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Formulation and Evaluation of Flavanosomes Encapsulated with Sesamol and Curcumin

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ABSTRACT

The objective of the present study was to prepare flavonosomes loaded with sesamol and curcumin in order to improve the bioavailability of the flavonoids. The flavonosomes loaded with sesamol and curcumin were prepared using bulk co-loading method using lecithin as the lipid molecule. The particle size of the flavonosomes was determined using zeta sizer and ranged from 501.42 nm to 167.08 nm. The entrapment efficiency of F4 has been calculated to be 93.12%. The flavonosome F4 was studied for release of the entrapped flavonoids by dialysis method. After the first hour, the entrapped flavonoids released in a steady manner from the flavonosome depicting and almost complete release (88.27% for sesamol and 93.66% for curcumin) from the formulation. The best formulation with respect to particle size and anti-oxidant action was F4 that contained 4:1 ratio of lecithin: flavonoids. DPPH radical scavenging assay was used to determine the antioxidant action of the individual flavonoids and the flavonosome formulation. It was found that the formulation F4 was having higher antioxidant activity in comparison to sesamol and curcumin. The IC_{50} of sesamol, curcumin and flavonosome were found to be 233.76 µg/mL, 181.87 µg/mL and 164.30 µg/mL respectively. The results led to conclude that the prepared flavonosomes present better stability, prolonged release and good anti-oxidant activity

Keywords: *Flavonosome, curcumin, sesamol, anti-oxidant, DPPH*

1. INTRODUCTION

The foundation for treating human diseases is the identification of novel chemical entities, and natural items, including minerals, plants, and animals, play a key role in this process. Because of their enormous structural variety, natural products provide a good starting point for research into potential novel medicines, which could have applications in areas such as immunosuppression, neurological disorders, cancer, and infections.[1, 2] Complex formulations including several herbal and mineral components are widely used in Ayurvedic medicine. These formulations are created over the course of several days. Individual, non-toxic herbs typically have dosage recommendations ranging from 1 to 6 g/day whether taken as a powder, tincture, or decoction.[3]

Because of their enormous molecular size, which prevents water-soluble phytochemicals like polyphenols and flavonoids from being absorbed by passive diffusion, and because of their poor lipid solubility, which severely limits their passage across the lipid-rich biological membranes, these compounds have low bioavailability and are thus poorly absorbed in the body. To greatly alter their bioavailability and absorption, phytosomes construct lipid-compatible molecular complexes by incorporating water-soluble phytochemicals and medicinal plant active components into phospholipids. High stability, high carrier capacity, the ability to incorporate phytoconstituents, and the feasibility of routes of administration are the key technological advantages of phytosomes as drug carriers. One possible solution to the problem of patients not following their treatment plans is the phytosome, which has the ability to increase medication bioavailability while decreasing dosage frequency.[4]

The bioavailability of water-soluble phytoconstituents (such as tannins, flavonoids, terpenoids, etc.) is reduced because of their poor lipid solubility and miscibility, as well as their large molecular size with multiple rings that prevents passive diffusion absorption.[5, 6] Incorporating various polyphenolic secondary metabolites found in plants and frequently ingested by humans, flavanosomes are specialized phytosomes that serve as a delivery method for flavonoids. Research has demonstrated that flavanosomes modulate cellular enzyme functioning and possess antioxidant, anti-inflammatory, and anticancer characteristics. The immune system, cardiovascular health, and aging could all benefit from flavanosomes.

In this work, we have prepared and optimized flavonosomes encapsulating curcumin and sesamol and evaluated the betterment of antioxidant potential of the formulation

2. MATERIAL AND METHODS

Sesamol and curcumin was purchased from Yucca enterprises, Mumbai. Various chemicals and reagents used for preliminary phytochemical screening of extracts and other reagents for testing of anti-oxidant activity were purchased from CDH, SD Fine and Oxford Fine Chemicals Pvt Ltd, Mumbai.

