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FORMULATION AND EVALUATION OF ANTI-DIABETIC POLYHERBAL CAPSULES

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ABSTRACT

Diabetes mellitus is a chronic metabolic disorder characterized by imbalance in carbohydrate, protein and lipid metabolism resulting in hyperglycemia this is mainly caused by inadequate insulin secretion or insulin dysfunction.[1] Worldwide there is a drastic increase in Diabetes mellitus patients especially in developed countries. According to International Diabetes Federation (IDF), in 2021, approximately 537 million adults are suffering from this heterogenous metabolic disorder. By 2030, it is estimated to rise by 643 million adults.[2] Diabetes mellitus should be diagnosed and effective treatment should be provided, if not, it can further lead to complications such as Diabetic Retinopathy, Diabetic Neuropathy, Diabetic Nephropathy [Micro vascular complications], Cardiovascular Diseases, Atherosclerosis, Stroke [Macro vascular complications] and many more.[3] Synthetic Antidiabetic formulations shows side effects like Weight gain, Hypersensitivity reactions, Hepatotoxicity, GI disturbances, Lactic acidosis, Vitamin B12 deficiency, Ocular disturbances, Lipoatrophy and many others.[4] Therefore to avoid complications and side effects of synthetic preparations, there is a need for a polyherbal antidiabetic formulation which shows effective and potent action in comparison to synthetic formulations. Hence in the present study, an attempt was made to formulate polyherbal antidiabetic formulation, using *Cucurbita maxima, Moringa oleifera, Acalypha indica, Phyllanthus emblica, Nigella sativa, Trigonella foenum-graecum, Murraya koeniggi, Ocimum sanctum, Curcuma longa, Cinnamon cassia, Zingiber officinale* in the form of capsules. The prepared formulation was evaluated for Uniformity in weight, Bulk density, Tapped density, Angle of repose, Hausner's ratio, Carr's index, Stability test, Moisture content, Disintegration test, Dissolution test and was found to be satisfactory.

KEYWORDS: Anti diabetic, Polyherbal, *Cucurbitamaxima*, *Moringaoleifera*, capsules.

INTRODUCTION

Diabetes mellitus is a category of metabolic illnesses characterized by chronic hyperglycemia, caused by decreased insulin action or secretion. It is divided into two types: Type 1 and Type 2. Type 2 diabetes accounts for more than 90% of diabetes cases and causes problems with glucose, lipid, and protein metabolism. Controlling hyperglycemia effectively in diabetic individuals is crucial for lowering the risk of micro and macrovascular disease.[5]

The link between the formation of free radicals, particularly reactive oxygen species (ROS), and the pathophysiology and progression of diabetes mellitus has increased. Metabolic stress arising from alterations in energy metabolism, inflammatory mediators, and reduced antioxidant defence mechanisms may all contribute to the production of free radicals in Diabetes mellitus.[6] Hyperglycemia causes oxidative stress by producing too many reactive oxygen species, resulting in an imbalance between free radicals and the cell's antioxidant defence mechanism. It has been shown that oxidative stress, which affects glucose, lipid, and protein metabolism, increases in diabetic individuals, and causes endothelial cell failure and atherosclerosis progression. High blood glucose levels in diabetes are known to cause cell death by inducing oxidative stress. These individuals have a higher risk of cardiovascular disease.[7] A preventative strategy of maintaining normal blood glucose, reducing oxidative stress through some polyherbal formulations should be explored.

In the present study, an attempt was made to formulate polyherbal antidiabetic formulation, using *Cucurbita maxima, Moringa oleifera, Acalypha indica, Phyllanthus emblica, Nigella sativa, Trigonella foenum-graecum, Murraya koeniggi, Ocimum sanctum, Curcuma longa, Cinnamon cassia, Zingiber officinale* in the form of capsules.

