DESIGN, DEVELOPMENT & EVALUATION OF ANTI-DIABETIC HERBAL TABLET- A RESEARCH ARTICLE

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ABSTRACT:
It is the fact that diabetes can ít be cured and it has never been reported that someone had recovered totally from diabetes. The rapidly increasing incidence of diabetes mellitus is becoming a serious threat to mankind health in all parts of the world. Moreover, during the past few years some of the new bioactive drugs isolated from plants showed anti diabetic activity with more efficacy than oral hypoglycemic agents used in clinical therapy. The traditional medicine performed a good clinical practice and is showing a bright future in the therapy of diabetes mellitus. Many studies have confirmed the benefits of medicinal plants with hypoglycemic effects in the management of diabetes mellitus. The effects of these plants may delay the development of diabetic complications and correct the metabolic abnormalities. WHO has pointed out this prevention of diabetes and its complications is not only a major challenge for the future. In recent years, considerable attention has been directed towards identification of plants with antidiabetic ability that may be used for human consumption. It emphasizes strongly in this regard the optional and rational uses of traditional and natural indigenous medicines. There are vrious Herbs viz Neem Charaita Jamun Karela Katuj Babila Bahera are proved their anti-diabetic activity. These herbs used in single and in compound for various formulation to control the Diabetes in male and female.

Keyword: Diabetes, Herbal formulation

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DOI: 10.53555/ecb/2021.10.2.03

I. Introduction of Diabetes.

Diabetes definition**:** Diabetes mellitus is the condition of improper regulation of carbohydrate, protein and fat metabolism. It is a metabolic disorder characterized by hyperglycemia, glycosuria, and hyper lipidemia (Tripathi KD 2014) (Singh et al.) Metabolic abnormalities in carbohydrates, lipids, and proteins result from the importance of insulin as an anabolic hormone. Low levels of insulin to achieve adequate response and/or insulin resistance of target tissues, mainly skeletal muscles, adipose tissue, and to a lesser extent, liver, at the level of insulin receptors, signal transduction system, and/or effector enzymes or genes are responsible for these metabolic abnormalities. The severity of symptoms is due to the type and duration of diabetes. Some of the diabetes patients are asymptomatic especially those with type 2 diabetes during the early years of the disease, others with marked hyperglycemia and especially in children with absolute insulin deficiency may suffer from polyuria, polydipsia, polyphagia, weight loss, and blurred vision. Uncontrolled diabetes may lead to stupor,coma and if not treated death, due to ketoacidosis or rare from nonketotic hyperosmolar syndrome (balaji l et al)

A. Types of Diabetes

Diabetes mellitus, commonly known as diabetes, is a metabolic disease that causes high blood sugar. The hormone insulin moves sugar from the blood into your cells to be stored or used for energy. With diabetes, body either doesn't make enough insulin or can't effectively use the insulin it does make. Untreated high blood sugar from diabetes can damage your nerves, eyes, kidneys, and other organs. There are a few different types of diabetes:

Type 1 diabetes: is an autoimmune disease. The immune system attacksand destroys cells in the pancreas, where insulin is made. It's unclear what causes this attack. About 10 percent of people with diabetes have this type.

Type 2 Diabetes: occurs when the body becomes resistant to insulin, andsugar builds up in the blood.

Prediabetes: occurs when the blood sugar is higher than normal, but it's not high enough for a diagnosis of type 2 diabetes.

Gestational Diabetes: is high blood sugar during pregnancy. Insulin-blocking hormones produced by the placenta cause this type of diabetes.

A rare condition called diabetes insipidus is not related to diabetes mellitus, althoughit has a similar name. It's a different condition in which the kidneys remove too much fluid from the body. Each type of diabetes has unique symptoms, causes, and treatments.

B. Causes of Diabetes

Diabetes causes vary depending on the genetic makeup, family history, ethnicity, health and environmental factors. There is no common diabetes causes that fits every type of diabetes. The reason for no defined diabetes cause is because the causes of diabetes vary depending on the individual and the type. For instance; the causes of type 1 diabetes vary considerably from the causes of gestational diabetes.

C. Risk Factors for Type Diabetes

Although the exact cause of type 1 diabetes is unknown, factors that may signal an increased risk include:

Family history. The risk increases if a parent or sibling has type 1 diabetes.