Calibration curve of sesamol and curcumin

Following the preformulation studies[5] the calibration curve of both the flavonoids was prepared in suitable solvents. Stock solutions of curcumin containing 100 µg/mL were prepared in methanol and its aliquots were transferred in a series of 10 mL volumetric flasks in varying fractions and their volumes were made with methanol to prepare different standard dilutions (5-25 µg/mL) and absorbance at 421 nm was recorded.[6] The calibration curve of sesamol was prepared by using methanol as the solvent. 5mg sesamol was dissolved in 5 mL of the solvent and further diluted to obtain solutions of 10, 20, 30, 40 and 50 µg/mL concentration. These standard solutions were analyzed for their absorbance at 295 nm using a UV-visible spectrophotometer.[7]

Preparation of flavonosomes

The specific amount of sesamol, curcumin (Table 1) were dissolved in 10 mL acetone in an Erlenmeyer flask.[8] In another flask required quantity of soya lecithin (Table 6.1) was dissolved 10 mL of dichloromethane. The two solutions were mixed and the mixture was sonicated for 2h at room temperature. The sonicated mixture was transferred to a round bottom flask and allowed the solvent was allowed to evaporate using rotary vacuum evaporation resulting in the formation of thin film. The thin film was then dissolved using 10 mL of DCM and added dropwise into 40 mL of distilled water under moderate magnetic stirring at room temperature overnight. Consequently, the DCM phase steadily got evaporated with stirring overnight, resulting in the formation of flavonoid-loaded phytosomes.[9]

Table 1 Batch formula for flavonosome

Formulation	Lecithin : sesamol : curcumin
F1	1:0.5:05
F2	2:0.5:0.5
F3	3:0.5:0.5
F4	4:0.5:0.5
F5	5:0.5:0.5
F6	6:0.5:0.5

Particle size and size distribution

Using the autocorrelation function of the intensity of light scattered from the particles, we expected a circular type of particle using the Malvern Zeta sizer. This allowed us to compute the particle size (z-average) and size distribution of the manufactured flavonosomes.

Entrapment Efficiency

A syringe filter (0.22µm) was used to filter the flavonosome formulation (F4) that had been made. The amount of non-entrapped sesamol and curcumin was measured in the supernatant using UV spectrophotometry. A formula was used to determine the entrapment efficiency[9]:

$$Entrapment\ (\%) = \frac{Total\ Flavonoids\ Used - Nontrapped\ Flavonoids}{Total\ Drug\ Used} X100$$

***In vitro* release study**

We used dialysis to find out how much sesamol and curcumin leaked out of the flavonosomes in a controlled laboratory setting. One milligram of each flavonoid was added to a dialysis bag, which was then submerged in a solution of phosphate buffer with a pH of 7.2. The mixture was kept at 37°C and agitated with a magnetic stirrer set at 50 rpm. Fresh medium was added to the bulk at regular intervals after sampling the medium. The absorbance was measured using a UV spectrophotometer in comparison to solvent blanks to ascertain the quantity of sesamol and curcumin in the sample.[10]

***In vitro* antioxidant study**

To measure the free radical scavenging activity of the synthetic compounds, we used the stable radical DPPH to measure their hydrogen-donating or radical-scavenging capabilities. Following their synthesis in DMSO, 100 μL of test samples ranging from 100 to 500 µg/mL were mixed with 1.0 mL of DPPH solution. Methanol was then added until the final amount reached 4 mL. The absorbance of the resulting solution was measured at 517 nm using a visible spectrophotometer. Ascorbic acid was used as the reference material. The lower absorbance of the reaction mixture demonstrated that it had a higher free radical scavenging activity. According to Mishra et al. (2017), the radical scavenging activity was measured by the proportion of free radicals that the sample blocked.[11]

Results and Discussion

The preformulation studies of sesamol revealed pale brown crystalline powder with melting point 62-65°C and solubility in ethanol and methanol. The curcumin sample was pale yellow in color with melting temperature of 181-185°C and solubility in methanol and ethanol. The calibration curve of sesamol and curcumin were obtained by UV spectrophotometry in methanol (Figure 1a, b).

