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Original Article

Formulation and development of Carica papaya leaf extract loaded proniosomes: Dose reduction and enhanced absorption

Dr. Harshada I. Patil[a*], Anjali A. Patil [a], Deepika D. Patil [a], Kiran A. Wadkar[b] Archana V.Vanjari[c]

[*a] Department of Pharmaceutics, Dr. Shivajirao Kadam College of Pharmacy, KasbeDigraj, 416 305 Sangli,Maharashtra, India.
[b] Department of Pharmacognosy, Dr. Shivajirao Kadam College of Pharmacy, KasbeDigraj, 416 305 Sangli,Maharashtra, India.
[c]Department of Pharmacology, Dr. Shivajirao Kadam College of Pharmacy, KasbeDigraj, 416 305 Sangli,Maharashtra, India.

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ABSTRACT

In traditional medicine, Carica papaya leaf extract has been used for a considerable period of time to alleviate the fever in a variety of infectious diseases, such as dengue, malaria and chikungunya. The present work was carried out to deliver carica papaya leaf extract through proniosomes In this study, the leaf extract of C. papaya was encapsulated in proniosomes to increase its absorption. Sonication, a green extraction technology, was used to extract the leaf extract of C. papaya. Proniosomes powder was prepared with the slurry method, with a mixture of non-ionic surfactants, i.e. Span 60, and cholesterol as a bilayer stabilizer. The optimized formula F3 was loaded with different concentrations (200, 300, 400 and 500 mg) of C. papaya extract to investigate the effect of the drug load on the percentage release of the drug. The entrapment efficiency, particle size, zeta potential and in-vitro dissolution studies were evaluated. The results showed that the niosome derived from the proniosomes were of size 250.4 nm, with a Zeta potential of -28.2 mV. The encapsulation efficiency was 97.32%. Conclusion: The formulated proniosomes shows inceased dissolution hence, the dosage requirement has been reduced due to enhanced bioavailability of the drug

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Introduction

A member of the Caricaceae family, papaya (C. papaya Linn.) is highly valued for its nutritional and medicinal qualities worldwide. Since ancient times, the many parts of the papaya plant have been utilised for medicinal purposes. Plants have been utilised for medical purposes since ancient times, and roughly 80% of the world's population directly receives their primary healthcare from plants[1].

Approximately 40,000 plant species are known to have therapeutic qualities in India[2]. Natural compounds isolated from these plants have shown significant advantages over synthetic drugs, such as cost-effectiveness, ease of use, and minimal side effects [3]. As numerous studies have shown, there is a wide range of diseases that can be controlled using medicinal plants. Worldwide, people have utilised carica papaya Linn., a plant native to South America and Central America that is frequently produced in India, for its therapeutic benefits [4]. The papaya plant is a perennial tree, usually unbranched, with a smooth stem and long leaf segments with 5-6 lobes. It can rise to 20 metres [5]. As a tropical species, Carica papaya (papaw or papaya) is known for its use of all its parts. The plant continues to develop as a tropical species throughout the winter, even though growth slows and fruit production stops during the coldest months [6].

Corresponding author:

Dr. Harshada I. Patil
Department of Pharmaceutics,
Dr. Shivajirao Kadam College of Pharmacy,
KasbeDigraj, 416 305, Sangli, Maharashtra, India.

Email: drharshadapatilskcp@gmail.com

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In Indonesia, papaya export demand comes from Germany, Hong Kong, Japan, Malaysia, Singapore, Taiwan, and the United States. Export volumes remained high between 2009 and 2020 [7]. Dengue is a severe viral disease transmitted by arthropods that affects predominantly tropical regions and can cause both morbidity and mortality in humans. According to a World Health Organization (WHO) study, dengue is affecting 40% of the world's population [8].

Recently, papaya leaf juice has become popular among patients with dengue, as the leaf juice increases platelet count. Based on clinical research, doctors recommend patients to take fresh papaya juice to treat dengue. However, daily fresh juice extraction and bitterness of the juice are the main disadvantages of treatment. In addition, the dosage of the tablet is about 1 gm (concentrated leaf extract) and frequency is three times a day. Papaya leaf extracts have been provided as supplements for the world market under the names Rochway, Iowa Select Herb, Herb Papaya and Sido Muncul Herb, but are produced by microfiltration, fermentation, and liquid extraction [9].