Environmental factors. Circumstances such as exposure to a viral illness likelyto play some role in type 1 diabetes.

The presence of damaging immune system cells (autoantibodies). Sometimes family members of people with type 1 diabetes are tested for the presence of diabetes auto-antibodies. If the person has these auto-antibodies, they have an increased risk of developing type 1 diabetes. But not everyone who has these autoantibodies develops diabetes.

Geography. Certain countries, such as Finland and Sweden, have higher rates oftype 1 diabetes.

II. Plant Description.

A. Neem **Synonyms**: Neem, Vembu, Nim

Plant Biological Source: Neem consists of the fresh or dried leaves and seed oil of Azadirachta indica J. Juss (Melia Indica or M. azadirachta Linn. of Family: Meliaceae.

Chemical Constituents: Nimbosterol and flavonoids like kaempferol, melicitrin, nimbin, nimbinin, nimbidin, azadirachtin, azadiradione, frax

Pharmacological use: Anti-inflammatory Antiarthritic Antipyretic Hypoglycaemic Antigastric ulcer Spermicidal Antifungal

Antibacterial Diuretic (Bijauliya. R., Alok. S .IJPSR, (2018)

B. Chirayata Synonyms: Chota chirayata
Plant /Biological Source: Chirata consists of the entire herb of *Swertia chirata* Buch-Ham, belonging to family Gentianaceae. It contains not less than 1.3% bitter constituent.

Chemical Constituents: Betulin, a triterpene sapogenin, catechins, saponins, steroids, vanillic acid, syringic acid
Pharmacological use: Antimicrobial activity, Antihelminthic activity, Hypoglycemic activity, Anti hyperlipidaemic activity, Hepato protective activity (Sranaya.R. et al.,APJTB, (2013)

C. Jamun Synonyms: Jamun
Plant /Biological Source: The black plum, Syzygium cumini (family Myrtaceae), also known as java plum or jamun, is originated from Southeast Asia.

Chemical Constituents: Jambosine, Gallic acid, Ellagic acid, Corilagin, Anthocyanins, Delphinidin, Petunidin
Pharmacological use: Astringent, Anti-diabetes, Appitizer, Antibilious, Hepato protective (Parveen. S., et al., WJPPS, (2017)

D. Kutaj Synonyms: Kutaj
Plant /Biological Source: *It consist of outer peet of the plant Holarrhena antidysenterica belonging to family* Apocynaceae.

Chemical Constituents: Alkaloids, Flavonoids, triterpinoids, Sterols, Saponins, Triterpinoid
Pharmacological use: Antidiabetic, Neuro protective, Antibacterial, Antimalarial. (Mrinal et. al., SAJP,(2018).

E. Karela Synonyms: Karela
Plant /Biological Source: Momordica charantia Linn. (Karela) commonly known as Bitter melon or Bitter gourd is tropical and subtropical climber of the family Cucurbitaceae.

Chemical Constituents: Steroidal saponin, Charantin, Momordicin, Alkaloid, glycoside, Saponin.
Pharmacological use: Stomachic, carminative, Rheumatism, Gout, Anti diabetic. (C.K. Kokate et al.,Drugs containing glycoside, (2012).

F. Babila Synonyms: Babila

Plant Biological Source: It consists of plant dried and fresh leaves of plant *Pterocarpus marsupium* Roxb. Belonging to family Fabaceae

Chemical Constituents: Ptero stilbene, alkaloids, tannins, protein, iquiritigenin, iso liquiritigenin, pterostilbene, pterosupin, epicatechin, catechin, kinotannic acid, kinoin, kino red,

Pharmacological use

Antimicrobial, Antiviral, Anti diabetic, Anti-hyperlipidemic. (Rahman et al., Pharmacognosy, (2018).

G. Bahera Synonyms: Bahera

Plant Biological Source: It consists of dried unripe fruits of *Terminalia belerica* Roxb. Of family Combretaceae.

Chemical Constituents: Beta cetosterol, gallic and ellagic tannins, Coloring matter, resins and a greenish yellow oil, ethyl gallate, galloyl glucose and chebulaginic acid, phenyllemblin, β-sitosterol, manitol, glucose, fructose andrhamnose.

Pharmacological use: Anticancer, Antidepressant, Angiogenesis, Anti diabetic (Kumar N. et al., IJNPS(2018).

