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Formulation, Evaluation and Comparison of the Poly Herbal Anti-Diabetic Tablet with the Commercial Tablets

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Authors' contributions

This work was carried out in collaboration among all authors. All authors read and approved the final manuscript.

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ABSTRACT

Objective: To formulate a poly herbal anti-diabetic tablet and to evaluate and compare its physicochemical properties with the marketed herbal tablets.
Materials and Methods: The poly herbal anti-diabetic tablet was formulated by adding the powder of extract of *Enicostemma littorale* in powder of roots of *Aconitum heterophyllum* rhizomes of *Picrorhiza kurroa* and fruits of *Piper longum* in different proportions to an aqueous 5 % Starch solution and Several tests such as visual inspection, ash values, moisture content, Water soluble extractive value and Alcohol soluble extractive value, disintegration time, Uniformity of weight of tablets, Determination of hardness of tablets, Determination of friability of tablets etc and Preliminary phytochemical screening and qualitative chemical examination were performed and compare Laboratory formulated tablets with commercial tablets.
Results: The study showed that Laboratory formulated poly herbal anti-diabetic tablet has good flow property and compressibility. The moisture content of laboratory formulations was found to be 4.8%. Water extractive value was found to be 28.14% W/V result shows that laboratory formulation consisted of higher amount of water soluble substances like carbohydrates. Alcohol extractive

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value was found to be 20.08% W/V denotes the amount of alcohol soluble constituents present in the formulation. Disintegration of tablet was found to be 3 mins results shows laboratory formulation was within the limit as it was prepared with starch paste (5%w/v) as a binding and disintegrating agent. Disintegration of tablet is not more than 30 minutes. The laboratory formulation was found to have 3 (Kg/Cm2) hardness, 0.38 % Friability and weight variation within pharmaceutical limits. However, further research and development is required to improve its quality and safety.

Conclusion: The aim of this study was to formulate a completely poly herbal antidiabetic tablet. Our Laboratory formulated tablets showed comparable good results as compare to that of marketed tablets but further research and development is required to improve its overall quality.

Keywords: Diabetes; herbs; medicinal plants; hyperglycaemia; madhumeha; antidiabetic herbal tablets; ash value.

1. INTRODUCTION

Diabetes is one of the major crippling diseases in the world. The persons suffering from this metabolic disease is considered to 'die-a-bit' and hence 'die-a-bit-is' (diabetes). Diabetes mellitus is a chronic disorder with interrelated metabolic and vascular components. A relative or absolute deficiency of insulin secretion and activity is associated with hyperglycaemia and altered lipid and protein metabolism. Studies conducted in India in last decade have highlighted that not only is the prevalence of diabetes high but also that it is increasing rapidly in urban population. It is calculated that there are approximately 33 million adults with diabetes in India this number is likely to increase to 57.2 million by the year 2025 [1-6].

Diabetes mellitus also known as simply diabetes is a group of metabolic diseases in which there are high blood sugar levels over a prolonged period. This high blood sugar produces the symptoms of frequent urination, increased thirst, and increased hunger. Untreated, diabetes can cause many complications. Acute complications include diabetic ketoacidosis and nonketotic hyperosmolar coma. Serious long-term complications include heart disease, stroke, kidney failure, foot ulcers and damage to the eyes. Globally, as of 2013, an estimated 382 million people have diabetes worldwide, with type 2 diabetes making up about 90% of the cases. This is equal to 8.3% of the adult's population, with equal rates in both women and men. Worldwide in 2012 and 2013 diabetes resulted in 1.5 to 5.1 million deaths per year, making it the 8th leading cause of death. Diabetes overall at least doubles the risk of death. The number of people with diabetes is expected to rise to 592 million by 2035. The economic costs of diabetes globally were estimated in 2013 at $548 billion and in the United States in 2012 $245 billion. Journal of Metabolic Syndrome publishes the articles related to diabetes [1-7].