Cucurbita maxima(Pumpkin) contains D-chiro-inositol which assists in increase of insulin secretion. D-chiro-inositol makes the receptors more receptive to insulin thus favoring regulation of blood sugars.[8] In addition to this, it also contains Carotenoid mainly Beta- carotene, Beta-cryptoxanthin, Lutein, Zeaxanthin which helps in

reducing oxidative stress caused by lack of physical activity.[9] It also contains lipid soluble antioxidant Tocopherol, which reduces the tissue damage caused by toxic free radical oxygen release as a result of oxidative stress. Presence of phenolic phytochemicals such as Flavonoids helps in inhibition of two enzymes (α-Amylase and α- Glucosidase)which is responsible for increase of postprandial hyperglycemia.[10]

Moringa oleiferacontains several phytoconstituents such as Flavonoids, Terpenes, Saponins, Alkaloids, Phenolic acids, Steroids, Tannins, Glucosinolates etc.[11] Anti-diabetic properties of flavonoids aid in carbohydrate digestion, insulin signalling, insulin production, glucose absorption and adipose deposition. They target a number of molecules involved in the control of many pathways including improvement of β-cell proliferation, increase of insulin secretion, lowering apoptosis and alleviating hyperglycemia by regulating glucose metabolism in the liver. The hydroxyl group and ketones in flavonoids are responsible for majority of the bioactivity.[12]

Acalypha indica (Indian nettle) contains Flavonoids such as Quercetin-3-O-rutinoside (rutin), kaempferol-3-O-rutinoside and isorhamnetin-3-O-glucoside, Organic acids like Caffeic acid and its esters, ferulic acid, chlorogenic, citric, fumaric, phosphoric acids etc. Minerals and trace elements such as Calcium, Potassium, Magnesium, Phosphorus, Iron, Sulphur, Zinc, Manganese, Copper, Nickel and Selenium are also present. It also contains vitamins like vitamin A (retinol), vitamin B2 (riboflavin), vitamin B5 (pantothenic acid), vitamin B9 (folic acid), vitamin C (ascorbic acid), vitamin K (phylloquinone). Other constituents such as Tannins, chlorophyll and carotenoids are also present.[13] When compared to glibenclamide, methanol extract significantly reduces serum blood glucose levels. Methanol extract of *Acalypha indica* reduced FBS levels in diabetic mice by 51%, while glibenclamide reduced sugar levels by 67%. In diabetic rats, methanol extract caused a significant ($P<0.01$) reduction in postprandial blood sugar levels.[14]

Phyllanthus emblica (Amla) contains flavonoids such as Quercetin and Kaempferol. Quercetin shows active interaction with a variety of molecular targets in small intestine, pancreas, skeletal muscle, adipose tissue, and liver to regulate glucose homeostasis throughout the body. Quercetin exhibits pleiotropic mechanisms of action which include reduction of intestinal glucose absorption, insulin secretory and insulin-sensitizing actions and enhanced glucose utilization in peripheral tissues.[15] It also contains excess amount of Ascorbic acid (VitaminC). Ascorbic acid, an antioxidant vitamin, is essential in preventing free radical damage. Antioxidant activity of vitamin C is important in the treatment and prevention of diabetes and its complications, because it can include suppressing Reactive Oxygen Species (ROS) formed either by inhibiting enzymes or by chelating trace elements involved in free radical generation.[16] Alkaloids like Phyllembein, Phyllantine, Phyllantidine, Amino acids including Glutamic acid, Proline, Alanine, Lysine, Aspartic acid, Cystine and sterols namely βsitosterol-3-O-β-D-glucoside and Stigmasta-7,22-dien-3-O-β-D glucoside also have anti diabetic effect.[17]

Nigella sativa (Black Jeera) conatins active chemicals likethymoquinone, thymohydroquinone, dithymoquinone, p-cymene, carvacrol, 4-terpineol, t-anethol, sesquiterpene longifolene, α-pinene, thymol etc. It also include two types of isoquinoline alkaloids, nigellicimine and nigellicimine N-oxide, and pyrazole alkaloids or imidazole alkaloids such as nigellidine and nigellicine. Furthermore, seeds of *Nigella sativa* contain alpha-hederin, a water-soluble pentacyclic triterpene, and saponin.[18] Among quinines present, Thymoquinone(TQ) is the most prevalent constituentresponsible for majority of pharmacological activities. TQ reduces hepatic gluconeogenesis and protects β-cells from oxidative stress. It inhibits insulin resistance, protein glycation, and diabetic nephropathy. Pharmacologically significance of TQ in *Nigella sativa*in the treatment of diabetes may be due to their antioxidant, cytoprotective, and immunomodulatory properties.[19] Meta-analysis of animal studies showed TQ has reduced the Serum glucose level significantly in the STZ-induced diabetes model. Furthermore, a meta-analysis of the effect of TQ on Body weight revealed that TQ has a statistically significant effect on Body weight of diabetic animals.[20]