III. Formulation of Tablet

No	Ingredient	Weight (mg)
1.	Powder Extract	250
2.	Starch Maize	25
3.	Microcystalline Cellulose	50
4.	Magnesium Stearate	25

Preparation of Granules:

The Polyherbal tablets were prepared by wet granulation method. The composition of tablet formulation is given in table no. 4. Weighed amount of crude drugs and excipients were taken in bowl and mixed manually for 5 min. Then the blend was mixed with starch using water as a granulating agent. Then the mass formed was sieved through 60 mesh screen and dried in hot air oven at 50ºC for 30 min. After that the dried granules obtain were compressed into tablets using single press tablet compression machine.

IV. Preformulation study: (Lachman et al., 1987)

A. Angle of repose:

The frictional force in powder can be measured by angle of repose. It is the maximumangle possible between the surfaces of pile of powder to the horizontal plain the blendthat has angle of repose between 20 -30˚ is best for compression as it has good flow property. Angle of repose is calculated by fixed funnel method in this method funnel was fixed to a stand so that the lower tip of funnel was 2.5 cm above the surface. A graph paper was placed on the flat surface the blend was allowed to fall freely on the graph paper through the funnel till the tip of heap formed just to touch the funnel. The radius of heap was noted and from this angle of repose was determined. The angle of repose θ can be calculated using the equation;

$\tan \theta = h/r$

Where; h = height of the heap, r = radius of the heap

The flow properties according to the angle of repose are as follows;

Flow property of powder

Sr. No.	Flow property	Angle of repose
1	Excellent	25-30
2	Good	31-35
3	Fair	36-40
4	Passable	41-45
5	Poor	46-55
6	Very poor	56-65
7	Very very poor	>66

B. Hausner's ratio:

It is defined as the ratio of tap density and bulk density. It is indicative of the easewith which a material can be induced to flow.

Hausner's ratio= Tap density/Bulk density

C. Carr's compressibility index:

It is indicative of the ease with which a material can be induced to flow. It can be determined as; Carr's compressibility index = [(Tap desnity-Bulk density) / Tap density] x 100

D. Bulk density:

Bulk density is defined as mass of powder divided by bulk volume. It is calculated using following formula;

Bulk density = weight of sample taken/ untapped volume

A sample of about 5 g was poured into 10 ml graduated cylinder. Then cylinder was dropped at 2 sec interval into a hard wooden surface, three times from a height of 1 inch.

E. Tap density:

It is the ratio of total mass of the powder to the tapped volume of powder. The volume was measured by tapping the powder for a fixed time. The maximum volume occupied in the cylinder and the weight was measured. The tapped density was calculated using the formula;

Tap density = weight of sample taken/ tapped volume

F. Compression of Tablets:

Desired quantity of granules were weighed and fed manually to a single press tablet compression machine (Pharmaceutical laboratory, UDPS Nagpur) and compressed at a weight of 300 mg where compression force was kept constant for all tablets.

V. Evaluations of tablet: (Lachman et al., 1987)

A. Hardness test:

Tablets require a certain amount of strength or hardness and resistance to withstand mechanical shock of handling in manufacture, packing and shipping. To perform this test tablets were placed between two anvils, force to the anvils and the crushing strength that just causes the tablets to break was recorded. Monsanto hardness tester was used to measure the hardness of tablets. The results were expressed in kg/cm2.

B. Friability test:

The friability (%) of tablets was determined by using Roche type friability testing apparatus. The tablets were subjected to the combined effect of abrasion and shock by utilizing a plastic chamber that revolves at 25 rpm, dropping the tablets at a distanceof six inch with each revolution. Twenty tablets were weighed and placed in the Roche friability test apparatus. After 100 revolutions, the tablets were deducted and weighed again. The friability was determined as the percent loss in weight of the tablets.

$$\text{Friability (\%)} = 1 - \frac{\text{Weight of tablets after 100 revolutions}}{\text{Initial weight of tablets}} \times 100$$

The acceptable % friability limit of conventional compressed tablet is 0.5 to 1.0 %.

C. Disintegration time: [Jozeff AL 2015] [USP 2019]

Disintegration test was performed using the digital microprocessor based disintegration test apparatus. One capsule was introduced into each tube and a disc was added to each tube. The assembly was suspended in water in a 1000 ml beaker. The volume of water at its highest point was at least 25 mm below the surface of the water and at its lowest point was at least 25 mm above the bottom of the beaker. The apparatus was operated and maintained at a temperature of 37 ± 2ºC.

