IJNRD.ORG ISSN : 2456-4184
INTERNATIONAL JOURNAL OF NOVEL RESEARCH AND DEVELOPMENT (IJNRD) | IJNRD.ORG
An International Open Access, Peer-reviewed, Refereed Journal

Formulation and Evaluation of Herbal Anti-Diabetics Nutraceutical Capsules

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ABSTRACT

The escalating global burden of diabetes necessitates innovative strategies for effective management of this deadly disease. Literature studies suggests that herbal supplements/formulation to target different facets of diabetes management, including glucose regulation, insulin sensitivity, and oxidative stress. Enriched with essential vitamins, omega-3&6 fatty acid, trans-anethole, phenolic acid, polyphenol, phytosterol, metallothionein have shown promise in complementing conventional treatment.

Anti-diabetic nutraceutical herbal capsules containing powdered fennel, flaxseed, pumpkin seeds and kidney beans were formulated. These ingredients were carefully selected for diabetes management, including glucose regulation, insulin sensitivity, and oxidative stress.The formulation underwent rigorous pre-formulation studies, followed by various evaluation parameters like weight variation, disintegration time, dissolution time etc.

This novel formulation could potentially provide a valuable adjunct to conventional therapies, contributing to holistic diabetes management while promoting overall health. Further investigations and clinical trials are warranted to confirm its therapeutic efficacy and safety, moving us closer to a more integrative and natural approach to diabetes management.

Key words: Diabetes, Glucose regulation, Herbal formulation, Anti-Diabetic.

INTRODUCTION

Creating an anti-diabetic nutraceutical capsule in solid dosage form involves formulating a product that combines specific natural or bioactive compounds known for their potential in managing diabetes. This formulation aims to provide a convenient, standardized, and effective way to deliver these compounds to individuals looking to manage their blood sugar levels. The capsule's solid dosage form ensures consistent dosing and easy consumption, offering a promising option for diabetic care through natural ingredients.

The formulation of an anti-diabetic nutraceutical capsule in solid dosage form involves utilizing herbal ingredients due to their documented properties in managing blood sugar levels. Herbal ingredients often contain bioactive compounds that have shown potential in regulating glucose metabolism, improving insulin sensitivity, and reducing complications associated with diabetes. Incorporating these natural components into a solid dosage form ensures convenient, standardized delivery of the beneficial compounds, offering a promising alternative or complementary approach to traditional diabetic management.

Ensure consistency and potency by standardizing the herbal extracts to contain specific concentrations of bioactive compounds responsible for their anti-diabetic effects. This involves extracting and concentrating these compounds to achieve desired therapeutic levels.

Herbal drugs are being used not only in primary health care in developing countries but also increasingly popular in those countries where conventional medicine is predominant. Herbal formulations, now a days are gaining importance for treating many diseases due to their significant effect and lesser side effects as compared to allopathic medicines. Anti-diabetic herbal formulations are widely used in the treatment of diabetes mellitus and its complications such as retinopathy, neuropathy, hepatotoxicity and nephrotoxicity etc.

Diabetes is a predominant public health concern as it causes substantial morbidity and mortality and long-term complications with increasing risk of childhood and adult obesity, diabetes is likely to become even more prevalent over the coming decades.1Diabetes mellitus (Madhumeha) has been well known as a wasting disease due to insulin deficiency in human beings of all age groups in all part of the world.

It is a major disorder of carbohydrate metabolism and characterized by high blood sugar level. The name is from Greek with the meaning “Diabetes” (siphons) “mellitus” (sweet). 2 Diabetes mellitus leads to the endothelium dysfunction and produces oxidative stress. Vascular complications of diabetes mellitus can affect not only large and medium arteries resulting in coronary heart diseases, but also small vessels leading to retinopathy and neuropathy and brain hemorrhage. Diabetes mellitus is associated with increased formation of free radicals and decreased in antioxidant potential. Under physiological conditions glucose may undergo auto- oxidation and contribute to ROS formation.

This may induce damage to the insulin producing pancreatin β- cells. Consequences of oxidative stress are damaged to DNA, lipids, proteins, nucleic acids, disruption in cellular homeostasis and accumulation of damaged molecules.4 Oxidative stress is increased in diabetes because of multiple factors. It includes decreased cellular antioxidant levels and reduction in activity of enzymes that dispose of free radical.

In addition, levels of some pro-oxidants such as ferritin and homocysteine are elevated in diabetes. Another important factor is the interaction of advanced glycation end products (AGEs). Glycation of protein alters protein and cellular function, and binding of AGEs to their receptors can lead to modification in cell signaling and further production of free radicals.