In Ayurveda diabetes is known as 'madhumeha' and several herbs are mentioned for its cure. One of the formulations in "Bhaisajya Samhita" is mamejva ghanvati which is used in diabetes. It is an Ayurvedic anti-diabetic formulation. It is well documented in Ayurvedic text for sugar lowering potential and used traditionally since ages for mild to moderate hyperglycaemia. In Ayurveda diabetes is known as 'madhumeha' and several herbs are mentioned for its cure. One of the formulations in "Bhaisajya Samhita" is mamejva ghanvati which is used in diabetes. It is an Ayurvedic anti-diabetic formulation. It is well documented in Ayurvedic text for sugar lowering potential and used traditionally since ages for mild to moderate hyperglycaemia. Several market formulations are also available [8-11].

Enicostemma littorale (Gentianaceae), commonly known as Chota-kirayata or Chota chirayata (Hindi) and Mamejavo (Gujarati), is being used as a folk medicine for the treatment of diabetes mellitus. The plant *Aconitum heterophyllum* is traditionally used for curing hysteria, throat infection, dyspepsia, abdominal pain, diabetes, and diarrhea. *Picrorhiza kurroa* (Scrophulariaceae) is a traditional Ayurvedic herb known as Kutki. It is used as a remedy for diabetes. *Piper longum* is beneficial for diabetics because it can regulate the rate at which glucose is released in the blood. Insulin production is also boosted by pippali herb. Hence, regular consumption of long pepper is beneficial for all diabetics.

Enicostemma littorale [12,13], *Aconitum heterophyllum* [14,15], *Picrorhiza kurroa* [16,17] and *Piper longum* [18,19] are used in preparation of antidiabetic Herbal Tablets.

2. MATERIALS AND METHODS

2.1 Collection and Authentication of plant Materials

The entire materials mamejva herb, roots of ativis, rhizomes of kutki and fruits of pippli were procured from the Ayurvedic drug supplier named M/S Lallubhai Vrajlal Gandhi (LVG), Ahmedabad.

2.1.1 Morphological and Microscopically study of plant materials

The morphology of all the plant materials obtained from the market was studied and compared with the standard literature. Powder study of *Enicostemma littorale*, *Aconitum heterophyllum*, *Picrorhiza kurroa* and *Piper longum* was done.

2.2 Collection of Market formulations

The market formulations of Mamejva ghanvati of different manufacturers 'BAPS Amrut', 'Shree Shanker' and 'Unjha' were procured from the local market of Ahmedabad in December 2019. Laboratory formulation was also prepared.

2.3 Formulation of Antidiabetic Herbal Tablets [20-27]

Initially 25.60 gm leaf powder of of *Enicostemma littorale* was taken and water was added and it was kept for 6 hours with constant stirring. It was then filtered with a cloth and heated until ghan (solid extract) prepared. Then 0.4gm powders of *Aconitum heterophyllum, Picrorhiza kurroa* and *Piper longum* were added in their respective quantities. The ingredients were passed through sieve number 60 and the granulation was done by wet granulation technique. 5% starch paste was added as a binding and disintegrating agent.

All the ingredients were mixed properly and the resulting solid mixture was used to prepare granules with the help of sieve no. 10. The granules were sun dried and then passed through sieve no. 22 and 44. Granules was collected on sieve no. 44 and were stored in air tight pot bottle and used for preparation of tablets in the tablet machine.

The die and punches used for making tablets were of 7mm. The tablet machine used was RSB-4 Minipress, Rimek India, Single head Rotary tablet compression machine.

Table 1. Composition of Formulation of Herbal Tablets

Sr No	Ingredients	Quantity
1	*Enicostemma littorale*	256 mg
2	*Aconitum heterophyllum*	4 mg
3	*Picrorhiza kurroa*	4 mg
4	*Piper longum*	4 mg
5	Starch	2 mg

Weight of each tablet was of 270 mg. A batch size of 100 tablets was prepared.

