2300 – 2600cp. The pH of the formulations was measured using digital pH meter in the range of 6 – 6.8. The F4 batch showed viscosity 2191cp and pH 6.8 which was found to be optimum.

3.3. Permeation studies

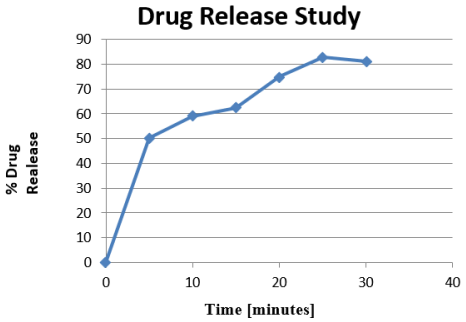

Fig. 1: In-vitro release study of optimized batch

Table 3: Physical evaluation

Formulation	Color	Odour	Texture
F1	yellowish	Characteristic	Smooth
F2	Pale yellow	Characteristic	Smooth
F3	Pale yellow	Characteristic	Smooth
F4	Pale yellow	Characteristic	Smooth
F5	Pale yellow	Characteristic	Smooth
F6	Pale yellow	Characteristic	Smooth

Table 4: Viscosity and pH of formulated batches

Formulation	Viscosity (cp)	pH
F1	2200	6.6
F2	2523	6.2
F3	2326	6.2
F4	2191	6.8
F5	2258	6.5
F6	2359	6.3

3.4. Antibacterial activity of formulated gel

The antibacterial activity of Psidium guajava leaves extract microparticles loaded gel were determined in this study and zone of inhibition was compared with standard.

The anti-bacterial activity was carried out against Staphylococcus areus and Ecoli. The anti-bacterial activity was observed against both the strains and was more evident against E coli as seen in the Figure 2.

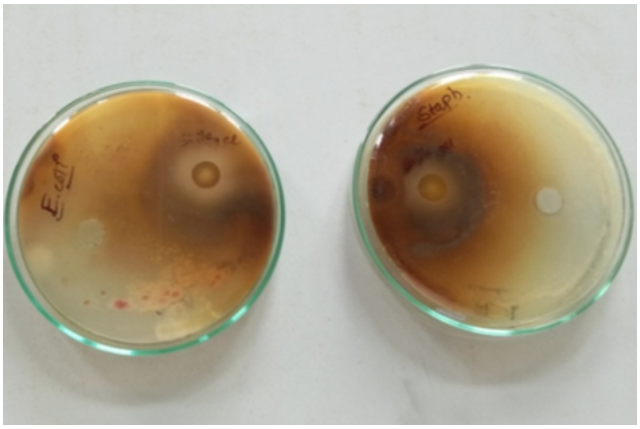

Fig. 2: Antibacterial activity of optimized batch

4. Discussion

Aphthous ulcer is oral disease characterized by one or several recurrent ulcers on oral mucosa. The aim of the treatment is to reduce the duration of ulcers. The recommended treatment often includes topical steroids that may have side effects on continuous application. The herbal medications have been widely used for different oral diseases. Due to the anti-ulcer, anti-microbial, anti-oxidant and healing properties, the *Psidium guajava* leaves can prove effective in the treatment of oral ulcers. We decided to make use of these effects to design a suitable, stable and easily accessible formulation of this herb.

In this study the *Psidium guajava* leaf extract microparticles loaded gels were prepared as mucoadhesive formulation. This formulation may prove very effective for the treatment of oral ulcers as it offers the ease of application, good distribution and ability of adhesion to remain on the oral mucosa for a long enough time to release the drug. To prepare the microparticle loaded gel, polymers like Carbopol, HPMC were used. These polymers are water soluble and useful in pharmaceutical industries. Many gels, specially the water-based ones are susceptible to microbial growth and hence the use of a suitable preservative decreases the chance of microbial contamination and the change in formulation properties. In this study, methyl and propyl paraben were used as preservatives.

In release studies with franz cell diffusion method, are as demonstrated in Figure 1.

5. Conclusion

Psidium guajava, a plant well-studied in terms of safety and a multitude of medicinal activities has been explored for the formulation and characterization of oral gel for the treatment of mouth ulcers. Different batches of microparticles were tried and evaluated. The microparticles with different drug-polymer ratio and polymer-polymer ratio were tried and the optimum batch was evaluated. The particle size, DSC, FT-IR, and X-Ray diffraction studies were carried out. The microparticles were found to have been useful for the release of drug at a controlled rate for a prolonged duration. The microparticle-loaded gel was formulated with Carbopol, HPMC as viscosity enhancers and gelling agents. The polymers were found to

be compatible with the *Psidium guajava* leaf extract. The varying concentration of polymers was found to influence the gel parameters like viscosity and spreadability. The attempt was made to combine the traditional knowledge of herbal medicines with the conventional drug delivery system by formulating *Psidium guajava* leaf extract-loaded gel. Among the six batches formulated, the results of the F4 batch were satisfactory making it a most optimized batch with significant antibacterial properties. Hence, it can be concluded that the *Psidium guajava* leaf extract microparticles loaded gel is ideal for mouth ulcers.

Further studies including more extensive quantitative microbiological and in vivo studies are necessary to take the formulation from the laboratory to the human trials.

6. Abrevations

1. RPM – Rotations Per Min
2. Min – Minutes
3. Cp – Centipoises
4. HPMC – Hydroxypropyl Methyl Cellulose
5. DSC – Differential Scanning Calorimetry
6. FT-IR – Fourier Transformer Infrared

7. Source of Funding

None.

8. Conflict of Interest

None.

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