The disease is presently incurable with those affected growing in an epidemic manner. The number of those affected globally is estimated to be 415 million with type 2 diabetes mellitus constituting about 90%. The

number affected may reach up to 642 million by the year 2040 with more increase coming from low and middle-income countries.

Even though, a lot of progress has been made in the discovery of anti-diabetic drugs, search for new ones is still ongoing because of the inability of the present drugs to maintain normoglycemia, prevent complications of diabetes mellitus and are also of much cost to the greater number of diabetic populations.

Plant secondary metabolites are being researched as the possible source of new drugs for diabetes mellitus since plants have provided veritable sources of new drugs over time 3, 5. Secondary metabolites naturally protect plants from predators, pathogens and also against herbivores and microbes.

These secondary metabolites of plants have been found to be the active principles responsible for the therapeutic effects of medicinal plants and provide great opportunity for new drug discovery due to their abundance and diversity.

Accurate Dosage: Capsules provide precise and consistent dosing, ensuring that individuals receive the correct amount of medication or herbal ingredients required for managing diabetes.

Convenience: Capsules are easy to store, transport, and consume compared to other forms of medication. They offer a convenient way to take anti-diabetic supplements without the need for measuring or preparation.

Enhanced Stability: Encapsulating anti-diabetic ingredients can protect them from degradation due to light, air, or moisture, preserving their potency and effectiveness over time.

Reduced Taste and Odor: Some herbal ingredients might have strong tastes or odors that can be masked within capsules, making them more palatable for users.

Targeted Delivery: Capsules can be designed for delayed release or targeted delivery to ensure the active ingredients reach the intended site in the body for optimal absorption and effectiveness.

Compliance and Adherence: The standardized dosing and ease of consumption offered by capsules may improve patient compliance, as they are more likely to adhere to their treatment regimen.

Reduced Side Effects: Controlled release capsules can potentially minimize side effects by regulating the release of active ingredients, leading to better tolerance and fewer adverse reactions

Compatibility with Various Ingredients: Capsules allow for combining multiple ingredients or formulations, facilitating the creation of comprehensive anti-diabetic treatments with synergistic effects.

Alternative to Traditional Medications: For individuals preferring natural or herbal approaches to managing diabetes, capsules containing herbal ingredients provide an alternative to conventional medications.
Capsules, as a delivery system, offer a blend of convenience, precision dosing, stability, and potential targeted release that can enhance the effectiveness and user experience of anti-diabetic treatments

Fennel: *(Foeniculum Vulgare)*
In human, the enzymes which are involved in the digestion of starch are salivary amylase, alpha-glucosidase and pancreatic amylase. Alphaglucosidase converts complex carbohydrates to simple carbohydrates in the small digestive system before assimilation. Drugs that restrain the activity of alpha-amylase are amylase inhibitor and drugs that restrain alpha-glucosidase are glucosidase inhibitor. Both Amylase inhibitor and Glucosidase inhibitor prevents the breakdown of complex carbohydrates and thus stops the absorption of

carbohydrate. In the regulation of post prandial blood sugar level in diabetes mellitus patient the inhibition of amylase and glycosidase enzyme**.(3,4,7,11)**

Figure: Fennel Seeds

Kidny Beans: ***(Phaseolus Vulgaris L.)***

Kidney bean contains a glycoprotein named as α-amylase inhibitor (α-AI), which can inhibit starch digestion**.**Previous studies showed that the α-AI proteins extracted from beans showed a strong inhibitory activity on α-amylase and the ingestion of white bean extracts that contain α-AI can mitigate the obesity, furthermore, the resistant starch (RS) and phenolics were the dominant components that contribute to the low GI of starchy foods. As such, these active ingredients may possess the potential to control postprandial blood levels, which provide health benefits to the patients with type II diabetes**.(23,28,7,18,33)**

Figure: Kidney Beans

Flaxseed: ***(Linum Usitatissimum)***

Flax seeds contain high levels of Omega-3 fatty acid (Burdge & Calder, 2005), fiber components and phytochemicals such as lignans bioresource (Vijaimohan et al., 2006). The main physiological benefits of flax seeds are attributed primarily to the high linoleic acid content which contributes to their antioxidant properties (Simopoulos, 1991) against various diseases, including atherosclerosis, diabetes, hypertension, anti-inflammatory, and anticarcinogenic effects (Fukuda, Osawa, Namiki, & Ozaki**.(38,26,17)**