2.4 Evaluation of Formulated and Commercial Poly Herbal Diabetic Tablets [28-33]

To evaluate the quality of commercial and prepared formulations, several quality control tests including organoleptic parameters, ash values, moisture content, extractive values, disintegration time, uniformity weight of tablets, hardness of tablets, friability of tablets, tests were performed

2.4.1 Organoleptic parameters

All the four formulations were evaluated for their appearance, colour and odour. Its results were noted down in Table 2.

2.4.2 Physicochemical parameter

2.4.1.1 Determination of ash values

a. Total ash:

2 to 3g of the air dried drug was weighed accurately in a silica dish and incinerated at a temperature not exceeding 450°C until free from carbon, cooled and weighed. The percentage of ash on dried drug basis was calculated.

b. Acid insoluble ash:

The ash obtained in (a) was boiled with 25 ml of 2M hydrochloric acid for 5 minutes, the insoluble matter was collected on an ashless filter paper, washed with hot water, ignited, cooled in desiccators and weighed. The percentage of acid insoluble ash on the dried drug basis was calculated.

c. Water soluble ash:

The ash obtained in (a) was boiled for 5 minutes with 25 ml of water, the insoluble

matter was collected on an ashless filter paper, washed with hot water and ignited for fifteen minutes at a temperature not exceeding 450°C. The weight of the insoluble matter was subtracted from the weight of the ash; the difference in weight represented the water soluble ash. The percentage of water soluble ash on dried basis was calculated.

2.4.1.2 Determination of moisture content

2gm of powdered formulation was taken in previously dried petridish. Then drying was carried out in an oven at 60°C till constant weight was obtained. The difference in the weight before and after drying was calculated. Difference in weight was content of moisture in sample.

2.4.1.3 Determination of extractive values

a. Water soluble extractive value and Alcohol soluble extractive value

5g of air dried of all formulations; coarsely powdered was macerated with 100 ml of water in a closed flask for 24 hours, with frequent shaking during the first 6 hours and allowed to stand for 18 hours. Thereafter this was filtered rapidly taking precaution against loss of water, 25 ml of filtrate was evaporated to dryness in a tared flat bottom shallow dish and dried at 105° C and weighed. The percentage of water soluble extractive was calculated with reference to air dried drug. Similar procedure is carried for alcohol soluble extractive value using ethanol instead of water.

b. Determination of disintegration time

Place 5 tablets in a tube of disintegration apparatus and the apparatus were started for up and down movement of the tube in such a manner that the complete up and down movement was repeated 30 times a minute. The tablets were disintegrated when no particle remain above the gauge which would not readily pass through it. The time required for the five tablets to disintegrate in the manner described should be not more than 30 minutes.

c. Uniformity of weight of tablets

The average weight was determined by weighing 20 tablets. The tablets were also weighed singly. The deviation from the average weight in each case were also calculated and expressed as percentage. It was necessary that not more than two tablets of all tablets deviates from the average weight by a greater percentage than the limits and no tablet deviates by more than double that percentage.

d. Determination of hardness of tablets

Tablet was placed between the plungers of the Monsanto hardness tester as mentioned above and then upper plunger was forced against the spring by turning threaded bolt until the tablet fractures. When tablet fractured, reading on the scale of hardness tester was noted.

e. Determination of friability of tablets

For determination of friability of tablets, 20 tablets were preweighed and then tablets were placed in plastic chamber of Roche friabilatior and apparatus was started to revolve for 4 minutes at the 25rpm. After 4 minutes tablets were unloaded from the chamber, dusted and again reweighed. The difference in the weight was calculated.

2.4.3 Preliminary phytochemical screening and Qualitative Chemical Examination

25 gm powder of each formulation was taken and extracted in soxhlet apparatus with the solvents of increasing polarity i.e. Petroleum ether, Toluene, Chloroform, Acetone, Methanol and water [24,26].

The extracts obtained in the above procedure were subjected to various Chemical tests for present or absence of phytoconstituents such as Alkaloids, Flavonoids, Glycosides, Carbohydrates, Phytosterols, Tannins and phenolic compounds, Saponins [28,29,30].