Trigonella foenum-graecum (fenugreek) has Polyphenols, steroids, lipids, alkaloids, saponins, flavonoids, hydrocarbons, carbohydrates, galactomannan fiber, and amino acids.[21] In type 2 diabetic rats, fenugreek powder considerably decreases postprandial sugar levels. It also helps to normalise other clinical symptoms linked with diabetes, such as polyuria, polydypsia, weakness, and weight loss. According to majority of studies, the gum component of the seeds is primarily responsible for decreasing plasma glucose levels, thus having a considerable positive influence on serum lipid profiles. These mostly due to a decrease in glucose, cholesterol, and bile acid absorption from the intestine.[22] 4-Hydroxyleucine, a novel amino acid derived from fenugreek seeds, enhanced insulin release in isolated islet cells from rats, mice, and humans. *Trigonella foenum-graecum* has been shown in vitro and in vivo to trigger glucose-induced insulin release. The amino acid hydroxyisoleucine, which accounts for 80 percent of the free amino acids in *Trigonella foenum-graecum* seeds, may have insulin-stimulating characteristics.[23] *Trigonella foenum-graecum* seeds may improve insulin sensitivity due to the effects of fibre, which slows carbohydrate metabolism, resulting in lower insulin and blood glucose levels. The anti-hyperglycemic effect of *Trigonella foenum-graecum* seed and leaf extracts, powder, and gum has been attributed to delayed stomach emptying caused by the high fibre content,

inhibition of carbohydrate digesting enzymes and stimulation of insulin secretion.[24]

Murraya koeniggi (Curry leaves) has shown to possess hypoglycemic effect in rats with alloxan-induced diabetes. Increased insulin secretion and stimulation of the glycogenesis process are two possible mechanisms of action. The extracts were effective in modulating biochemical indicators related with diabetes, such as glucokinase and glucose-6-phosphatase activity. It also protects the pancreas by reducing oxidative stress and preserving pancreatic cell integrity. Alkaloids found in *Murraya koeniggi* leaves have been studied and found to have inhibitory effects on the aldose reductase enzyme, glucose utilisation and other enzyme systems, potentially contributinganti-diabetic effects. *Murraya koeniggi*was evaluated for α-glucosidase inhibition and it exhibited inhibition of α- glycosidase. Alpha-glucosidase inhibitors are commonly used in the treatment of type 2 Diabetices.[25] *Murraya koeniggi*was found to have antihyperglycemic effects in STZ-induced diabetic rats in another investigation. Oral treatment of an ethanolic extract of *Murraya koeniggi*at a dose of 200 mg/kg/b.w./day for 30 days dramatically reduced blood glucose, glycosylated hemoglobin, urea, uric acid and creatinine levels in diabetic treated mice. The extract's insulin stimulating impact was revealed by measuring plasma insulin levels. *Murraya koeniggi*appears to have statistically significant hypoglycemic potential in STZ-induced diabetic rats, according to the findings. *Murraya koeniggi*extract was found to be more effective than glibenclamide, a well-known drug in diabetes treatment.[26]

Ocimum sanctum (Tulsi) contains chemical constituents namely Oleanolic acid, Ursolic acid, Rosmarinic acid, Eugenol, Carvacrol, Linalool, and β-caryophyllene.[27] It reduces fasting blood glucose, serum lipid profile, lipid peroxidation products (LPO), and improves glucose tolerance. In addition, it reduced Lipid peroxidation (LPO), thiobarbituric acid reactive substances (TBARS) and increased antioxidant enzymes superoxide dismutase (SOD), catalase (CAT), glutathione peroxidase (GPX), glutathione transferase (GT)[28] and Carvacrol (CAR), a naturally occurring phenolic monoterpene. The study was conducted to evaluate CAR's neuroprotective effect on diabetes-associated cognitive deficit (DACD) in a rat model of diabetes, as well as its probable molecular mechanism. CAR was given to diabetic rats in dosages of 25, 50, and 100 mg/kg for 7 weeks. The Morris water maze was employed to assess memory behaviour. The cytoplasmic and nuclear fractions of the cerebral cortex and hippocampus were prepared for analysis of oxidative stress (MDA, SOD, and GSH), the NF-B p65 unit, TNF-, IL-1, and caspase-3. The rats showed a significant rise in escape latency after 7 weeks of streptozotocin injection, as well as increased oxidative stress (increased MDA level and decreased SOD, as well as reduced GSH), NF-B p65 unit, TNF-, IL-1, and caspase-3 in various locations of diabetic rat brain. It has been demonstrated that coadministration of CAR prevents behavioural, biochemical, and molecular alterations associated with diabetes.[29]

