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FORMULATION, DEVELOPMENT AND EVALUATION OF *TRIBULUS TERRESTRIS* EXTRACT CAPSULES DELIVERY SYSTEM AS AN ADVANCED PHYTOTHERAPY APPROACH FOR CONTROLLING DIABETES

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ABSTRACT

Diabetes is a serious health concern in many countries with high blood glucose, obesity, and multiple organ failures in late stages. Treating diabetes with effective drugs is still a challenging issue since most of the available diabetic drugs are not effective in combating diabetes, especially in secondary disease complications like obesity retinopathy, and nephropathy associated diabetes. Hence search for effective anti-diabetic medication, especially from natural sources is mandatory with no adverse side effects. The *Tribulus Terrestris* is medicinal herb widely distributed in Yemen. It is medicinal herbs have been used in the treatment of diabetes, kidney disease, diuretic, antibacterial, liver disease, heart disease, anti-inflammatory, anti-tumor, anti-oxidant, anti-infertility, aphrodisiac activity, anti-stress, hepatoprotective activity, analgesic, antispasmodic and anthelmintic. In the present study the *Tribulus Terrestris was f*ormulated as capsules and evaluated for organoleptic properties of methanol extract of *Tribulus Terrestris* using tests as weight variation, drug content, in-*vitro* dissolution and other parameters. It was concluded that among the all formulations of *Tribulus Terrestris* extract capsules the F5 was found to be as an optimized capsules according to drug release percentage 94% within 60minutes in buffer medium, so the F5 was the best formulation of *Tribulus Terrestris* medicinal herbs extract

capsules delivery system as an advanced phytotherapy approach for controlling diabetes.

KEYWORDS: *Tribulus Terrestris*, Extract, Capsules, Medicinal herbs**,** Antidiabetic, Phytotherapy.

INTRODUCTION

The herbal products were discarded from conventional medical use in the mid-20th century, not necessarily because they were ineffective but because they were not as economically profitable as the newer syn- thetic drugs. Plant materials are used through developed and developing countries as home remedies, over the counter drug products and raw materials for the pharmaceutical industry, and represent a substantial proportion of the global drug market. Herbal medicines have been used in the treatment of diabetes for a long time so the maintenance of a health care is got possible.[1-8]

Diabetes Mellitus[9-13]

Diabetes mellitus is a heterogeneous group of diseases characterized by chronic elevation of glucose in the blood. It arises because the body is unable to produce enough insulin for its own needs, either because of impaired insulin secretion, impaired insulin action, or both. Chronic exposure to high blood glucose is a leading cause of renal failure, visual loss and a range of other types of tissue damage. Diabetes also predisposes to arterial disease, not least because it is often accompanied by hypertension, lipid disorders and obesity. Many cases of diabetes and almost all of its unwanted long-term consequences are potentially avoidable, but this will require intervention at a societal as well as at a medical level. The management of diabetes is so important for diabetics to understand because it helps in controlling the disease and also in preventing complications. Maintenance of normal blood glucose levels suppresses the onset and progression of vascular and neurological complications in T1D patients. Strategies such as diet, exercise and stress management have been strongly recommended and adopted to control T2D.

Previous studies showed that the quality-of-life education can have positive effect on diabetes self-concept, and prevent physical and side effects of T2D. T2D can be totally controlled in some cases with diet and exercise. Prevention and treatment methods of obesity will help in the management and treatment of T2DM. Patients need to stop smoking, lose weight if obese. Diabetes is a serious health concern in many countries with high blood glucose, obesity, and multiple organ failures in late stages. Treating diabetes with effective drugs is still a

challenging issue since most of the available diabetic drugs are not effective in combating diabetes, especially in secondary disease complications like obesity retinopathy, and nephropathy associated diabetes. Hence search for effective anti-diabetic medication, especially from natural sources is mandatory with no adverse side effects.