3. RESULTS

3.1 Morphological and Microscopically powder study of plant materials

The morphology of all the crude plant materials and microscopy of powder was studied and compare with standard literature.

Morphological of plant materials

***Enicostemma littorale* plant**

***Aconitum hetrophyllum* root**

***Picrorhiza kurroa* rhizome**

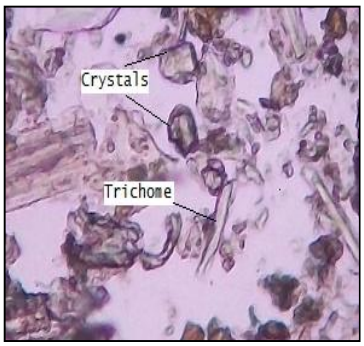
***Piper longum* fruit**

Fig. 1. Morphological of plant materials

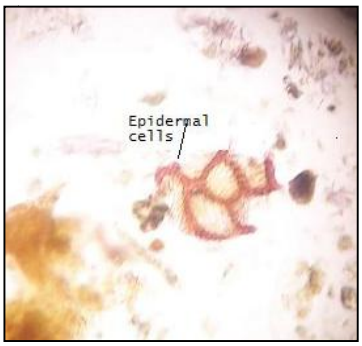
Microscopically powder study of plant materials

Xylem vessels

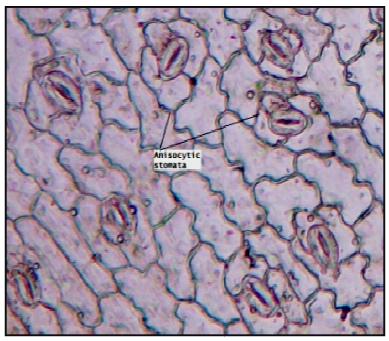
Seed coat and bordered pitted xylem vessels



Crystals and trichome

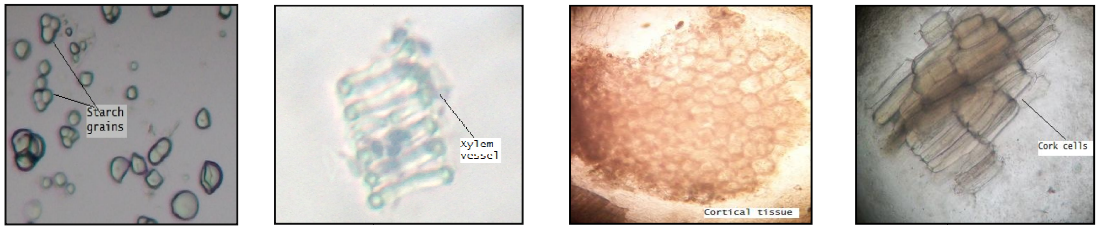


Epidermal cells



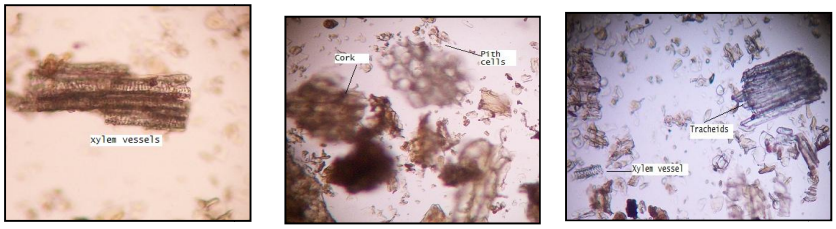
Anisocytic stomata in leaf Surface preparation