Figure: Flax Seeds

Pumpkin Seed: ***(Cucurbita Pepo)***

Polysaccharides, para-aminobenzoic acid, fixed oils, sterol, proteins, and peptides are biologically active ingredients, which are found in pumpkins. The chemicals within pumpkins such as the fruit pulp, oil from ungerminated seeds, and protein from germinated seeds have hypoglycemic properties. Preliminary investigation showed that pumpkin seeds, and the macromolecules, therein, such as Trigonelline (TRG), Nicotinic acid (NA), and Dchiro-inositol (DCI), possess hypoglycemic properties and could assist in maintaining glycemic control.**(9,15,24)**

Figure: Pumpkin seed

MATERIALS AND METHODS

Table 1. Antidiabetic capsule formulation(200mg)

S.no	***Ingredients (powder)***	***Content (mg)***
1	Fennel	50
2	Flaxseed	50

3	Kidney beans	25
4	Pumpkin seed	25
5	Starch	10
6	Lactose	30
7	Talc	5
8	Magnesium stearate	5

❖ **Formulation of API'/Excipients Blend:**

- Dry all seeds for 30 minutes at 35° in Oven
- Triturate in mortar with the help of pestle individually
- Convert it into a fine powder
- Cold extraction by maceration using ethanol
- Dry the extract to prevent it from contamination
- Pass through Sieve no. 44
- Mix all the API's/Excipients according to the measured formula

Granulation

- Make the starch paste
- Make a dough by pouring starch into the sample by triturating
- Dry the dough at room temperature
- Then pass it through sieve no. 24
- Obtained granules were sterilized by **dry heat sterilization** at temperature at 35° to 40° in oven

❖ **Filling Of Capsule:**

- Weigh the sample of each capsule individually
- Fill the sample into capsules by manual method
- Precautions must be taken while filling

Micromeritic Properties of API's/Excipients Blend

The different batches blends were evaluated for various micrometric properties such as bulk density, tapped density, Hausner's quotient (HQ), Carr's compressibility index (CI), true density, flow rate and angle of repose.

Bulk and Tapped Densities:

A 10 g quantity of each the API's/excipients blend was weighed out and put in a 50 ml measuring cylinder and allowed to drop on the table from a height of about 10 cm. The volume occupied by the API's / excipients blend was read directly from the measuring cylinder and recorded as the bulk volume. Tapped volume was obtained by fixing the measuring cylinder containing a known weight of each batch on an automatic tapping machine Stampf volumeter (Karl Kolb, Driesch, Germany). The tapping by the machine continued until a constant volume was reached and this was recorded as the tapped volume. The bulk density (Db) and tapped density (Dt) were the calculated from Equations (Eqn.) 1 and 2 respectively. A total of 3 observations (n = 3) were made**.(2,9,13)**

Db = M/Vb ….Eq (1)

Where, M is the mass of the powder mixture (10g) and Vb is the bulk volume of the powder mixture

Dt = M/Vt …. Eq (2)

Where, Vt is the tapped volume of the powder mixture.

Parameter	***Powder***	***Granules***
Bulk density(g/ml)	0.3649	0.3751
Tapped density(g/ml)	0.4649	0.4748

Hausner's Quotient and Ratio Carr's Index:

Hausner's quotient (HQ) and Carr's compressibility index (C.I) were calculated using the Equations 3 and 4 respectively. *HQ = Dt /Db…. Eq (3)*

C.I. (%) = Dt-Db × 100 /Dt…. Eq (4)

Car's Index	*Powder*	*Granules*
Hausner's Ratio	1.13	1.19

Indication Of Powder Flow

Car's Index	*Powder*	*Granules*
Hausner's Ratio	11.19	13.2

Indication of Granules Flow

True Density:

The true density (DT) of each batch was determined by fluid displacement method using xylene a non-solvent fluid 10. A 50 ml pycnometer or density bottle was used. The weight of the pycnometer was noted. The density bottle was then filled with xylene and the new weight (W1) was noted. A known weight W (1 g) of each batch was added and the weight of the xylene with density bottle and the sample was noted as (W2). True density was then calculated from Equation 5. Triplicate observations were made (n = 3**). (40,37,31)**

DT = W × S.G/W1+W-W2…..Eq (5)

S.G. is the specific gravity of the non-solvent xylene

Parameter	*Powder*	*Granules*
True density(g/ml)	0.4649	03842

Flow Rate and Angle of Repose:

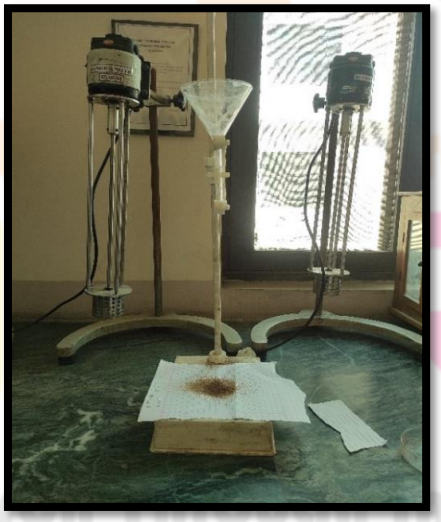
Methods described by Hamzah et al., 2018 were used in determination of the angle of repose 11. A plastic funnel was placed in metal ring support clamped on to a retort stand and placed 10 cm above the bench. The orifice of the funnel was closed temporarily with small sheet of cardboard paper, and a 10 g quantity of each batch was put into the funnel. The sheet of paper covering the orifice was removed, and a stopwatch timer started simultaneously. The granules were allowed to flow freely on to a plain sheet of paper. The time of flow (t), i.e., time taken for the sample to flow from the funnel till all the powder had passed through the orifice of the funnel, height of heap (h) formed and diameter (d) of heap formed were noted. The flow rate (F) and angle of repose (θ) were calculated using Equations 6 and 8 respectively**.(40,38,37)**

F = Mass/Time of flow…. Eq (6)

Tan θ = h/0.5d…..Eq (7)

θ = Tan-1 h/0.5d…. Eq (8)

Materials	*Angle of repose(θ)*	*Types of flow*
Powder	*20.3*	*Good*
Granules	*18*	*Excellent*



Physical Evaluation of optimized formulation:

Weight Variation Test:

Was performed on capsules as it reveals the uniformity in filling the desired contents in each capsule in each batch. The procedure adopted for weight variation test was as per Indian Pharmacopoeia 1996. The result of weight variation test is given in table 2. The uniformity of weight was evaluated by selecting 20 capsules randomly from each batch. The weight of the 20 capsules was noted together with the average weight and

the individual weight of each capsule. The percentage deviation of the weight of each capsule from the average weight was then calculated. The weight of a batch of capsules is considered uniform if the weight of the individual capsules falls within 90 - 110% of the average weight. If this condition is not fulfilled, the fill or net weight of each capsule is determined and compared with the average net weight of the capsules. Capsules are considered satisfactory if not more than 2 capsules are greater by 10% of the average net weight, or none is outside the range of 75 - 125%. **(35,28)**

Table 2. Weight variation test

Average Weight of 20 capsules contents(gm)	***Standard Deviation (%)***
0.48	0.032

Disintegration Test:

The disintegration test of capsule was carried out as per Indian Pharmacopoeia 1996. The results of weight variation test are given in table 3. Disintegration time test was carried out in the same apparatus as tablets; however a little strand of copper wire was attached to each capsule to ensure that they sink to the bottom of the disintegration cell. The disintegration time test was carried out using an Erweka disintegration machine (Erweka, type ZT4 Nr32440, Germany). Distilled water maintained at a temperature of 37.0 ± 1.0 °C was used as the disintegration medium. Six randomly selected capsules from each batch were put singly into each tube of the disintegration unit whose lower end was closed by a screen of 2 mm aperture. The tubes were raised up and lowered in a bath containing the disintegration medium steadily until the capsule breaks up and pass through the mesh of the tube. Capsules are said to be disintegrated if no particle of the capsule remains on the screen except fragments of the capsule shell. The time taken for this to happen was noted. The mean and the standard deviation were calculated. **(19,16,33)**

Table 3. Disintegration test

Disintegration time (min)	***Mean (min)***	***Standard Deviation (&)***
Capsule	11.28	1.43

Content Uniformity:

Content uniformity test was carried out by assaying individually 10 randomly selected capsules spectrophotometrically 13, 14. The assay was carried out using an established standard Beer's plot for kaempferol obtained at 268 nm wavelength. A batch of capsules is said to be satisfactory if 9 out of the 10 assayed are within potency range of 85 - 115% and a tenth are within 75 - 125% 13. If not more 20 are assayed and the requirement is met if all the 30 are within the 75 – 125% of the specified potency range and not less than 27 of the 30 are within the 85 - 115%. **(1,8,3)**

Dissolution Rate:

A standard Beer's plot was first constructed at the wavelength of maximum absorption (λmax). The drug obeyed Beer's law at the concentration range of 0.01 - 0.08 mg/ml used and a regression equation of the absorbance is 7.817.

[Drug] - 0.080, R2 = 0.999 and at a maximum (λmax) absorption of 268 nm in 0.1 N HCl. Dissolution studies were carried out using the dissolution apparatus with a paddle (U.S.P. model 2, Erweka, Germany) with 0.1N HCl as the dissolution medium. A 900 ml volume of the dissolution medium was measured into the dissolution apparatus maintained at 37.0 ± 1.0 °C. The machine was allowed to equilibrate for 30 minutes after which one capsule was introduced.