Herbal Treatment for Diabetes[14-16]

The treatment for diabetes mainly involves the regulation of blood sugar levels and to prevent diabetic complications. Medicines, diet, and exercise are included in treatment. Lifestyle modifications and oral anti-diabetic medications are recommended for initial treatment of DM.

Herbal Treatment for Diabetes: *Tribulus Terrestris*, Bitter Gourd (Momordica charantia), Bael (Aegle marmelos), Gurmar Leaves (Gymnema sylvestrae), Fenugreek (Trigonella foenum graecum), Turmeric (Curcuma longa), Onion (Allium cepa), Nayantatra (Vinca rosa), Neem (Azadirachtha indica), Garlic (Allium sativum), and sagar gota (Ceasalpinia crista) are the most useful herbs for diabetic treatment. EA is a polyphenol naturally occurring in berries and nuts has shown many properties such as antioxidant, antimicrobial and antimutagenic agent. Leaf extract of Terminalia arjuna (Combretaceae), an Ayurvedic plant has recently been shown to possess antihyperglycemic activity in streptozotocin-induced diabetic rats. Several plants derived compounds have been shown to activate glucose transport through leaf extract leaf extract AMP Activated Protein Kinase (AMPK) activation.

Fig. 1: *Tribulus Terrestris*.

Tribulus Terrestris

Tribulus Terrestris is medicinal herb effective in the treatment of many diseases. *Tribulus Terrestris* is an annual plant in the caltrop family (Zygophyllaceae) widely distributed around

the world, such as Yemen as shown in Figure 1, that is adapted to grow in dry climate locations in which few other plants can survive. It is an invasive species in North America. Like many weedy species, this plant has many common names, including goat's-head, Bindi, bullhead, burra gokharu, bhakhdi, caltrop, small caltrops, Cat's-head, devil's eyelashes, devil's-thorn, devil's-weed, puncture vine, puncturevine, and tack-weed.[17-20]

Pharmacological Activities of *Tribulus Terrestris*[21-40]

Tribulus Terrestris is medicinal herb effective in the treatment of many diseases. Several studies showed that the pharmacological activities of TT: Diabetes: Saponin from TT possesses hypoglycemic properties TT significantly reduced the level of serum glucose, serum triglyceride, and serum cholesterol. Previous studies showed that the preliminary promising hypoglycemic effect of *Tribulus Terrestris* in women with diabetes mellitus type 2. Antibacterial activity: All parts (fruits, stems, leaves, and roots) of Turkish and Iranian TT showed antibacterial activity against Enterococcus faecalis, Staphylococcus aureus, Escherichia coli, and Pseudomonas aeruginosa, only the fruits and leaves of Indian TT were active exclusively against E. *coli* and *S.* aureus. It provided scientific evidence to support uses of *Tribulus Terrestris* and its mixture with C. bursa-pastoris and G. glabra for the treatment of oral infections.

Kidney disease: The protective effect of aerial parts of the *Tribulus Terrestris* extract on acute kidney injury (AKI). the results found that oral administration of *Tribulus Terrestris* extract can decrease kidney functional disturbance, oxidative stress, and cellular damages. Anti-oxidant properties: The protective and anti-oxidant activities of the methanolic extract of *Tribulus Terrestris* fruits (METT). Hepatoprotective activity: The potential protective role of *Tribulus Terrestris* in acetaminophen- induced hepatotoxicity. Antitumor: Inhibitory effect of TT against the progression of castration-resistant prostate cancer. Cell cycle arrest and induction of apoptosis in cancer cells and endothelial cells might be plausible mechanisms of actions for the observed antitumor and antiangiogenic activities of TED. The antitumoral properties of TT the study shows experimental evidence that TT has a preventive efficacy against UVB- induced carcinogenesis and the molecular knowledge on the mechanisms through which TT saponins regulate cell death suggests great potential for TT to be developed into a new medicine for cancer patients.