Fig. 2. Powder study of *Enicostemma littorale*



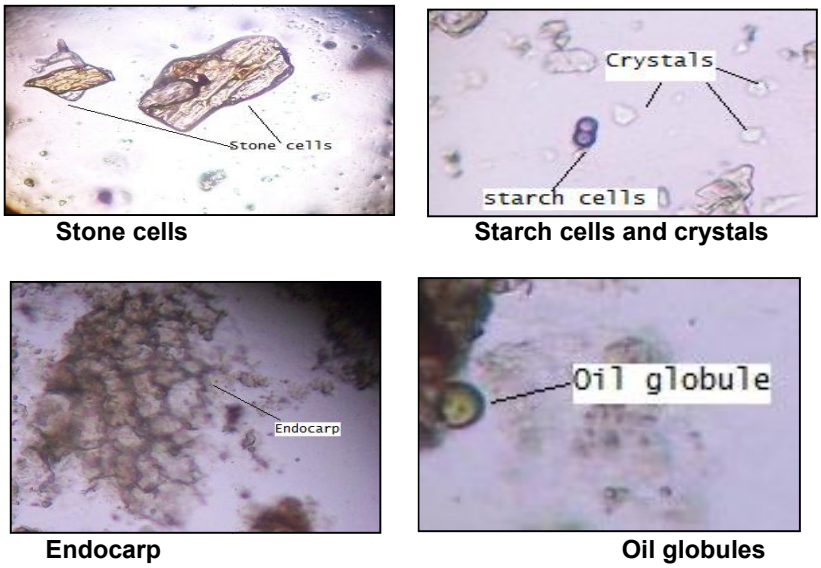
Starch cells **Xylem vessel** **Cortical tissue** **Cork cells**

Fig. 3. Powder study of *Aconitum heterophyllum*



Xylem vessels **Pith cells and Cork cells** **Tracheids and pitted xylem vessel**

Fig. 4. Powder study of *rhizomes of Picrorhiza kurroa*



Stone cells **Starch cells and crystals**

Endocarp **Oil globules**

Fig. 5. Powder study of *Piper longum fruits*

3.2 In the Following Results

MF 1 denotes BAPS formulation
MF 2 denotes SHANKER formulation
MF 3 denotes UNJHA formulation
LF denotes Laboratory formulation

3.3 Organoleptic Parameters

3.3.1 Appearance, colour and odour of formulations

Appearance, colour and odour of all three marketed formulation and laboratory formulation are studied in Table 2.

Table 2. Appearance, Colour and Odour of Formulations

SR. NO.	Sample	Appearance	Colour	Odour
1.	MF 1	Smooth coated	Black	None
2.	MF 2	Smooth coated	Black	None
3.	MF 3	Uncoated	Brownish black	Characteristic
4.	LF	Uncoated	Greenish brown	Characteristic

3.3.2 Physicochemical parameter

i. Determination of ash values

Total ash, acid insoluble ash and water soluble ash were found to be present in order MF 2> MF1> MF3> LF. Lowest values were found in LF and highest values were found in MF2. Higher ash values indicate contamination due to extraneous material which contains carbonates, phosphates, silicates and silica. High acid insoluble ash is due to present of greater amount of silica especially sand and siliceous earth.

ii. Determination of moisture content

Low moisture content of the formulation is needed to prevent it from microbial spoilage and degradation of active constituents. The moisture content of the all formulations was in limit as found to be in order as LF> MF3> MF2> MF1. Highest moisture content was found in LF whereas lowest was found in MF1.

iii. Determination of extractive values

Water extractive value denotes the amount of polar substances present in the formulation. It was found in order as LF>MF3>MF1>MF2. Highest value was found in LF whereas lowest value was found in MF2. The result shows that laboratory formulation consisted of higher amount of water soluble substances like carbohydrates.