D. Weight variation test:

Twenty tablets were selected randomly from each formulation batch and weighed individually. The average weight and % weight variation was calculated. as per USP, not more than two of individual weight should deviate percentage limit and none deviate more than twice that percentage limit.

Table No. 5: Weight variation limits for uncoated tablets as per USP

Sr. No.	Average Weight of Tablet(mg)	Maximum % Difference Allowed
1	130 or less	± 10
2	130-324	± 7.5
3	More than 324	± 5

E. Determination of pH: (Lognathan et al., 2001)

The pH measurement was carried out by using a calibrated digital type pH meter by dipping the glass electrode and the reference electrode completely into the formulation so as to cover the electrodes. The pH meter was calibrated by using standard pH tablets of 4, 7 and 9.2 pH respectively.

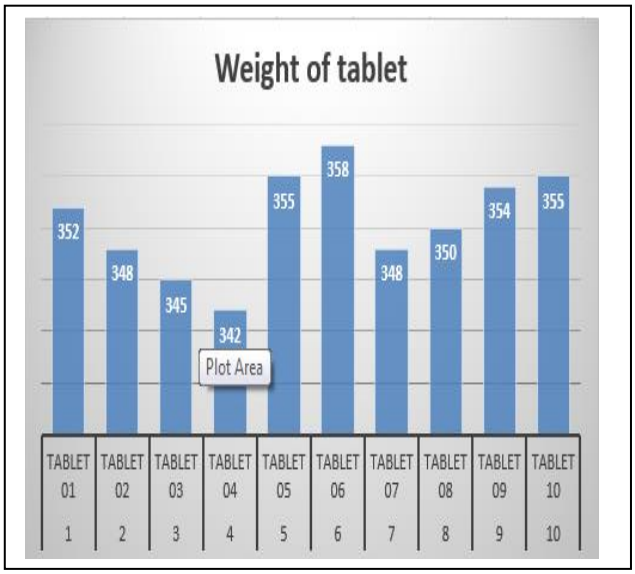
VI. Extraction of Raw Material: Cold Maceration Method.

In the cold maceration method of extraction, weighed a required quantity of coarsely powdered crude drugs and transferred it to a closed vessel. To this vessel required volume of menstrum (Distilled water) is added. To this solution few drops of chloroform is added as preservative. The system is allowed to stand for seven days, with occasional shaking. After seven days of occasional shaking the liquid is filltered off and the mark (solid residue) is pressed to recover as much occluded solution as possible, combined liquid is clarified by filtration or decantation after standing.

Physico-chemical Evaluations:

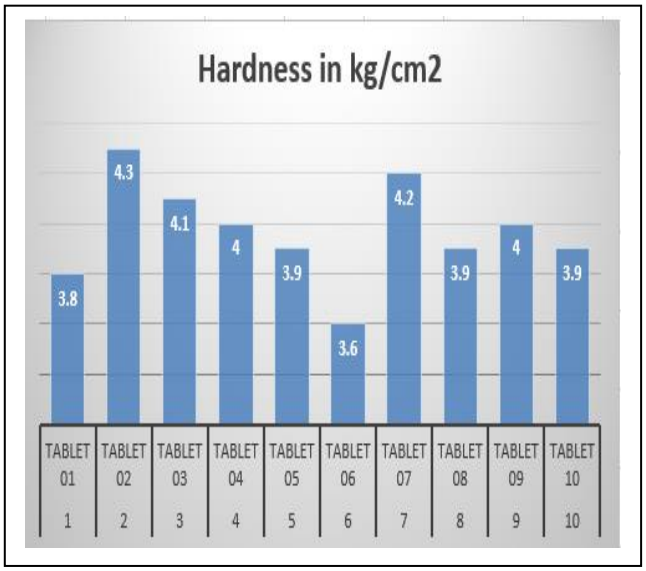
A. Weight variation of tablet

No.	Number of Tablet	Weight of tablet
1	Tablet 01	352 mg
2	Tablet 02	348 mg
3	Tablet 03	345 mg
4	Tablet 04	342 mg
5	Tablet 05	355 mg
6	Tablet 06	358 mg
7	Tablet 07	348 mg
8	Tablet 08	350 mg
9	Tablet 09	354 mg
10	Tablet 10	355 mg