Anti-infertility: The effects of *Tribulus Terrestris* on semen quality and physiological

parameters. The result showed significant enhancement in sperm concentration, motility and liquefaction time. Protodioscin, the main phytochemical agent of the Tribulus genus, acts on sertoli cells, germ cell proliferation and growth of seminiferous tubules. This component is known to convert testosterone into dihydrotestosterone, which plays important roles in male attributes. Heart disease: The protective effect of partially characterized *Tribulus Terrestris* fruit methanol extract against mitochondrial dysfunction in cell based (H9c2) myocardial ischemia model.

Anti-inflammatory effects: Anti-inflammatory active extract fractions of *Tribulus Terrestris* (family Zygophyllaceae) these findings indicate that CT isolated from *Tribulus Terrestris* is a novel and potent modulator of inflammatory responses. Thus, it may prove beneficial to further evaluate CT as a possible treatment for chronic.

Aphrodisiac activity: The influence of *Tribulus Terrestris* extract on androgen metabolism in young males. The findings anticipate that *Tribulus Terrestris* steroid saponins possess neither direct nor indirect androgen- increasing properties. The study will be extended in the clarifying the probable mode of action of *Tribulus Terrestris* steroid saponins. Findings of pervious study validate the traditional use of *Tribulus Terrestris* as a sexual enhancer in the management of sexual dysfunction in males. Anti-stress: The effect of *Tribulus Terrestris* saponins (TTS) on behavior and neuroendocrine of chronic mild stress (CMS) depression rats. Oxidative stress: The effect of *Tribulus Terrestris* on different parameters of oxidative stress and gene expression profiles of antioxidant enzymes. *Tribulus Terrestris* also reduced hyperoxaluria- caused oxidative stress, and restored antioxidant enzyme activity and their expression profile in kidney tissue. Hyperplasia: The effectiveness and tolerability of an oral formulation, comprising standardized extracts. *Tribulus Terrestris* leaves, versus tamsulosin in the treatment of symptomatic BPH.

Tribulus Terrestris Extract Dosage Range[41-48]

Effective dose of TT: Effective doses used in clinical settings are 750 to 1500 mg per day TT in Ayurveda.

Fruit TT: 3-6 g of the drug in powder form; 20-30 g of the drug for decoction Root: 20-30 g of the drug for decoction.

Previous studies showed that the potential blood sugar-lowering effect used 1,000 mg per day, while research examining libido enhancement used doses from 250–1,500 mg per day. Other studies dosages relative to body weight. For example, several studies have used doses

of 4.5–9 mg per pound (10–20 mg per kg) of body weight. So, if you weighed about 155 pounds (70 kg), you might take a dose of 700–1,400 mg per day TT.

The Capsule Delivery System[49-57]

Capsules offer many advantages: Capsules, because of their elongated shape, are easy to swallow, which is one reason for the number of capsule- shaped tablets manufactured today, Flexibility of formulation is another advantage of the capsule dosage form. However, the biggest formulation advantage of capsules is that there is less need for additional excipients, since capsules are tasteless, they effectively mask any unpleasant taste or odor of their contents, they offer rapid release characteristics, due to the rapid dissolution rate of the capsules, The use of hard capsules is also a common feature in clinical trials, as the filling of tablets or even capsules themselves will blind the dosage forms studied.

Herbal capsules are solid dosage forms containing drug and usually, appropriate filler (s) enclosed in a gelatin container. Capsules may be available in hard gelatin for dry powdered herbal ingredients or granules or soft gelatin shells for herbal oils and for herbal ingredients that are dissolved or suspended in oil. The gelatin shell readily ruptures and dissolves following oral administration. Drugs are normally more readily released from capsules compared to tablets. Capsules may help mask the unpleasant taste of its contents and uniformity of dosage can be relatively readily achieved. Herbal capsules normally consist of hard-shelled gelatin capsules with the plant material finely milled and sifted and filled into shell or extracts of the herbal material(s) with appropriate excipients such as fillers.

In the present study the *Tribulus Terrestris* freeze -dried extract powder solid dosage form of *Tribulus Terrestris* medicinal herbs capsules delivery system was prepared and evaluated as an advanced phytotherapy approach for controlling diabetes.