Novel drug delivery methods have arisen, incorporating many routes of administration to accomplish accurate and controlled drug distribution. One such mechanism that helps to decrease toxicity through selective absorption and extending the time a drug is in the systemic circulation is drug encapsulation in vesicles. Numerous vesicular drug delivery methods, including liposomes, niosomes, proliposomes, and proniosomes, have been created based on this technology. [10].

Like liposomes, proniosomes are a modern lipid-based delivery system that can be used to encapsulate many phytoconstituents with polyphenol bases to improve their absorption when administered in the context of herbal delivery systems. Proniosomes, also known as dry niosomes, have

several qualities that make them a promising industrial product. In this study, proniosome formulations were prepared using the slurry method to encapsulate different dosages of extracts, and the optimal formulation was selected from them.

2.Materials and Methods

Materials

Maltodextrin, Span 20, Span 60 and Cholesterol were obtained from LOBA CHEME PVT. Ltd, Ethanol and chloroform from Fine Chemical Co. Ltd

Plant Materials

Fresh leaves of Carica papaya were collected during February. Fresh leaves were manually isolated from the aerial parts, washed with water and wiped with a clean cloth to remove dust.

2.1 Preparation of Extract

Extraction was conducted with slight modification [11],50 g of fresh leaves are directly ground in mixer with 50 ml of water, then 20 ml of extract, is diluted with ethanol in 1:1 ratio (v/v). The mixture kept in an Ultrasonicator at 37 ºC for 10 minutes. To create a concentrated extract, the resulting solution is next evaporated in a water bath that is kept at a temperature of 70 ºC.

2.2 Formulation of Proniosomes

Proniosomes were formulated by modifying the non-ionic surfactant and cholesterol concentration, incorporating maltodextrin as a carrier by slurry method.

Slurry method

Surfactants and membrane stabilizers solution was preparedwith a ratio (2:1) of chloroform: ethanol solution. 2 ml of the stock solution and 200 mg extract of carica papaya leaves were added into a 100 ml round bottom flask containing the carrier material, namely maltodextrin (1g). The flask is mounted on a rota evaporator, to evaporates solvents at 60-80 rpm, the temperature is 45°C, and the pressure is reduced gradually to 600 mm Hg, till the mass in the flask becomes a dry and good flowing material.

These materials were dehydrated overnight in a desiccator at room temperature under vacuum. This dry material is known as proniosome. Proniosomes, the end product, were kept refrigerated in a container that was securely closed until they were evaluated further[12, 13]. The composition of the proniosome formulation containing various concentrations of Carica papaya leaf extract load is shown in Table 2.

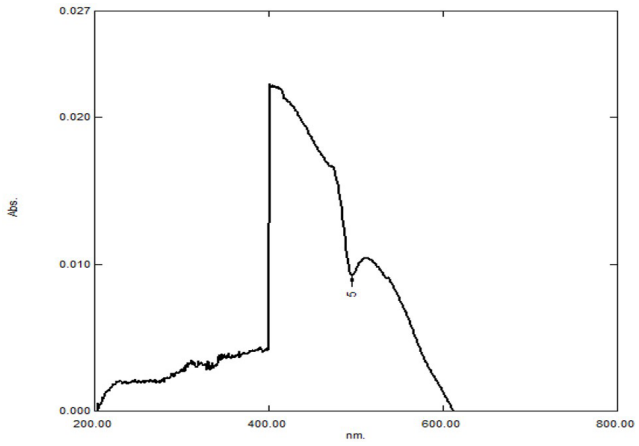
Table 1 The composition of proniosomes formulation loaded with Carica papaya leaf extract

Sr. No	Formula-tion Batch	Tween 80 (mg)	Span 60 (mg)	Choles-terol (mg)	Carica papaya leaf extract
1	F1	180	-	20	200 mg
2	F2	180	180	20	200 mg
3	F3	-	180	20	200 mg
4	F4	-	125	20	200 mg
5	F5	125	-	20	200 mg

2.3 Characterization

2.3.1 Calibration curve of Carica papaya leaf extract

To create the main stock solution (1.0 mg/ml or 1000 µg/ml), an exact weight of 100 mg of Carica papaya leaf extract was added into the volumetric flask (100 ml). A little amount of ethanol was added to dissolve, and diluted with pH 6.8 phosphate buffer solution to 100 ml. To obtain 100 µg/ml of Carica papaya extract, 1 ml from the stock solution (1 mg/ml) was diluted with phosphate bufferpH 6.8 in a 10 ml volumetric flask. A series of dilutions are carried out using aliquots of the stock solution (100 µg/ml) to achieve the final concentration of 200, 400, 600, 800, and 1000 µg/ml. These samples' absorption was determined using a UV-visible spectrophotometer at 401 nm. Papaya leaf extract concentrations from unknown specimens were determined using standard graphs and straight-line equations derived from regression analysis[14,15].