Curcuma longa(Turmeric), a rhizome of herbaceous perennial plant. The active component of turmeric is Curcumin which helps in reducing glycemia and hyperlipidemia. It is extremely safe and it also exhibits several pleiotropic effects. Curcumin helps in improving insulin resistance and cholesterol levels. It also helps in preventing Prediabetes, also called impaired glucose tolerance. The curcumin in turmeric also acts on certain receptor cells in the pancreas that are adrenergic and helps to regulate the release of insulin. Turmeric also help in improving the immune response of type 1 diabetic patients.[30] The administration of turmeric or curcumin to diabetic rats considerably lowered blood sugar, haemoglobin and glycosylated haemoglobin levels. The diabetic rats' oxidative stress was also lowered by turmeric and curcumin administration. Lower levels of TBARS were found, which could be related to a decrease in glucose input into the polyol pathway, resulting in an enhanced NADPH/NADP ratio and increased activity of the powerful antioxdiant enzyme Glutathione peroxidase. Furthermore, treatment with turmeric or curcumin reduced the activity of SDH (Sorbitol dehydrogenase), which catalyses the conversion of sorbitol to fructose. These findings also appeared to show that curcumin was more effective than turmeric in reducing diabetes-related alterations.[31]

Cinnamon cassia (Chinese cinnamon)has main constituents like cinnamaldehyde, cinnamate, cinnamic acid, and numerous essential oils. Cinnamon has been found to have a variety of biological actions. Procyanidins, tannins, mucilage and trace levels of coumarin are also present. Cinnamaldehyde (trans-cinnamaldehyde) is the most important component of cinnamon barkoil.[32] A study was conducted on *Cinnamon cassia* in which Cinnamon extract was given at various doses (50, 100, 150, and 200 mg/kg) for six weeks. Blood glucose concentrations were observed to be considerably lower in a dose-dependent manner in the 200 mg/kg group compared to the control group. After 6 weeks of dosing, serum insulin levels and HDL–cholesterol levels were significantly elevated, but triglyceride, total cholesterol, and intestinal -glycosidase activity were significantly decreased. These findings imply that, cinnamon extract regulates blood glucose and lipid levels, as well as it has a blood glucose-lowering effect through enhancing insulin sensitivity or decreasing carbohydrate absorption in the small intestine.[33]

Zingiber officinale(Ginger) has around 400 distinct chemicals according to chemical studies. Carbohydrates (50–70%), lipids (3–8%), terpenes, and phenolic chemicals are the main components of ginger rhizomes. Zingiberene, β-bisabolene, α-farnesene, β-sesquiphellandrene, and β-curcumene are terpene components of ginger, while gingerol, paradols, and

shogaol are phenolic chemicals. These gingerols (23–25%) and shogaol (18–25%) are detected in higherconcentrations than others. Apart from these, it also has amino acids, raw fibre, ash, protein, phytosterols, vitamins (such as nicotinic acid and vitamin A), and minerals.[34] In type 2 diabetic individuals, ginger supplementation lowered Fasting Blood Sugar, Hemoglobin A1c (HbA1c), Apolipoprotein B (Apo B), Apolipoprotein A-I, and (Malondialdehyde) MDA levels while increasing Apo A-I levels, according to the study. Ginger may be effective for diabetics.[35]

MATERIALS AND METHODS

Dry herbs of *Cucurbita maxima, Moringa oleifera, Acalypha indica, Phyllanthus emblica, Nigella sativa, Trigonella foenum-graecum, Murraya koeniggi, Ocimum sanctum, Curcuma longa, Cinnamon cassia, Zingiber officinale* was collected from local market and powdered. According to the formula given below, herbal ingredients were weighed as per ascending order of its weight. Weighed ingredients were triturated using mortar and pestle. The powdered herbal materials were sieved through the mesh size of 120. The powdered polyherbal formulation was encapsulated. Size #0 capsule was selected for encapsulating the desired strength (150 mg) of the drug (blended extract). The composition of developed formulation is summarized in Table 1.