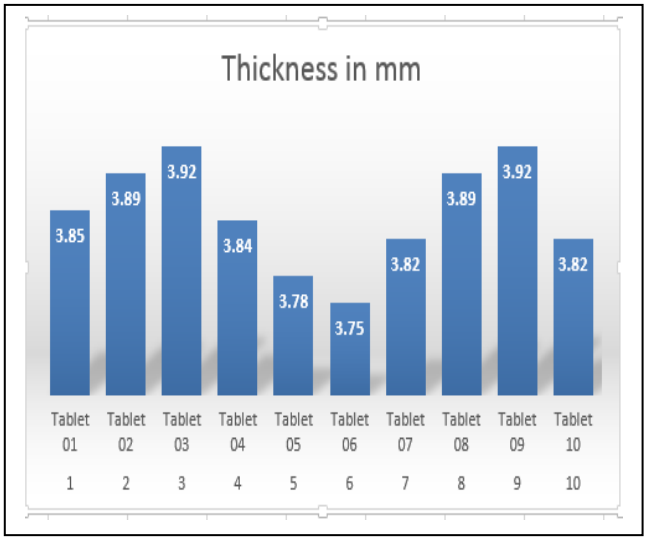
B. Hardness Variation

No.	Number of Tablet	Hardness in kg/cm^2
1	Tablet 01	3.8 kg/cm^2
2	Tablet 02	4.3 kg/cm^2
3	Tablet 03	4.1 kg/cm^2
4	Tablet 04	4.0 kg/cm^2
5	Tablet 05	3.9 kg/cm^2
6	Tablet 06	3.6 kg/cm^2
7	Tablet 07	4.2 kg/cm^2
8	Tablet 08	3.9 kg/cm^2
9	Tablet 09	4.0 kg/cm^2
10	Tablet 10	3.9 kg/cm^2



C. Thickness Variation

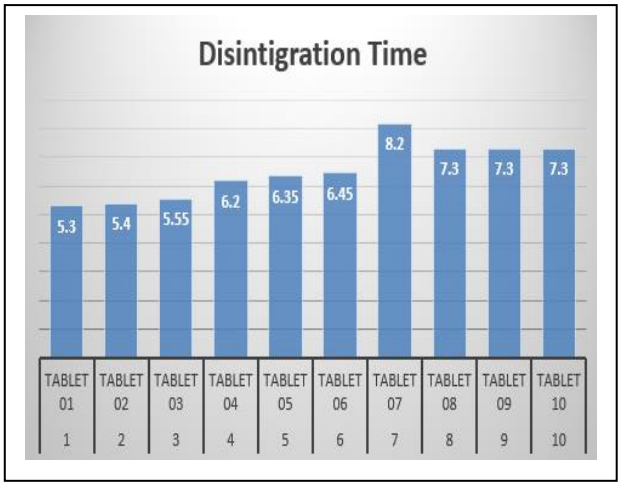
No.	Number of Tablet	Thickness in mm
1	Tablet 01	3.85 mm
2	Tablet 02	3.89 mm
3	Tablet 03	3.92 mm
4	Tablet 04	3.84 mm
5	Tablet 05	3.78 mm
6	Tablet 06	3.75 mm
7	Tablet 07	3.82 mm
8	Tablet 08	3.89 mm
9	Tablet 09	3.92 mm
10	Tablet 10	3.82 mm



D. Disintegration time.

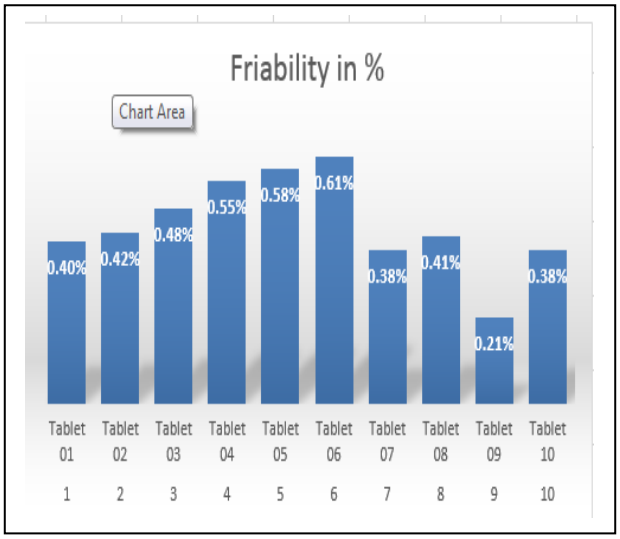
No.	Number of Tablet	Disintigration Time
1	Tablet 01	5.30 minutes
2	Tablet 02	5.40 minutes
3	Tablet 03	5.55 minutes
4	Tablet 04	6.20 minutes
5	Tablet 05	6.35 minutes