MATERIALS AND METHODS

The freeze-dried of methanol semisolid extract of *Tribulus Terrestris* was prepared and gift from (Prof Dr. Amina El-Shaibany, Professor Dr. of Pharmacognosy, Department of Pharmacognosy, Faculty of Pharmacy, Sana'a University, Sana'a, Yemen). Hard Gelatin Capsules (Size 0), Colloidal Silicon Dioxide (Aerosil), Magnesium Stearate, Microcrystalline Cellulose MCC, Starch, Lactose, Sodium Starch Glycolate, Corspovidone, Talc, Sodium Lauryl Sulphate, Hydrochloric Acid (0.1NHCl), Phosphate Buffer Solution, Ethanol and Methanol. were obtained from Sigma Aldrich. All chemicals used were all of analytical grade

and other materials were gift from (Modern and Global Pharmaceutical Industry Company-Yemen).

Formulation and Evaluation of *Tribulus Terrestris* Extract[58-87]

Determination of The Organoleptic Properties of Extract

The following organoleptic properties of the plant materials were assessed: physical appearance, odor and taste. For these samples of *Tribulus Terrestris* extracts were inspected and assessed using the natural senses (e.g. eyes, nose, mouth).

Determination of The Solubility of Extract

The solubility of a substance fundamentally depends on the solvent used as well as on temperature and pressure. The extent of solubility of a substance in a specific solvent is measured as the saturation concentration where adding more solute does not increase its concentration in the solution. Oral ingestion is the most convenient and commonly employed route of drug delivery due to its ease of administration, high patient compliance, cost-effectiveness, least sterility constraints, and flexibility in the design of dosage form. As a result, many of the generic drug companies are inclined more to produce bioequivalent oral drug products. So, the solubility application according to standard parameters of solubility as shown in Table 1.

Table 1: Standard of Approximate Solubility.

Description	Part of The Solvent Required Per Part of Solute
Very Soluble	Less than 1
Freely Soluble	From 1 to 10
Soluble	From 10 to 30
Sparingly Soluble	From 30 to 100
Slightly Soluble	From 100 to 1000
Very slightly Soluble	From 1000 to 10,000
Practically Insoluble	More than 10,000

Determination of The Density of Extract

Preformulation parameters like bulk density, tapped density, carr's index, and angle of repose. A known quantity of powder was poured into the measuring cylinder carefully level the powder without compacting, if necessary and read the unsettled apparent volume, Vo, to the nearest graduated unit as shown in Table 2.

Calculate the bulk density, in gm per ml, by the formula:

Bulk density = Bulk Mass/ Bulk Volume

Carr's compressibility index

Carr's index (%) = (Tapped density – Poured density) / Tapped density

Table 2: Carr's Index of Powder Flowability.

Carr's Index%	Type of Flow
5 -15	Excellent
12 – 16	Good
18 – 21	Fair to Passable
23 – 35	Poor
33 – 38	Very Poor
>40	Extremely Poor

Formulation of *Tribulus Terrestris* Extract Capsules[58-87]

A uniform powder is obtained by mixing the semisolid *Tribulus Terrestris* extract of with the appropriate adsorbent microcrystalline cellulose, starch and lactose, superdisintegrant as sodium starch glycolate and crospovidone, lubricant as magnesium stearate and talc, glidant as colloidal silicon dioxide (Aerosil), and sodium lauryl sulphate the materials filled into the capsules as shown in Table 3.

Table 3: Formulation of *Tribulus Terrestris* Extract Capsules.