Table 1: Formulation of polyherbal capsule.

SL.NO	INGREDEINTS	QUANTITY (Per Capsule)
01.	*Cucurbita maxima*	30mg
02.	Moringa oleifera	20mg
03.	Acalypha indica	15mg
04.	*Phyllanthus emblica*	15mg
05.	*Nigella sativa*	10mg
06.	*Trigonella foenum-graecum*	10mg
07.	*Murraya koeniggi*	10mg
08.	*Ocimum sanctum*	10mg
09.	*Curcuma longa*	10mg
10.	*Cinnamon cassia*	10mg
11.	*Zingiber officinale*	10mg

EVALUATION

The formulated antidiabetic capsule was subjected to physical and physicochemical evaluation as below.

A. PHYSICAL PARAMETERS

1. Determination of Bulk Density

Weighing about 10g of sample and placing it in a dried graduated measuring cylinder, the volume was recorded as V1 mL. The measuring cylinder containing the sample was placed in the bulk density instrument and tapped for 50 times. The powder's volume was recorded as V2 ml and computed using the given formula.[36]

Bulk density = Untapped density - Tapped density

2. Determination of Hausner's ratio

The Hausner's ratio is a measure of the ease with which powder flows; it is determined using the following formula:[37]

Hausner's ratio = Tapped density / Untapped density

3. Determination of Carr's Index

Compressibility is the simplest way to quantify a powder's free flow property; it's a measure of the ease a material can be made to flow. It's computed as follows:[37]

Carr's index = Tapped density – untapped density / Tapped density * 100

4. Determination of Angle of Repose

The burette stand was attached with a clean and dry funnel with a 30 mm diameter circular stem and flat tip. A graph paper sheet was put beneath the funnel, with a 2cm gap between the lower tip of the funnel and the sheet. From the top of the funnel, the sample was poured until a heap of powder formed and reached the funnel's bottom tip. To cover the full amount of sample powder, a circle was drawn around the stack. The average diameter and radius of the circle, as well as its height, were measured and calculated using the formula provided.[36]

$$\Theta = \tan^{-1} h/r$$

5. Determination of Loss on Drying

2 grams of sample was placed in the oven at 105°C and weighed. The loss of weight is determined using the specified formula as a percentage loss on drying:[36]

%Loss on drying = Weight of sample after drying / Sample Weight *100

B. PHYSICOCHEMICAL PARAMETERS

1. DISINTEGRATION TEST

Complete disintegration is described as a soft mass with no viscerally solid core, with the exception of fragments of the insoluble coating or capsule shell, remaining on the screen of the test device or adhering to the lower surface of the disc if employed. To establish the capsule disintegration time, six capsules were used. A 1000 ml beaker was filled with distilled water (about 900ml) for the test. A total of six capsules were put to the test. The

time it took for the last capsule to disintegrate was recorded.[37]

2. IN-VITRO DRUG RELEASE STUDY [DISSOLUTION TEST]

The rate of absorption and bioavailability is determined by how quickly the drug dissolves in the gastrointestinal fluid. This indicates that drugs taken orally in solid dosage forms (tablets, capsules, etc.) dissolve in the gastrointestinal fluid before being absorbed. As a result, dissolution is employed as a bioavailability indicator. The IP Dissolution Test Apparatus Type was used to determine the release rate of formulated poly herbal capsules (basket type). At the start of each test, granules were first combined into an empty hard gelatin capsule of size #0 and then placed in a dry basket. The dissolution test was performed using 900 ml of phosphate buffer pH 6.8 and another acid buffer pH 2.5 at 50 rpm with the basket lowered in the dissolution media and the apparatus running at 50 rpm. 30 minute intervals were used to withdraw 1ml of sample solution. This was kept at the same temperature and then added to the bulk. Whatman filter paper No. 41 was used to filter the samples. A UV-Visible spectrophotometer was used to test the absorbance of these solutions. Cumulative percentage drug release was calculated using an equation obtained from a standard curve.[37]

3. STABILTY TEST

Stability testing was carried out for one month in accordance with ICH requirements at 40°C±2°C, 75% RH±5%. The disintegration time, and in-vitro drug release of the formulation have all been tested.[37]

RESULTS AND DISCUSSSION

The results of formulated anti-diabetic polyherbal capsule subjected to evaluation are as below:

A. Physical Evaluation

The physical evaluation such as Bulk Untapped density, Tapped density, Angle of repose, Hausner's ratio, Carr's index, Loss on drying(%) was carried out as per standard method and tabulated in Table 2.