6	Tablet 06	6.45 minutes
7	Tablet 07	8.20 minutes
8	Tablet 08	7.30 minutes
9	Tablet 09	7.30 minutes
10	Tablet 10	7.30 minutes



E. Friability Test

No.	Number of Tablet	Friability in %
1	Tablet 01	0.40 %
2	Tablet 02	0.42%
3	Tablet 03	0.48%
4	Tablet 04	0.55%
5	Tablet 05	0.58%
6	Tablet 06	0.61%
7	Tablet 07	0.38%
8	Tablet 08	0.41%
9	Tablet 09	0.21%
10	Tablet 10	0.38%



F. Chemical Evaluation test

No.	Parameters	Observations (% w/w)
1	Ash Value	
	Total ash	20.35
	Water Soluble ash	10.09
	Acid –Insolubleash	4.18
2	Extractive Value	
	Alcohol Soluble	7.2
	Water Soluble	25.1
3	Loss on Drying	9.45

G. Organoleptic Properties of Powder Formulations:

No.	Parameters	Observations
1	Colour	Greenish Yellow
2	Odour	Characteristic
3	Texture	Smooth
4	Shape	Powder
5	Taste	Sweet

H. Preliminary Phytochemical Screening:

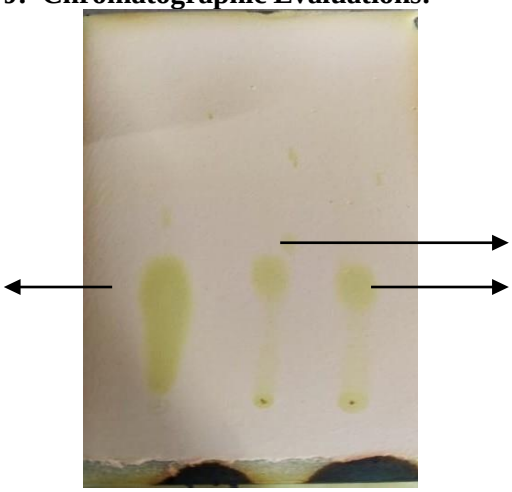
No.	Plant Constituents	Test Reagents	Inference
1	Carbohydrates	Molish's test	+
2	Proteins	Biuret test	+
		Xanthoprotic test	+
3	Amino Acid	Ninhydrin test	+
4	Sterols	Salkowaski reaction	+
5	Glycosides	Killer Killiani	+
		Foam test	+
6	Alkaloids	Dragen dorff's reagent	+
		Mayer's Reagent	+
		Hager's reagent	+
		Wagner's Reagent	+
7	**Tannins and Phenols**	Ferric chloride Test	+
		Lead Acetate	+
		Potassium dichromate test	+
		Bromine water	+
8	**Flavonoids**	Shinoda test	+
		NaOH + Acid test	+

I. Quantitative Estimations:

No.	Parameters	Results
1	Total Phenol Content (mg/g)Eq. Gallic acid	88.51±6.08
2	Total flavonoid content (mg/g)Eq. Quercetin	25.46±1.57
3	Total Saponin content (mg/dl)Eq. Diosgenin	181.19±12.12
4	Tannin Content (mg/g) Eq. Tannic acid	679.77±184.22
5	Total alkaloids (% w/w)	0.30±0.01
6	Total carbohydrate content (mg/dl) Eq. Dextrose	836.04±35.18
7	Total flavonol content (mg/g)Eq. Quercetin	17.96±1.29

Eq: Equivalent Values are expressed as Mean ± SEM (n=3)