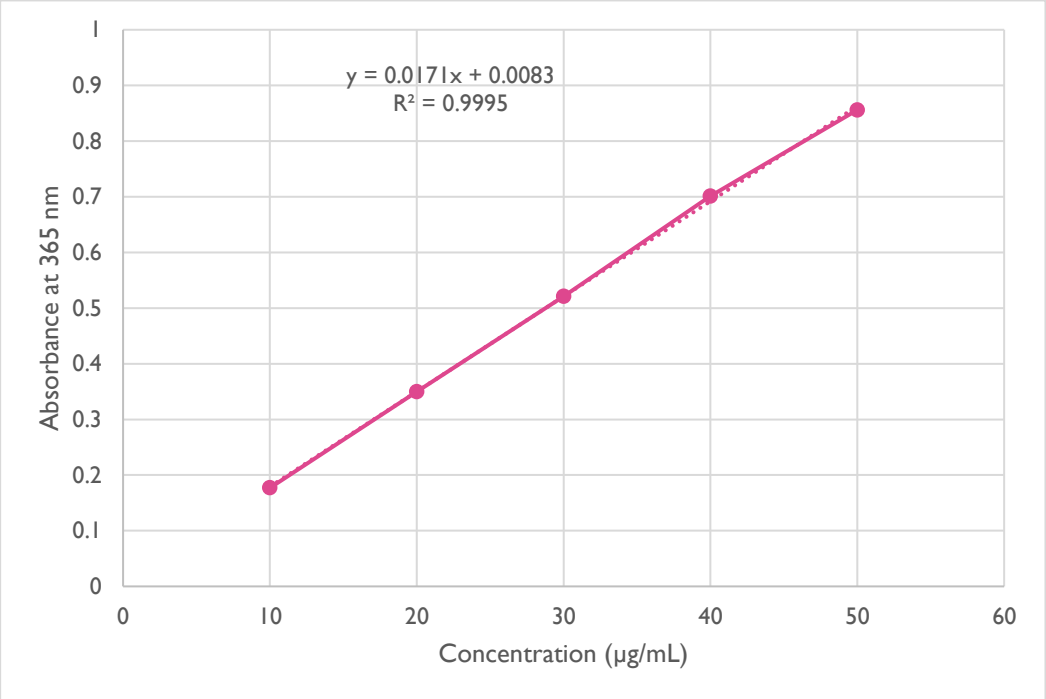

Figure 1a. Calibration curve of sesamol

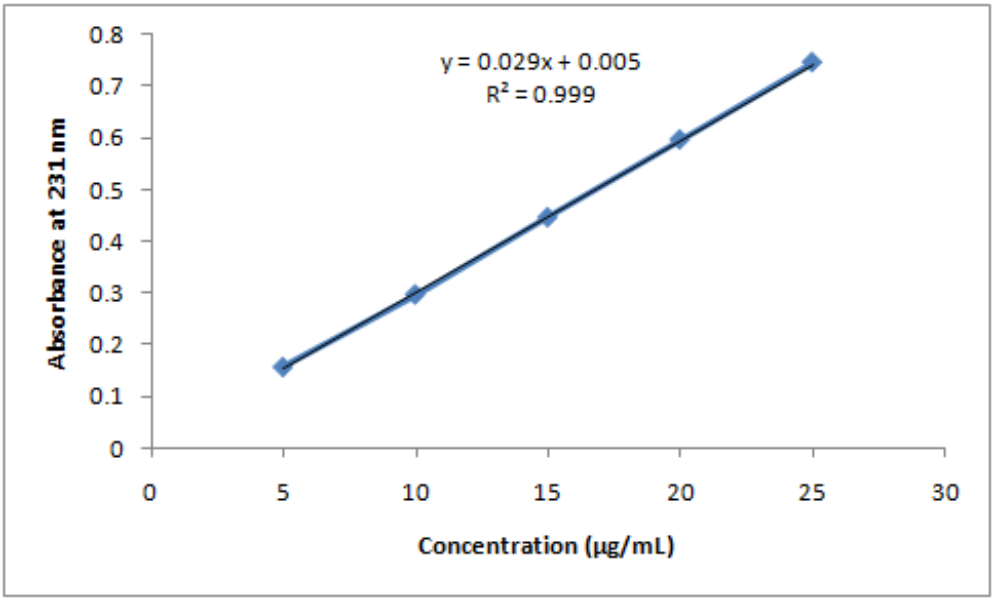

Figure 1a. Calibration curve of curcumin

Preparation of flavonosomes

The flavonosomes loaded with sesamol and curcumin were prepared using bulk co-loading method. The formulations ranged from 501.42 nm to 167.08 nm in size with a polydispersity index varying between 0.413 - 0.711 (Table 2). The entrapment efficiency of flavonosome preparation F4 was determined by measurement of the non-entrapped flavonoids and subtracting from the total flavonoids used to obtain the flavonoids entrapped in the formulation. The entrapment efficiency of F4 has been calculated to be 93.15%.

Table 2. Evaluation parameters of flavonosomes

Formulation Code	Particle Size (nm)	Polydisperisty Index (PDI)	Entrapment Efficiency (%)
F1	335.41	0.415	88.24
F2	297.13	0.549	90.11
F3	248.05	0.563	91.6
F4	167.08	0.413	93.15
F5	247.35	0.711	93.87
F6	501.42	0.608	94.01

The results indicated that increase the ratio of lipid to extract was able to reduce the particle size of the flavonosomes. Nevertheless, on increasing the ratio of lipid to extract to more than 4:1 resulted in a paradoxical increase in particle size of the flavonosomes. This could be due to fact that at lower concentration of lecithin, the dispersion could not achieve desired stability and on higher concentration of lecithin aggregation of particles might have occurred. Previously reported where the size of phytosomes loaded with drug extract decreased by increasing the lipid concentration.