Ingredients	Quantity Per Capsule (mg)					
	Formulation Code					
	F1	F2	F3	F4	F5	F6
***Tribulus Terrestris* Extract**	150	150	150	150	150	150
Microcrystalline Cellulose	138	108	81.5	39	129	119
Starch	---	---	---	9	---	---
Lactose	---	---	58	90	---	---
Aerosil	---	30	---	---	---	10
Magnesium Stearate	3	3	3	---	---	3
Talc	---	---	---	3	3	---
Sodium Starch Glycolate	---	---	---	9	---	---
Crospovidone	6	6	6	---	12	12
Sodium Lauryl Sulphate	3	3	1.5	---	6	6

Evaluation of *Tribulus Terrestris* Extract Capsules[58-87]

Determination of Uniformity of Weight and The Amount of *Tribulus Terrestris* Capsules

For the determination of the uniformity of weight, the British Pharmacopoeia method was used. In which Twenty of the *Tribulus Terrestris* capsules prepared. Not more than two of the

individual weights (masses) had to deviate from the average weight (mass) by more than 7.5% and none of the deviates by more than twice that percentage. The amount of powder actually filled into the capsules was also compared with the desired quantity and the difference (in percentage) between the desired and actual quantity calculated. According to the formulation, 150mg *Tribulus Terrestris* extract was to be filled in one capsule. Twenty capsules were thus randomly chosen, their contents weighed, the percentage difference between this and the desired weight calculated and averaged for the 20 capsules to assess the accuracy of the filling process.

Determination of Moisture Content of *Tribulus Terrestris* Extract Capsules

The presence of water plays an important role in the physical and chemical stability of the active pharmaceutical ingredients, and pharmaceutical preparations, because they may lead to their degradation. Water in pharmaceutical substances and preparations, provides a favorable environment for bacterial growth. Once a composition which contains a certain number of bacteria enters the organism, in the gastrointestinal tract may come to the death of bacteria and release of endotoxin. Even a small amount of endotoxin in the body causes the formation of antibodies against the endotoxin. During gastrointestinal crises, the blood stream can be penetrated by a large amount of endotoxin, which leads to an anaphylactic reaction, which results in a hard shock. The moisture content of the material is a decisive economic factor both in production and in sales. This is one of the main factors that influences the course of production and stability of the finished product, determining the quality and prices of many pharmaceutical products. Therefore, the presence of water in the pharmaceutical substances affect; quality of the finished product, commercial reasons, i.e. process ability of the product, storage of the finished product, accuracy of the finished product, analytical indicators on the dry matter, since it is necessary to know the water content for their calculations.

***In-Vitro* Dissolution Studies of *Tribulus Terrestris* Extract Capsules**

The dissolution test measures the rate at which a drug is released into solution from a dosage form and is used as an indication of the bioavailability of a pharmaceutical product and of product quality. In the present study the basket method was used. The quantitation of the amount of extract dissolved was measured based on UV absorbance measured at 277.5 nm, the wavelengths for maximum UV absorbance of solutions of the *Tribulus Terrestris* extract determined by using a UV- Vis Spectrophotometer. For the dissolution study the following requirements and Procedure were used: Apparatus: Basket. Medium: Phosphate buffer pH

7.2. Volume of medium: 900ml. Temperature: 37±0.5°C. Rotation speed: 100 rpm. Dissolution time: 5,10,20, 30, 45 and 60 minutes. 900 ml of Phosphate buffer pH 7.2 was degassed, introduced into the vessel of the apparatus, warmed to 37±0.5°C in the water bath. One capsule was placed in each vessel, the basket was lowered into position and the apparatus were operated immediately at the rotation speed 100 rpm. At various time points, viz. at 5,10,20, 30, 45 and 60 minutes after start, 3 ml samples of the medium were withdrawn from a point half- way between the surface of the dissolution medium and the top of the rotating basket and not less than 10 mm from the wall of the vessel. Each time the withdrawn medium was immediately replaced by 3 ml of Phosphate buffer pH 7.2 introduced into the vessel. The UV absorbance of the solution was determined at the wavelengths mentioned earlier and using the solution of one of the empty capsule shells dissolved in the 900 ml volume of dissolution medium as a blank reference solution.

RESULTS AND DISCUSSION

The Organoleptic Properties of Freeze -Dried of *Tribulus Terrestris* Extract

As shown in Table 4, the organoleptic properties of the freeze-dried extract.

