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Formulation & Evaluation Of Naringenin-Phospholipid Complex For Treating Diabetes

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Abstract

Diabetes mellitus is a syndrome that is characterized by hyperglycemia, change in the metabolism of lipids, carbohydrates, and proteins. Herbal medicines and plant components with insignificant toxicity and no side effects are notable therapeutic options for the treatment of this disease around the world. Thus, this study deals with formulation and evaluation of naringenin entrapped phospholipid complex. At first preformulation studies were carried out to confirm the naringenin. By that the phospholipid complex were prepared and evaluated for various parameters. The results showed that except acetone, acetonitrile, DMSO and distilled water all other solvents showed good solubility profile of Naringenin. Maximum absorbance wavelength (λ max) of naringenin was 288 nm. The highest aqueous solubility was found with that Naringenin–PC complex (1:5) 92.84±0.005. Particle size of all the formulations found within range within 931.59±0.56 to 1263.38±0.33 nm. The entrapment efficiency of the phytosomes was found to be in the range of 56.73±0.58 to 70.46±0.36 %. Cumulative Percentage Drug Release was found to be increased appreciably with time. Thus, it can be concluded that naringenin entrapped phospholipid complex could increase the therapeutic effect of naringenin.

Keywords: Phospholipid complex, Herbal medicine, Diabetes, Naringenin

INTRODUCTION

Currently available therapies for diabetes include insulin and various oral antidiabetic agents such as sulfonylureas, biguanides and α-glucosidase inhibitors which are used as monotherapy or in combination, to achieve better glycemia regulation. Many of these oral antidiabetic agents have a number of serious adverse effects. Thus, the management of diabetes without any side effects is still a challenge (Mehanna,2013).

Herbs have been utilized in a wide assortment of dosage form, since they were first found to have restorative characteristics. These incorporate the new or dried herb plant parts, including the leaves, stems, roots, blossom, seeds or organic products. Numerous botanists promote utilization of the fresh plant materials. Naringenin (4′,5,7-trihydroxyflavanone) is the aglycone of naringin, a flavonoid specific to citrus fruits and the predominant flavanone in grapefruit (Citrus paradisi) (up

to 10% of the dry weight) responsible for the bitterness of grapefruit juices. This bioflavonoid possesses antidiabetic, anti-inflammatory, anticarcinogenic, and antitumour effects (Jung *et al*., 2006; Patil *et al*., 2011; Salehi *et al*., 2019).

Novel vesicular drug delivery systems aim to administer the medicine at a pace determined by the body's requirement during the treatment time, while also channelling the active substance to the site of action. To achieve targeted and regulated medication delivery, a number of innovative vesicular drug delivery systems embracing diverse routes of administration have emerged. Targeted drug delivery is a mode of delivering the therapeutic agent to the tissues of interest while reducing the relative concentration of therapeutic agent in remaining tissues which improves the therapeutic efficacy and reduces the side effects. Drug targeting means the delivery of drugs to receptor, organs or any other specific part of body to which one wishes to deliver the entire drug (Kamboj *et al*., 2013; Myneni *et al*., 2011).

The pharmacosomal drug delivery system is advancing as a method used for delivery of various drug like non-steroidal anti-inflammatory drugs (NSAIDs), cardiovascular drugs, antineoplastic drugs and proteins. Pharmacosomes bear unique advantages over liposome and noisome vesicles and serve as an alternative to conventional vesicles. They are the colloidal dispersions of drugs covalently bound to lipids (Lee *et al*., 2000).

MATERIAL AND METHODS

Preparation of Phospholipid Complex

Naringenin phospholipid complex was prepared by taking naringenin with a molar concentration 1:1, 1.5:1, 2:1, 2.5:1and 3:1 respectively of phosphatidylcholine (PC). The equimolar concentration of PC and naringenin were placed in a 100 mL round bottom flask and refluxed with dichloromethane for 3 h. On concentrating the solution to 5–10 mL, add 30 mL of n-hexane to get the complex as a precipitate followed by filtration. The precipitate was store in vacuum desiccators.

Table1: Different formulations of Naringenin Phospholipid Complex

Formulations	Lecithin Concentration (%)	Drug Concentration (%)	n-hexane (ml)
NPC-1	1	1	30
NPC-2	1	1.5	30
NPC-3	1	2	30
NPC-4	1	2.5	30
NPC-5	1	3	30
NPC-6	1	3.5	30
NPC-7	1	4	30
NPC-8	1	4.5	30
NPC-9	1	5	30

Apparent Solubility:

To determine the change in solubility due to complexation, solubility of drug and the complex was determined in buffer/water and n-octanol by shake flask method. 50 mg of drug (and 50 mg equivalent in case of complex) was taken in a 100 mL conical flask. 50 mL of distilled water was added and then stirred for 15 min. The suspension was then transferred to 250 mL separating funnel with 50 mL of n-octanol and was shaken well for 2 h. Then the separating funnel was allowed to stand for about 30 min. These samples were measured spectrometrically at 288 nm using UV spectrophotometer (Mosharraf *et al*., 2003).