2.3.2 Entrapment efficiency

To calculate the entrapment efficiency (EE, %) of the Carica papaya leaf extract in the resultant niosomes, 50 millilitres of pH 6.8 phosphate buffer were used to dissolve the proniosomal powder.The dispersion was centrifuged at 10,000 rpm and filtered through whatman filter paper. The collected supernatant was analyzed by UV-visible spectroscopy at 401 nm. The entrapment efficiency (EE, %) was determined by below formula [16].
Entrapment efficiency= (total drug– unentrapped drug /total drug) *100

2.3.3 Determination particle size and zeta potential

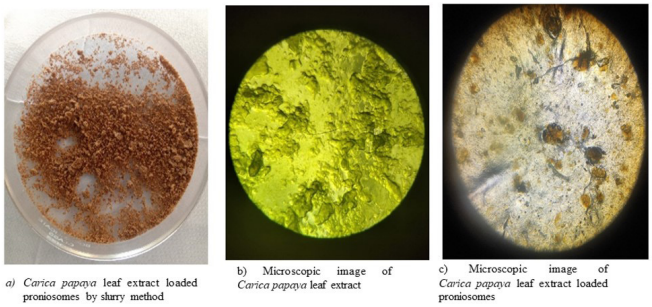
The average size, distribution of particles, and Zeta potential (ZP) of proniosomes was determined by photon correlation spectroscopy using HORIBA SZ-100 for Windows [Z Type] Ver2.40. The sample material was diluted at a corresponding concentration 1:10 (w/v) with phosphate buffer of pH 6.8. The size analysis was carried out at 25°C and the detection angle was 90°C. The size, polydispersity index and average zeta potential values (SD) of proniosomes were obtained from the instrument [17].

2.3.4 In vitro release study

In vitrorelease study of proniosomes powder (200 mg, 300 mg, 400 mg and 500 mg), filled in capsules(size 0) was conducted in USP type I (Basket) apparatus consisting phosphate buffer of pH 6.8. The dissolution medium (900 ml) was kept at temperature37 ± 0.5 °Cat 50 rpm throughout the experiment. At regular time intervals (5, 10, 20, 30, 45, 60, 90, 120, 150, 180, 210, 240 and up to 600 minutes). Each time, 5 ml sample was taken out and replaced with fresh dissolution medium (buffer solution) to maintain sink condition. The amount of drug in samples were analysed by UV spectrophotometer [18].

3.Results and discussion

3.1 Calibration curve of Carica papaya leaf extract



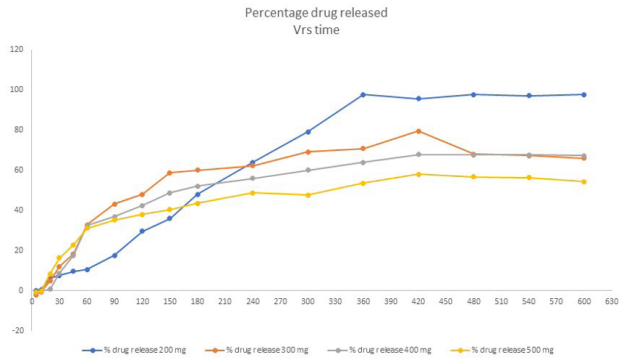
a) *Carica papaya* leaf extract loaded proniosomes by slurry method

b) Microscopic image of *Carica papaya* leaf extract

c) Microscopic image of *Carica papaya* leaf extract loaded proniosomes

Figure.2 Carica papaya leaf extract loaded proniosomes and microscopic images of Carica papaya leaf extract and Carica papaya leaf extract loaded proniosomes

The Carica papaya leaf extract calibration curve was plotted at λmax 401 nm, phosphate buffer pH 6.8 was used as blank. The UV absorption spectra of Carica papaya leaf extract is shown in Figure 1



3.2 Formulation of proniosomes

The main ingredients of the proniosomes utilised in the formulation are non-ionic surfactants, which function as carriers or coating materials, membrane stabilisers, and permeability enhancers. One of the carriers that facilitates the flexible inclusion of surfactants and other substance in varying ratios is maltodextrin, which is utilised in the proniosome manufacturing process [19].

