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Fast disintegrating tablets of spray dried poly-herbal extract: a promising hypoglycemic and diabetic wound healing activity

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Abstract

Many herbal products have been used to control blood glucose level and minimize complications of diabetes mellitus. However, the feasibility of using such herbal product has been hindered due to the lower stability of their extracts and patients incompliance.
Objective: An optimized fast disintegrating tablet preparation of spray dried aqueous extract of poly herbal blend has been formulated to maximize the therapeutic activity of such herbal extract.
Methods: different ratios of superdisintegrants were evaluated in terms of reducing disintegration time and wetting time of the prepared formulations. The potential of the optimized formula in reducing blood glucose level and promoting wound healing in streptozotcin (STZ)-induced diabetic rats was determined.
Key finding: Oral administration of the optimized formula (F6) had significant superior effect in reducing blood glucose level and promoting wound healing of diabetic rats compared receiving the aqueous extract of the herbal blend ($P<0.05$, $p<0.01$, respectively). That may be attributed to the enhanced stability and the accurate dosing of such solid dosage form. In addition, no remarkable toxic manifestations or histologic changes were observed in treated animals.
Conclusion: These findings uncover the potential of the formulated dosage form in enhancing the hypoglycemic and wound healing activity of the herbal extract.

Key words
Fast disintegrating tablets, herbal blend, spray dried, hypoglycemic, wound healing

1. Introduction

Diabetes mellitus includes a group of disorders characterized by defects of protein, lipid and carbohydrate metabolism. When uncontrolled, hyperglycemia causes micro and/or macrovascular complications including: cardiovascular problems, neuropathy, nephropathy, and retinopathy [1]. According to the World Health Organization, 170 million people worldwide were suffering from diabetes in 2000. The disease is increasing rapidly, and it is predictable that this number will almost be doubled by the year 2030 [2]. Combined various mechanisms including reduced cell and growth factor response, reduced peripheral blood flow and diminished local angiogenesis can lead to a delayed wound healing in diabetic persons [3]. In fact, impairment of wound healing in diabetic patients is a major cause of morbidity and mortality [4].

Medicinal Herbs presents valuable therapeutic agents, in both traditional systems and modern medicine [5]. More than four hundred traditional herbal remedies for diabetes have been described, However, a small number of these have gained medical and scientific assessment to evaluate their efficacy and safety [6]. Allium cepa [7], *Trigonella foenum-graecum [8]*, *Zingiber officinale* [9], *Cinnamomum zeylanicum* [10], *Syzygium aromaticum* [11], *Sinapis alba* [12] and *Rheum ribes* [13] are among the herbs with reported effects in glycemic control and the associated impaired wound healing [14]. For example, the anti-diabetic effect of Allium cepa (onion) was attributed to S-methyl cysteine sulphoxide (sulphur containing amino acid) which controls lipids and blood glucose and alters the activities of liver hexokinase and glucose 6-phosphatase towards normal [15]. The anti-oxidant effects of fenugreek and the reversal effect on enzymes catalase, glutathione peroxidase, superoxide dismutase and glutathione peroxidase were responsible for the anti-diabetic and wound healing effects in treated rats [16]. In a study using cinnamon extracts, an enhanced extracellular glucose consumption was observed in cinnamon treated rats compared to control group with improved insulin sensitivity in a type 2 diabetes mellitus model [17]. Clove or Syzygium aromaticum exerted its hypoglycemic activity in type 2 diabetic mice via activation of human peroxisome proliferator-activated receptor (PPAR) [18]. Rheum ribes was recently considered as a prophylactic treatment in diabetic risk groups due to its protective effect against diabetes induction and diabetic neuropathy in pre-alloxinated rats [19].

Amazingly, combinations of those herbs have revealed a significant improvement in diabetic disease and its

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complications compared to conventional allopathic medicines [20]. Those combinations have been popular due to their minimal side-effects, potential efficacy and synergistic actions [21]. Treatment of diabetic rats with a blend of ginger and garlic showed reduced glycated haemoglobin (GHb) levels in erythrocytes of treated rats [22]. The aqueous extract of a blend of *Aloe vera* gel and cinnamon bark was reported to have an obvious antioxidant properties with accelerated wound healing effects in diabetic rats [23]. The aqueous extract of combined garlic, ginger and cayenne pepper showed a pronounced hypoglycemic effect and protection of liver, kidney and blood against diabetic injury [24].