Entrapment efficiency

Entrapment efficiency (EE) was measured using UV visible spectrophotometer (UV-1601, Shimadzu). Weighed quantities of phospholipid complex equivalent to 10 mg of naringenin were added to 50 ml methanol in a 100 ml beaker. The contents were stirred on a magnetic stirrer for 4

hours and then allowed to stand for one hour. Clear liquid was decanted and centrifuged at 5000 rpm for 15 minutes. After centrifugation the supernatant was filtered through 0.45 µ whatman filter paper and after suitable dilution absorbance was measured in UV at 268 nm; the concentration of drug was measured. All measurements were performed in triplicate.

Drug content:

To determine the drug content in the complex, complex equivalent to 100 mg were weighed and added in 100 mL of methanol taken in a 100 mL volumetric flask. The volumetric flask was stirred continuously for 24hr on a magnetic stirrer. Dilutions were made suitably and measured for the drug content UV spectrophotometrically by Shimadzu 1601 UV/Visible Spectrophotometer.

Dissolution study

Dissolution Study (in-vitro drug release) The in vitro dissolution profiles of prepared Naringenin complex were obtained.115 The dissolution studies were carried out in a USP XXIII, six station dissolution test apparatus, type II (Electrolab. Model No. TDL-08L) at 100 rpm and 37°C. An accurately weighed amount of complex 50 mg was put in to 900 ml of pH 6.8 phosphate buffer. Samples (3 ml each) of dissolution fluid were withdrawn at different time intervals and replaced with an equal volume of fresh medium to maintain sink conditions. Samples were withdrawn and filtered through a 0.45 µm membrane filter, diluted suitably and then analyzed spectrophotometrically at 268 nm to determine drug release from the complex and the drug.

Determination of release kinetic of drug release mechanism

Release kinetics is an integral part for the development of a dosage form because if the kinetics of drug release is known, one can also have established IVIVC correlation. Mathematical model approach is important in research and development because of its simplicity and their inter relationship may minimize the number of trials in final optimization, thereby improving the formulation development process. Various kinetic models were used to analyse the in vitro drug release i.e Zero order, First order, Higuchi and Korsmeyer–Peppas model. Release profile of optimized formulation was compared with the conventional extract.

RESULTS

Table 1: Aqueous Solubility of Naringenin and Phospholipid Complex

Formulation	**Solubility (µg/ml; mean±SD, n=3)**
Naringenin	4.63±0.002
Naringenin–PC complex (1:1)	73.21±0.004
Naringenin–PC complex (1:1.5)	83.62±0.005
Naringenin–PC complex (1:2)	84.17±0.003
Naringenin–PC complex (1:2.5)	87.73±0.005
Naringenin–PC complex (1:3)	88.23±0.002
Naringenin–PC complex (1:3.5)	89.31±0.006
Naringenin–PC complex (1:4)	89.73±0.005
Naringenin–PC complex (1:4.5)	91.68±0.003
Naringenin–PC complex (1:5)	92.84±0.005

Table 2: Particle size and entrapment efficiency of Naringenin Phospholipid Complex

Formulations	**Particle Size**	**Entrapment Efficiency**
NPC-1	282.59±0.56	63.11±0.21
NPC-2	292.38±0.33	68.36±0.11
NPC-3	183.82±0.54	73.18±0.63
NPC-4	256.35±0.77	56.73±0.58
NPC-5	**220.11±0.68**	**70.46±0.36**
NPC-6	274.51±0.14	68.11±0.53

NPC-7	283.33±0.71	76.14±0.28
NPC-8	236.58±0.63	66.33±0.35
NPC-9	254.63±0.41	73.83±0.41

Table No 3: Composition of Best formulation

Formulation Code	Particle Size	Entrapment Efficiency
NPC-5	220.11±0.68	70.46±0.36

Table No 4: In Vitro Drug Release Data for NPC-5

S. No.	Time (Hrs)	Square Root of Time	Log Time	Cumulative* Percentage Drug Release	Log Cumulative Percentage Drug Release	Cumulative Percent Drug Remaining	Log cumulative Percent Drug Remaining
1	1	1	0	6.38	0.804	93.62	1.971
2	2	1. 414	0.301	18.82	1.274	81.18	1.909
3	3	1.732	0.477	32.28	1.508	67.72	1.830
4	4	2	0.602	45.38	1.656	54.62	1.737
5	6	2.449	0.778	67.94	1.832	32.06	1.505
6	8	2.828	0.903	79.28	1.899	20.72	1.316
7	10	3.162	1	88.29	1.945	11.71	1.068

CONCLUSION

In conclusion, the phospholipid complex for Naringenin, were successfully prepared. Further application of phytosome with entrapped naringenin can increase the bioavailability. In vivo studies with respect to various biological parameters related to diabetes are needed to extend its application.

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