Table 4: The Organoleptic Properties of *Tribulus Terrestris* Extract.

Properties	***Tribulus Terrestris* Extract**
Physical Appearance	Small particulate powder
Color	Dark green
Odor	Characteristic Odor
Taste	Bitter

The bitter taste and characteristic odor normally result in poor patient acceptance of dosage forms. Hopefully these negative characteristics still present in the extract can be masked when incorporated in capsule form.

The Solubility of Freeze -Dried of *Tribulus Terrestris* Extract

For oral solid dosage forms aqueous solubility is a crucial factor influencing the bioavailability of drugs. The results obtained in the solubility testing of the *Tribulus Terrestris* extract show that the extract is soluble in water as shown in Table 5.

Table 5: The Solubility of Freeze -Dried of *Tribulus Terrestris* Extract.

Solvent	*Tribulus Terrestris* Extract
Water	Soluble
(0.1N HCl) Acid	Soluble
(KH2PO4) Buffer	Very Soluble

Table 6: Evaluation Parameters of *Tribulus Terrestris* Extract.

Testing	*Tribulus Terrestris*
The Solubility of Extract	Very Soluble in Phosphate Buffer
Carr's Index (%)	10.4%
Angle of Repose	38°
Particle Size	Moderately-Fine Powder
The Moisture Content (%)	0.57%

The Flowability of Freeze -Dried Extract

The carr's index of compressibility for *Tribulus Terrestris* extract is 10.4% and the angle of repose is 38°, show that the *Tribulus Terrestris* freeze -dried extract powders can all be categorized as having excellent flowability for the manufacture of capsule dosage form as shown in Table 6.

Moisture Content of *Tribulus Terrestris* Extract Capsules

The results of these tests are indicated that the moisture level of the contents of *Tribulus Terrestris* capsules when analyzed in the pre-formulation study, the moisture content for *Tribulus Terrestris* extract was found to be 0.57%, as shown in Table 6.

The Uniformity of Weight and The Amount of *Tribulus Terrestris* Extract Capsules

The average deviation in weight from average for *Tribulus Terrestris* capsules were found to be 7.5% and average total content per capsule is within the limit on the acceptable deviation in weight from average for capsules therefore, mentioned results thus indicated that the *Tribulus Terrestris* capsules are within the limit of the British Pharmacopoeia specifications.

***In-Vitro* Dissolution Studies of *Tribulus Terrestris* Extract Capsules**

Table 7: The Drug Release Percentage of *Tribulus Terrestris* Extract Capsules.

Formulation Code	Drug Release %					
	Time (min)					
	5	**10**	**20**	**30**	**45**	**60**
F1	9	14	36	46	73	92
F2	35	64	72	78	82	86

F3	15	38	62	63	67	69
F4	43	57	64	68	70	74
F5	33	53	82	84	86	94
F6	19	46	64	68	69	69

The *in-vitro* dissolution percentage of *Tribulus Terrestris* extract capsules is one important of the results of dissolved active ingredient, *Tribulus Terrestris* extract, as shown in Table 7. The results of formulation have shown that the drug release of F5 was found to be 84% within 30 minutes in buffer medium. The results of formulation have shown that the drug release of F5 was found to be 86% within 45 minutes in buffer medium. The results of formulation have shown that the drug release of F5 was found to be 94% within 60 minutes in buffer medium. It was concluded that the formulation of *Tribulus Terrestris extract* capsules F5 can be taken as an optimized capsules for drug release percentage 94% within 60 minutes in buffer medium and drug release so, it was found to be among the all formulations the F5 was the best formulation.

CONCLUSION

It was concluded that among the all formulations of *Tribulus Terrestris* extract capsules the F5 was found to be as an optimized capsules according to drug release percentage 94% within 60 minutes in buffer medium, so the F5 was the best formulation of *Tribulus Terrestris* medicinal herbs extract capsules delivery system as an advanced phytotherapy approach for controlling diabetes.

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