J. Chromatographic Evaluations:



Standard Gallic acid
Spot 1: Powder extract
Spot 2: Powder extract

K. Rf value = Distance travelled by sample / Distance travelled by the solvent front

No.	Mobile Phase	Rf Value		
		Standard	Spot 1	Spot 2
1.	Tolune: Ethyl acetate: Methanol: Formic acid(6:3:1:0.5)	0.437	0.437	0.425

L. Pre-formulation Studies:

No	Parameters	Observations	Flow Property
1	**Angle of repose (θ)**	29.29°	Excellent
2	**Hausner's ratio**	1.186	Good
3	**Carr's index (%)**	15.68	Good
4	**Bulk density (g/cm^3)**	0.43	-
5	**Tap density (g/cm^3)**	0.51	-

M. Preparation of In-house Tablet:

N. Organoleptic Properties of Tablets:

No.	Parameters	Observations
1.	Colour	Greenish Yellow
2.	Odour	Characteristic
3.	Texture	Smooth
4.	Shape	Standard concave
5.	Taste	Sweet

Summary & Discussion

The marketed formulation in the form of crude powder in sachet, due to its peculiar practice of dose consumption leads to poor patient compliance. Therefore, a new dosage form for the contents is required. Before the preparation of new dosage form, Estimation of different physicochemical and phytochemical parameters of crude powder is carried out. It helped maintaining quality and purity of that particular drug and its formulation and also helped to prevent it from being adulterated by drug of same genus or other species having low potency. The physicochemical parameters such as LOD, ash value, extractive values were evaluated. The results showed the presence of negligible moisture content in polyherbal extract. Extractive value determines the amount of activeconstituents in a given amount of medicinal plant material when extracted with solvents. Unwanted parts of drugs sometimes possess a character, which will raise the Ash value. Ash value was found to be within the limit as per

Indian Pharmacopoeia. The chemical nature of the active constituents present in the polyherbal extract which is identified by performing preliminary phytochemical screening. It showed the presence of flavonoids, tannins, saponins, alkaloids, phenols, carbohydtrates, proteins, amino acids, glycosides .The quantitative estimation performed in the present study depicted the presence of polyphenol, flavonoid, saponin, tannin, alkaloidal, carbohydrate and flavonols content. Tannins and carbohydrate content was found to be in higher amount while the others were present in quite considerable amount.In TLC finger printing study, Rf value of one of the constituent matches with the standard Gallic acid in Tolune: Ethyl acetate: Methanol: Formic acid(6:3:1:0.5) ratio as a solvent system.Various pharmaceutical parameters for tablet Formulations were performed. The pharmaceutical parameters before compression of tablet includes angle of repose, Hausner's ratio, Carr's compressibility index, bulk density, tap density, pH and Parameters after compression of tablets includes organoleptic properties, weight variation, hardness, friability and disintegration test. These parameters were found to be within the limits stated by Indian Pharmacopoeia.

CONCLUSION

In the present research work, attempts were made for the physicochemical, phytochemical and chromatographic evaluation of polyherbal tablet formulation for its potential against Diabetes Mellitus. The physicochemical parameters were evaluated and were found to be within the prescribed limits as per standard values mentioned in API. Pharmaceutical parameters of polyherbal tablet formulations were evaluated and found to be within the prescribed limit as per standard values of IP and USP. Phytochemical study revealed the presence of mainly alkaloids, flavonoids, tannins, polyphenol, saponin and carbohydrates which were found to be in considerable amount in polyherbal extract. The quantitative estimation performed in the present study depicted the presence of polyphenol, flavonoid, saponin, tannin, alkaloidal, carbohydrate and flavonols content in extract. Tannins and carbohydrate content was found to be in higher amount while the others were present in quite considerable amount. The TLC analysis of Polyherbal extract showed the presence of gallic acid in Tolune: Ethyl acetate: Methanol: Formic acid (6:3:1:0.5) ratio as a solvent system. In conclusion, we have successfully evaluated the physicochemical, phytochemical, and chromatographic evaluations of polyherbal tablet formulation which will act as a referential source for standardization of other formulations. The present research work suggests that, there are various synthetic drug present for treatment of Diabetes Mellitus which can produce major side effects but the use of this type of polyherbal tablet formulations in combination is efficacious and safe in the treatment of Diabetes Mellitus. Thus from the overall study we have scientifically justified the traditional claims of plant extract included in the polyherbal tablet formulation used in the treatment of Diabetes Mellitus by performing physicochemical, phytochemical and chromatographic evaluation.

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