Table 2: Results of Physical evaluation.

Sl.no	Parameters	Observation
01.	Bulk Untapped density (gm/ml)	15 gm/ml
02.	Tapped density	11 gm/ml
03.	Hausner's ratio	0.733
04.	Carr's index	36.6
05.	Angle of repose	19±0.122º
06.	Loss on drying (%)	9%

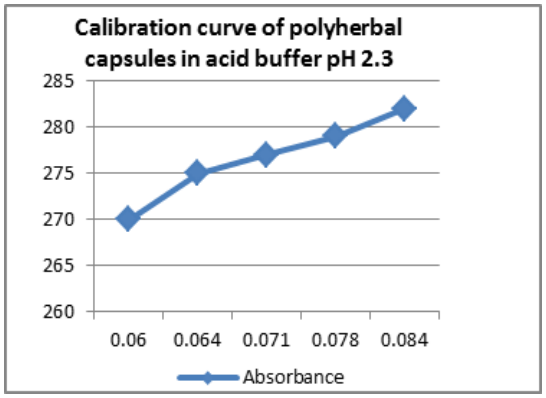
The formulated polyherbal anti-diabetic capsule showed, Bulk untapped density of 15 and Tapped density of 11 and the difference between these two values is 4, which shows good porosity value. Hausner's ratio was 0.733. From density data % compressibility was calculated and was found to be 36.6. Angle of repose was 19±0.122º which shows good flow property of encapsulated powder. 9% of loss on drying value shows a good stability.

B. Physicochemical evaluation

The results of physicochemical evaluation, such as Uniformity weight variation, Dissolution test, disintegration testwas carried out as per standard method and tabulated in table 3, table 4 and table 5 respectively.

Table 3: Dissolution test observation.

SL.NO	ACID BUFFER (pH 2.3)		NEUTRAL BUFFER(pH 6.8)	
	Wavelength	Absorbance	Wavelength	Absorbance
01.	270 nm	0.060 Au	270 nm	0.076 Au
02.	275 nm	0.064 Au	271 nm	0.078 Au
03.	277 nm	0.071 Au	274 nm	0.079 Au
04.	279 nm	0.078 Au	276 nm	0.081 Au
05.	282 nm	0.084 Au	279 nm	0.076 Au



Anti-diabtetic polyherbal formulationin hard gelatin capsule form shows steady release of drug content from capsules, especially in acid buffer solution within the time period of 30 minutes, therefore drug contents are well dissolved in gastric pH. In Neutral buffer solution, drug release shows slight unstable drug release patterns compared to acid buffer solution, which indicates that acid buffer is much better and drug release in gastric pH is comparatively good.

Table 4: Disintegration test observation.

SL.NO	CAPSULE.NO	OBSERVATION
01.	Capsule 1	3.33 minutes
02.	Capsule 2	3.13 minutes
03.	Capsule 3	2.48 minutes
04.	Capsule 4	3.35 minutes
05.	Capsule 5	2.55 minutes
06.	Capsule 6	3.10 minutes
	Average	**2.99 minutes**

The formulated hard gelatin polyherbal capsules shows average disintegration time of 2.99 minutes.

Table 5: Stability test observation.

Test after months	Disintergration time (Average Value)	Disolution test (AverageValue)	Loss on drying (%)
0	2.99 mins	0.0714 Au	9%
1	3.23mins	0.079 Au	8%

Stability study of anti-diabetic polyherbal hard gelatin capsule was done to comprehend the effect of temperature and humidity on capsules during the storage time. Capsules were evaluated periodically (0 and 1 months) for disintegration time, and in-vitro drug release. Stability study results show that there was no significant change in disintegration time, and in-vitro drug release of the formulation, which proves it's stability.

CONCLUSION

The formulated polyherbal anti-diabetic capsule has met with almost all the parameters values and comes under the specified limits. The developed polyherbal capsules were evaluated for its angle of repose, bulk density, tapped density, Hausner's ratio and Carr's index and was found to be satisfactory. Disintegration test, dissolution test and stability test was conducted on formulated polyherbal capsules and has shown gratifying values.

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