The main challenge for using these combination is to formulate dosage forms which are convenient for the patient to use and show improved patient compliance [25]. Oral delivery of drugs is considered the gold standard due to its convenience, safety and cost effectiveness. Fast disintegrating tablet, have been developed for rapid disintegration and dissolution in saliva [26]. They are very appropriate for geriatrics, pediatrics, patients suffering from repeated emesis, motion sickness, dysphasia, mental disorders and travellers since these patients will not need to swallow large quantity of water [27]. Moreover, drugs formulated as fast disintegrating tablets exhibit satisfactory absorption from the oral mucosa and show immediate pharmacological effect [28].

In this study, we report, for the first time, the hypoglycemic and wound-healing effect of a new herbal blend in diabetic rats. A blend of the aqueous extracts of seven medicinal plants was spray dried and an optimized fast disintegrating tablet formula was selected to estimate the hypoglycemic and wound healing effect of the blend extract in STZ-diabetic rates. Toxicological profile of this blend was also evaluated at both therapeutic and high doses in healthy rats.

2. Experimental

2.1. Materials

Avicel PH-101, magnesium stearate, mannitol, Croscarmellose sodium (CCNa) and Crospovidone were purchased from Sigma-Aldrich (St Louis, MO, USA. Dried onions (*Allium cepa*), dried cinnamon bark (*Cinnamomum zeylanicum*), dried Syrian rhubarb roots (*Rheum ribes*)**,** dried clove flower buds (*Syzygium aromaticum*), dried white mustard seeds (*Sinapis alba*), dried fenugreek seeds (*Trigonella foenumgraecum*), dried ginger roots (*Zingiber officinale*), and peppermint Oil, were purchased from Harraz Food Industry and Natural Products (Cairo Egypt). All other chemicals and solvents were of reagent grade.

Animals:

Male and female Wistar rats (220-270 g), approximately 8 weeks old) were purchased from the Animal Production and Health Department, AL-Nahda University, Beni Suef, Egypt). The protocol procedures were accepted by the research ethics committee, faculty of pharmacy, Minia university.

2.2. Methodology:

2.2.1. Extraction of plants

Allium cepa, *Trigonella foenumgraecum*, *Zingiber officinale*, *Cinnamomum zeylanicum*, *Syzygium aromaticum*, *Sinapis alba*, and *Rheum ribes* were cut into pieces. Ten g of each plant were transferred to a 100 ml volumetric flask with 10 ml glacial acetic acid (5% w/v). The volume was completed to 100 ml with distilled water. After filteration, one hundred ml of each Aqueous Extract were mixed before the total volume was spray dried (spray dryer MSD 1.0, Labmaq, SP, Brazil).

2. 2. 2. Evaluation of the spray dried extract before compression

Powder characteristics of the spray dried extract were tested as follows [29, 30]:

Angle of repose: was evaluated using the funnel method as follows:

$$(\text{Tan } \Theta = h/r) \quad (1)$$

Where Θ, h and r are the angle of repose, height of the cone (cm) and radius of the cone base (cm), respectively.

Compressibility index was calculated using the following equation:

Compressibility Index (%) = [(tapped density-bulk density)/tapped density] x 100 (2)

- Bulk density is the ratio of the mass to the volume of an untapped powder sample.
- Tapped density is obtained by the mechanical tapping a graduated cylinder of the sample until little volume change is observed.

Hausner's ratio was calculated as follows:

Hausner's ratio = Tapped density x 100/Poured density (3)

2. 2. 3. Tablet preparation

The preparation of six different oral fast disintegrating tablet formulations (FDTs) of the spray dried extract was carried out using Avicel and mannitol as fillers. Crospovidone and croscarmellose were used as disintegrants in different ratios. Magnesium stearate and talc were used as lubricants **(Table 1)**. Components of each formulation were weighed and mixed using spatula and morter. The determined amount of lubricant was added then components were compressed using a single-punch tablet machine (Korsch-Berlin, Ek/0, Frankfurt, Germany) to obtain tablets of final weight 350 mg.

2. 2. 4. Characterization of the tablets

The six formulated FDTs were subjected to various quality control tests [31].