***In vitro* release of flavonoids from flavonosome**

The flavonosome F4 was studied for release of the entrapped flavonoids by dialysis method. The high release of the flavonoids from the flavonosome in the first hour of the study might be due to loosely surface bound flanonoids (Figure 2). After the first hour, the entrapped flavonoids released in a steady manner from the flavonosome depicting and almost complete release (88.27 % for sesamol and 93.66 % for curcumin) from the formulation. This suggests that the formulation owing to its sustained and controlled release property might be able to improve the bioavailability of the entrapped flavonoids.

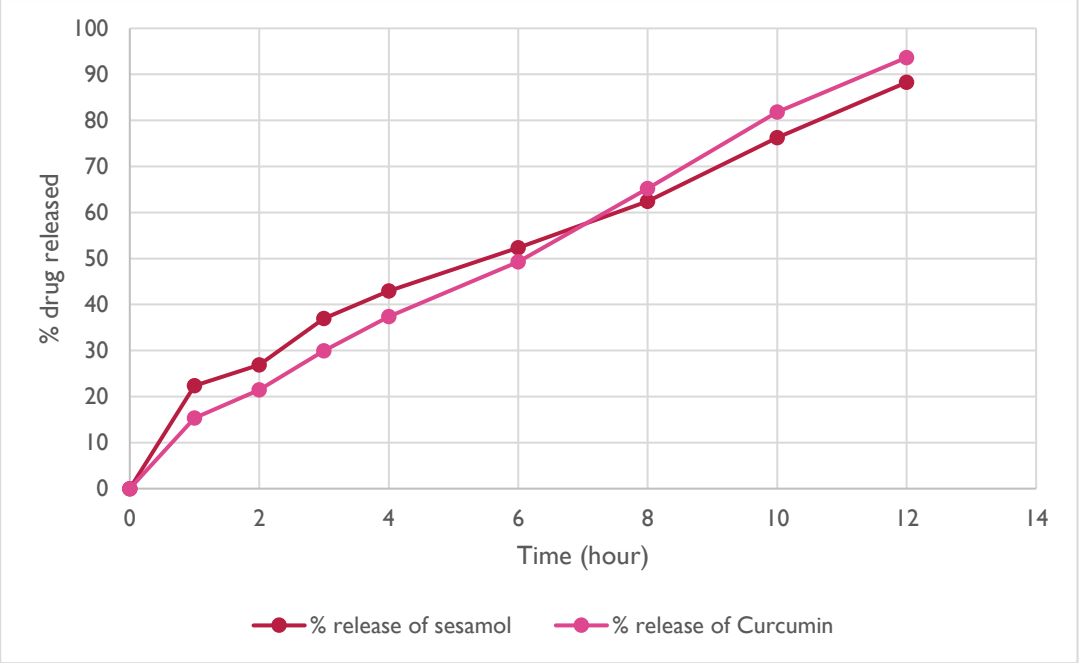

Figure 2. Release of sesamol and curcumin from flavonosome

***In vitro* antioxidant action of flavonosome**

DPPH radical scavenging assay was used to determine the antioxidant action of the individual flavonoids and the flavonosome formulation. The inhibition of DPPH radical was calculated from the absorbance of the test sample measured at 514 nm. It was found that the formulation F4 was having higher antioxidant activity in comparison to sesamol and curcumin. This could be due to the fact that the flavonosome was composed for a mixture of both the flavonoids. The added effect of the flavonoids contributed to the higher antioxidant potential of the flavonosome. The IC_{50} value of both the individual flavonoids and the flavonosome was calculated from the plot of inhibition against concentration (Figure 7.8). The IC_{50} of sesamol, curcumin and flavonosome were found to be 233.76 µg/mL, 181.87 µg/mL and 164.30 µg/mL respectively.

3. CONCLUSION

The study presented in this thesis reveals the excellent potential of flavonosome based drug delivery system for improving the bioavailability as well as antioxidant potential of flavonoids. We can conclude that flavonosome based formulation could be a valuable approach to improve the therapeutic efficacy, to reduce dose and improvement in dosage regimen for flavonoids

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