Alcohol extractive value denotes the amount of alcohol soluble constituents present in the formulation. Results suggested that alcohol extractive values were in order as LF> MF3> MF1>MF 2. Highest value was found in LF and lowest value was found in MF2.

iv. Determination of disintegration time

It was found from the results that all the three market formulations did not pass the disintegration test as per IP 2007 whereas laboratory formulation was within the limit as it was prepared with starch paste (5%w/v) as a binding and disintegrating agent. Disintegration of tablet is very crucial as if the tablet does not disintegrate in time; it remains in the body without any effect as there would be no absorption of the phytochemical constituents.

v. Uniformity of weight of tablets

The weight variation of MF1 and MF2 were found to be higher. Higher weight variation leads to unequal dose delivery and that would ultimately result in less/more therapeutic effect or adverse effect. The permitted percentage in weight of tablet is 7.5% for tablets of weight 130mg -324mg.

vi. Determination of hardness of tablets

The limit of hardness is 3 -5 kg/cm^2. So the market formulations do not pass the limit but the laboratory formulation was found to have proper hardness within pharmaceutical limits. Appropriate hardness is required for proper handling during manufacture and storage of formulation.

vii. Determination of friability of tablets

Friability of laboratory formulation was found to be highest. Lower friability is needed for proper production, transportation and storage. But all the formulations were found to be within the limits of friability which is 1%.

3.3.3 Successive solvent extractive value and physical characteristic

25 gm powder of each formulation was taken and extracted in soxhlet apparatus with the solvents of increasing polarity i.e. Petroleum ether, Toluene, Chloroform, Acetone, Methanol and water. Successive solvent extractive value and physical characteristic of LF and MFs are given in Table 3.

3.3.4 Qualitative chemical examination of all formulations

The extracts of all formulations were subjected to various Chemical tests for phytoconstituents such as Alkaloids, Flavonoids, Glycosides, Carbohydrates, Phytosterols, Tannins and phenolic compounds, Saponins (Table 4).

Table 3. Ash values of formulations

Sr.No	Parameter	Ash Value			
		MF1 (%w/w)	MF2 (%w/w)	MF3 (%w/w)	LF (%w/w)
1.	Total ash	11.378	12.172	10.823	6.254
2.	Acid insoluble ash	3.147	4.256	3.059	2.205
3.	Water soluble ash	6.539	8.648	5.735	4.384

Table 4: Moisture content of formulations

Sr. No.	Sample	Moisture Content
1.	MF 1	2.1%
2.	MF 2	2.3%
3.	MF 3	3.6%
4.	LF	4.8%

Table 5. Water soluble extractive value of formulations

Sr. No.	Sample	Water Extractive Value (%W/W)	Alcohol Extractive Value (%W/W)
1.	MF 1	27.08	18.72
2.	MF 2	26.48	18.68
3.	MF 3	27.22	19.72
4.	LF	28.14	20.08

Table 6. Disintegration time of formulations

Sr. No.	Sample	Disintegration Time
1.	MF 1	1 hr 22 min
2.	MF 2	42 min
3.	MF 3	1 hr
4.	LF	3 min

Table 7. Weight variation of formulations

Sr. No.	Sample	Weight of 20 Tablets (gm)	Average Weight (gm)	Weight Variation (%)
1.	MF 1	7.59	0.379	0.5%- 9.2%
2.	MF 2	6.77	0.338	0.5%- 7%
3.	MF 3	7.39	0.369	0.5%-5%
4.	LF	5.35	0.267	0.5%-2.7%

Table 8. Hardness of tablets of formulations

Sr. No.	Sample	Hardness (Kg/Cm^2)
1.	MF 1	8
2.	MF 2	6
3.	MF 3	4
4.	LF	3

Table 9. Friability of tablets of formulations

Sr. No.	Sample	Friability (%)
1.	MF 1	0.12%
2.	MF 2	0.15%
3.	MF 3	0.32%
4.	LF	0.38%