The capsule was prevented from floating by attachment of a small strand of wire. A 5 ml volume of the dissolution medium was withdrawn after every 5 min and replaced with 5 ml of fresh 0.1 N HCl for 60 min. The samples withdrawn were then determined Spectro photo-metrically using ultraviolet spectrophotometer model (Shimadzu, Japan). **(6,37,28)**

Table 4. Dissolution test

Dissolution time (min)	***Mean (min)***	***Standard Deviation (%)***
Granules	13.8	1.48
Capsule	18.9	2.92

Drug Content:

The percentage of drug content was determined for each batch spectrophotometrically. The contents of 10 randomly selected capsules were weighed and a quantity corresponding to the mean weight was taken and assayed using spectrophotometer as above.

Stability Studies

Accelerated stability studies or accelerated stability test (AST) is a method that will help rapid prediction of a long-term stability of drug. It is a validated method by which the stability of the product is predicted by storage of the product under conditions. Here exaggerated conditions of temperature, humidity light and other various factors are used. By using accelerated stability studies one can predict reasonable accuracy, the relatively long shelf life at field conditions to a relatively short-term date. In presence of stability study, the capsules were subjected to accelerated storage conditions. Such accelerated stability study testing has

given the advantage of evaluating the stability of formulations in a short period of time (3 months) instead of waiting for long period of time i.e., 18 month or 2 year. **(7,35,40,23,17,19,20)**

Time and Temperature conditions

The capsule samples were kept at most commonly applied conditions such as 37°, 45°, and 4° for three months.

Sampling plan for testing

Twenty capsules were selected randomly and kept at 37°, 45°, and 4°. On 30th, 60th and 90th day the sample were taken out for testing. The results of stability testing of prepared antidiabetic capsules at different temperature are shows in table.

Table 5. Stability of capsules as per time and temperature

Sr. No.	*Time interval of testing*	*Temperature*		
		37℃	*45℃*	*4℃*
1.	*30 Days*	√	√	√
2.	*60 Days*	√	√	√
3.	*90 Days*	√	√	√

Table 6. Stability study of antidiabetic capsule

	Time and Temperature								
	30 Days			*60 Days*			*90 Days*		
Parameter	*37 ℃*	*45 ℃*	*4 ℃*	*37 ℃*	*45 ℃*	*4℃*	*37 ℃*	*45 ℃*	*4℃*
Appearance	*Hard Gelatin Capsule*	*Hard Gelatin Capsule*	*Hard Gelatin Capsule*	*Hard Gelatin Capsule*	*Hard Gelatin Capsule*	*Hard Gelatin Capsule*	*Hard Gelatin Capsule*	*Hard Gelatin Capsule*	*Hard Gelatin Capsule*
Appearance of capsule powder	*Normal*	Normal	Moisture Absorb	Normal	Normal	dark green	Faded green	Faded green	Yellowish green

Average weight (gm)	0.249	0.231	0.38	0.250	0.258	0.399	0.301	0.331	0.431
Disintegration on time (min)	10.8	9.6	13.8	10.52	8.5	13.99	11.2	8.001	14.3

RESULT

The Herbal Anti-diabetic nutraceutical capsule project enhanced blood sugar regulation and overall diabetes management by combining fennel, kidney beans, pumpkin seeds and flax seeds.
Positive outcomes include improved insulin sensitivity of stabilized HAa1c level and better lipid profile.
The antibiotic nutraceutical capsule blends fennel, kidney beans, pumpkin seeds and flax seeds for blood sugar regulation. Fennel aid glucose control while kidney beans provide soluble fiber for glycemic balance. Pumpkin seeds rich in magnesium and antioxidants support glucose metabolism.
Flaxseeds contribute omega-3-fatty acids and soluble fiber for diabetes management. Evaluation parameters include efficacy, safety, bioavailability, long term effects, tolerability and compliance.
Scientific validation and consultation with healthcare professionals are vital before considering such formulation.

CONCLUSION

From the above study, we conclude that the herbal anti diabetes nutraceutical capsule was prepared by manual method and gave satisfactory and acceptable result. The formulation containing herbal ingredient like fennel, kidney beans, flaxseed, pumpkin seed could be more beneficial as an anti-diabetes due to the presence of phenolic acid, polyphenol, phytosterol, metallothionein. From the above research work it was concluded that herbal nutraceutical capsule prepared in the form of cost-effective capsule to minimize patients' compliance in regarding suppressing side effects and enhancing positive effects on the body.

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