The non-hygroscopic nature of maltodextrin, its medication compatibility, and its additional benefits are among its benefits. Ultimately, maltodextrin's high surface and intact shape allow for the coating of the surfactant as a thin coating, which leads to effective rehydration. When the proniosome system is hydrated into gastric fluids, it can generate stable niosomes with high entrapment efficiency, which will yield the most advantage.

Structural lipids and cholesterol stabilise the bilayered membrane, highlighting drug encapsulation and preventing leakage. Despite being an additional option to cholesterol for membrane stabilisation, lecithin is not as commonly utilised as cholesterol due to its lower stability [19].

The vesicular systems of C. papaya leaf extract have been successfully prepared with an earlier report method [13], as shown in figure 2. Proniosomal systems provide a suitable and stable method of administration of liposomes and niosome vesicles. Proniosomal system has highest dose accuracy and flexibility in the management of solid dosage forms.

In addition, an appropriate inert carrier (maltodextrin) can increase the flowability of the formulation. Ethanol was selected as a solvent because of the high solubility of lipids in this mixture, and because ethanol is less toxic than methanol. Chloroform was added to increase the boiling point and thermal properties of the solution. There is no need to totally remove the solvent from the ethanol formulation by vacuum drying. The different types of spans have the similar polar group having different alkyl chains.

The highest encapsulation percentage has been detected, in spans that has higher phase transition temperature. Proniosomes with higher phase transition temperatures (Tc) have been shown to have greater entrapment efficiencies (EE) and fewer likely-to-leak drug from vesicles.

This is because lipophilic drugs can be entirely entrapped in a homogenous bilayer structure formed by a higher Tc. Lower phase transition temperatures are reported for span 80i.e -120C [20], whereas for span 20, 40, and 60 the phase transition temperatures were 16, 42, and 52 0C, respectively.

Span 60 was selected in current study, due to higher phase transition temperature (52°C)to enable stable vesicles, as it modulates membrane bilayers.

3.3 Entrapment Efficacy

The absorbance of filtrate was analyzed at 401 nm on UV-Visible spectrometry. The concentration of the non-trapped drug was calculated using the standard graph equation for Carica Papaya Leaf Extract. The entrapment efficacy of proniosome powder (F3) of Carica Papaya Leaf Extract was found to be ±97.32%. Whereas entrapment efficiency for F1, F2, F4, F5 was found to be 80 %, 87 %, 94 %, 75 % respectively.

3.4 Vesicle size and Zeta Potential

Vesicle size and Zeta potential has significant role in vesicular systems. It is well known that cholesterol concentration can affect these properties. In our investigations, we observed that F3 formulations that use Span 60 as a surfactant showed a small size and increased potential of zeta. In particular, the zeta potential of the proniosomal formula was measured at -28.2 mV, while the size of the vesicles was found to be 250.4 nm.

3.5 In vitro release study

The complicated process of dissolving solids is affected by solubility, surface area, crystal habit, humidity, and particle size, etc. Figure 3 shows the dissolution profiles of standard Carica Papaya leaf extracts and proniosome formulations in phosphate buffer pH 6.8. The optimized formula F3 was loaded at different concentrations (200, 300, 400 and 500 mg). Optimized proniosomes formulations showed increased drug dissolution. In the present study, we found that the amount of drugs loaded was crucial to determining the percentage of drug release.

As shown in Figure 3, when the drug was loaded with 200 mg, about 97.6 % of the drug was released after 10 hours, while as the drug loading increased from 200 mg to 500 mg, the amount of the drug released decreased considerably. The results of the dissolution study are confirmed by the fact that in the delivery of vesicular drugs, the drug itself is formulated with lipids to produce vesicles, which further promotes the efficiency of phytosomal capture. As a result, the dosage requirement has been reduced due to enhanced bioavailability of the drug.

4.Conclusion

Proniosomes are surfactant-coated, water-soluble carrier particles that can be hydrated right before usage to produce an aqueous noisome dispersion. Compared to liposomes and noisomes, they are more stable. They can include both lipophilic and hydrophilic medications. They have proven to be difficult drug delivery vehicles.

Due to the straightforward and affordable process for scaling up production, it has evolved into a viable dosage form for sustained drug delivery. Proniosomes have made it possible to resolve all stability issues with liposomes and niosomes, including fusion and aggregation during storage.

It was observed that proniosomes equivalent to 200 mg of extract shows plateau graph and prolonged release than 500 mg of extract. According to above result we conclude that when we increase the dose respectively decreases the drug release, because poor adhesion in matrix of components of proniosomes.

Declaration of interest

The authors report no conflicts of interest.

5.References

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