Thickness. Dimensions of 5 tablets of each formulation were measured using a digital caliper (ERWEKKA tester).

Weight variation. The individual weight of each of ten randomly selected tablets was determined using an electronic balance (Sartorius A200s, Germany) and the mean weight was taken.

Hardness. Hardness of five randomly selected tablets (from each formulation) was determined using Monsanto hardness tester (Pharma test, Germany).

Disintegration test. Disintegration time was determined by USP Tablet disintegration test apparatus ((Pharma test, Germany)) in 900 ml of distilled water. The time in seconds required for complete disintegration of the tablets was measured.

Wetting time. Capillarity and wetting time of the FDTs were measured at room temperature by placing tablets in a petri dish of 6.5 cm diameter containing 10 ml water. Time for complete wetting of tablets was recorded.

All experiments were carried in triplicates, mean and standard deviation in was calculated.

2.2.5. Therapeutic activity of prepared FDTs

To investigate the hypoglycemic and diabetic wound healing effects of the prepared tablets, Streptozotocin (STZ) - animal model of diabetes was established in rats [32]. Type-1 diabetes mellitus was induced by intra-peritoneal administration of STZ (70 mg/kg) to rats. This dose develops hyperglycemia, hypo-insulinemia and glucose intolerance, which usually last for 12 weeks [33]. The diabetic rats were used for the development of the wound model. Plasma glucose level was determined daily by using glucostar-BioSystems glucose monitoring device. Only rats with plasma glucose levels equal to or above 300 mg/dl were enrolled in the experiment. Rats were lightly anaesthetized and a portion of skin was removed from the backs of rats to induce full thickness wounds using surgical scalpels. Wound bearing rats were divided as follows (six animals each):

Group I (Control non-diabetic): non-treated normal control rats.

Group II (Control diabetic): non-treated diabetic rats.

Group III: diabetic rats which received daily oral amoxicillin (50 mg/kg).

Group IV: = diabetic rats which received daily oral plant extract (2 ml/kg).

Group V: diabetic rats which received daily oral FDTs (F6, 35 mg/kg).

The day of wound induction was defined as day 0. Planar metric measurements of wounds were carried out on digital photographs taken from each rat and the images were analyzed using Image J software (NIH, Bethesda, MD, USA). The area of the wound (mm^2) was daily estimated by counting the number of pixels within the region of the wound [34]. Blood glucose level, wound area and body weight were recorded daily for all the rats throughout the experiment period.

2.2.6. Toxicological investigation of the extract and the tablets:

To investigate the sub-chronic toxicity of the prepared tablets and their equivalent amounts of the plant extract, 25 male and 25 female rats (220 – 270 g) of approximately two months of age were randomly allocated into five groups of 10 animals each.

Group I: control non treated group.

Group II: high dose of F6 (106 mg/kg).

Group III : therapeutic dose of F6 (35 mg/kg).

Group IV: an equivalent high dose of the liquid plant extract (6.04 ml/kg).

Group V: an equivalent therapeutic dose of liquid plant extract (2 ml/kg).

These doses were chosen after preliminary screening on rats. The animals were fasted for 18 h prior to treatment. They were continuously observed for 3 h afterwards for activity (locomotion), urination, bowel movement, reaction to noise and reaction to pinch or mortality. Animals were monitored daily for 14 days for changes in body weight, sleep, salivation, lethargy as well as food and water consumptions [35, 36]. Weight loss was determined every two days during the experimental period.

2.2.7. Histopathological study:

Fourteen days after daily administration of different treatments, animals were anaesthetized by intra-peritoneal injection of thiopental sodium, euthanasia was followed by decapitation. Organs were collected and weighed. Relative organs weight was determined based on each animal's body weight. Vital organs (kidney, liver and spleen) were sent for histopathological assessment. Briefly, tissues were washed in normal saline and fixed in 10% buffered formalin for at least 24 h, dehydrated in 70% ethanol, and embedded in paraffin wax blocks, which were then cut into 4-5 μm thick sections. Haematoxylin and eosin (H & E) were used for staining and examination under a light microscope (Olympus CH02) [37].