Table 10. Qualitative chemical examination of all formulations

Sr. No	Chemical Test		Observation	Result
1	Dragendorff's test	Tests of Alkaloids	Orange brown precipitates	Alkaloids were present
2	Mayer's reagent		cream precipitate	Alkaloids were present
3	Wagner's reagent		reddish brown precipitate	Alkaloids were present
4	Shinoda test	Tests of Flavanoids	Formation of pink colour	Flavonoids were present.
5	fluorescence test		greenish fluorescence under U.V light in the ethereal layer	Flavonoids were present.
6	Borntrager's test	Tests of Glycosides	The ammoniacal layer was colourless	anthraquinone glycosides were absent.
7	modified Borntrager's test		The ammoniacal layer was colourless	anthraquinone glycosides were absent.
8	Fehling's test	Tests of Carbohaydrates	First yellow, then brick red precipitate	Carbohydrates were present.
9	Benedict's test		red precipitates	Carbohydrates were present.
10	Lieberman Burchard test	Tests of Phytosterols	Green precipitates	Phytosterols were present.
11	Salkowski test		chloroform layer appeared red	Phytosterols were present.
12	lead acetate test	Tests of Tannins and phenols	white precipitate	Tannins and phenols were present.
13	ferric chloride test		deep blue-black colour	Tannins and phenols were present.
14	Forth Test	Test of Saponins	Persistent froth was not produced	Saponins were absent.

4. DISCUSSION AND CONCLUSION

All the plant materials were authenticated by their morphological and microscopical studies by comparing the characters given in standard literature.

Tablets were prepared by formulation given in 'Bhaisajya Samhita' as mamejva ghan vati but modifications were done by adding disintegrant and binding agent to get more improved dosage form. Quality control parameters according to WHO guidelines were examined such as appearance, colour, odour, ash values, extractive value and moisture content.

Keeping in mind the urgent need of standardization as well as modernization of Ayurvedic formulations antidiabetic herbal tablets were made with a standard formula given in ancient literature and it was modernized by adding suitable excipient and hence the resulting tablets met the limits of disintegration and hardness given in IP 2007. Such was not the case with three market formulations as they lacked proper formulation which may be due to many reasons.

Higher ash values indicate contamination due to extraneous material which contains carbonates,

phosphates, silicates and silica. High acid insoluble ash is due to present of greater amount of silica especially sand and siliceous earth.

Low moisture content of the formulation is needed to prevent it from microbial spoilage and degradation of active constituents. The moisture content of the Antidiabetic Herbal Tablets formulations was found to be 4.8%.

Water extractive value denotes the amount of polar substances present in the formulation. The result shows that laboratory formulation consisted of higher amount of water soluble substances like carbohydrates.

Alcohol extractive value denotes the amount of alcohol soluble constituents present in the formulation.

It was found from the results that laboratory formulation was within the limit as it was prepared with starch paste (5%w/v) as a binding and disintegrating agent. Disintegration of tablet is very crucial as if the tablet does not disintegrate in time; it remains in the body without any effect as there would be no absorption of the phytochemical constituents.
Higher weight variation leads to unequal dose delivery and that would ultimately result in less/more therapeutic effect or adverse effect. The permitted percentage in weight of tablet is 7.5% for tablets of weight 130mg -324mg.

The limit of hardness is 3 -5 kg/cm^2. The laboratory formulation was found to have proper hardness within pharmaceutical limits. Appropriate hardness is required for proper handling during manufacture and storage of formulation.
Friability of laboratory formulation was found to be highest. Lower friability is needed for proper production, transportation and storage. The formulation was found to be within the limits of friability which is 1%.

Successive solvent extraction of all the four formulation was carried out and the chemical tests in all the formulations showed presence of alkaloids, flavonoids, carbohydrates, tannins, phenols and phytosterols.

Thus following this study, it can be concluded Our Laboratory formulated tablets showed comparable good results as compare to that of marketed tablets. So LF is more efficacious to that of MFs, but further more study on phytochemical analysis and the pharmacological screening are required to establish long term safety profile, and also assessment of the effect on vital and metabolic organs for the formulation for better results and ensure anti-diabetic activity.

CONSENT

It is not applicable.

ETHICAL APPROVAL

As per international standard or university standard ethical approval has been collected and preserved by the authors.

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COMPETING INTERESTS

Authors have declared that no competing interests exist.

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