3. Results

3.1. Evaluation of the fast disintegrating tablets

3.1.1. Pre-compression evaluation

The properties of different powdered tablet compositions were listed in table (2). Results demonstrated that pre-formulations F1, F2 and F3 showed good flowability with angle of repose values less than 30. Meanwhile, formulations F4, F5 and F6 showed lower values of angle of repose (19.23º, 19.89º and 19.56º, respectively), which indicates excellent flowability properties [38]. These results were confirmed by the Hausner**'s** factor, which was less than 1.25 for all the powdered pre-formulations except F-2 with Hausner**'s** ratio 1.31 **(Table 2)**.

Compressibility percent reflected the good flowability of all the powdered formulations with F4, showing compressibility percent of less than 12 [38].

3.1.2. Post-compression evaluation

The obtained characteristics of the prepared FDTs (F1-F6) **(Table 3)** demonstrate that the prepared FDTs formulations are acceptable, according to USP specification, with respect to their weights variation, hardness, thickness, disintegration time and wetting time [38]. The average weights of the prepared tablets showed weight variation of less than 5 % of the average weight. The thickness values of the different tablets ranged between

2.04 and 2.11 mm. The Hardness of the tablets had values within a range of 2.4 to 3.1 kg/cm^2. The disintegration and wetting time were significantly improved by addition of different ratios of crospovidone and croscarmellose **(Table 3)**.

Table (1): components of fast disintegrating tablets (mg)

Component	Component weight (mg)					
	F1	F2	F3	F4	F5	F6
Spray-dried extract	53	53	53	53	53	53
Crospovidone	0	3.5	3.5	3.5	10.5	17.5
Croscarmellose	0	3.5	7	10.5	17.5	35
Avicel	0	70	70	70	70	70
Mg Stearate	1.75	1.75	1.75	1.75	1.75	1.75
Talc	7	7	7	7	7	7
Mannitol	228.25	211.25	207.75	204.25	190.25	165.75
Total tablet	350	350	350	350	350	350

Table (2): Pre-formulation evaluation for the prepared powdered tablet formulae

Formulation Code	Angle of repose (degrees)	Compressibity Index (%)	Hausner's Ratio
F1	23.31	13.62	1.21
F2	21.45	13.69	1.32
F3	23.56	12.52	1.11
F4	19.23	11.96	1.21
F5	19.89	15.69	1.15
F6	19.56	16.65	1.22

Table (3): Post-compression evaluation of the prepared FDT's

Code	Thickness (mm)	Hardness (kg/cm2)	Weight Variation (mg)	Disintegration time(sec)	Wetting time(sec)
F1	**2.023**	**2.4±0.125**	**346±2.3**	**1230±180**	**1080±230**
F2	**2.101**	**3.1±0.095**	**355.8±1.56**	**37±2.3**	**44±3.5**
F3	**2.068**	**2.8±0.108**	**345.6±2.4**	**31±1.5**	**39±6.5**
F4	**2.048**	**3.1±0.047**	**351±3.4**	**27±6.2**	**38±6.9**
F5	**2.096**	**2.8±0.085**	**347±1.26**	**25±1.1**	**37±5.3**
F6	**2.113**	**2.7±0.135**	**355±1.5**	**22±2.8**	**26±1.3**

3.2. Therapeutic activity

3.2.1. Hypoglycemic effect

To investigate the hypoglycemic effect of the aqueous extract blend and the prepared tablets, the blood glucose levels of all groups of diabetic rats (control, antibiotic-treated, extract-treated and tablet-treated) and the non-diabetic control were monitored **(Figure 1a)**. Results show that after 7 days of treatment, blood glucose levels of tablet-treated rats were significantly reduced compared to the diabetic control group ($p<0.01$) and there was a significant difference between blood glucose level of the rats treated with the extract and that of rats treated with tablets ($p<0.005$). This observed reduction in blood glucose levels continued along the experiment period in rats treated with either the extract or the tablets. On the 22nd day of treatment, blood glucose level of tablet-treated rats was significantly reduced to 210±12.32 compared to 260.4±25.6 in extract-treated rats ($p< 0.05$). The reduction in blood glucose level was significant in both tablet-treated and extract-treated groups compared to the control group ($p< 0.005$ and $P< 0.01$ respectively).

3.2. Wound healing effect

Results show that there was no significant difference in the wound area of all groups of rats on day zero of incision **(Figure 1b)**. Wound area of each rat was measured on days 2, 4, 6, 8, 10, 16, 18 and 22 post-incision in all groups. The healing rate of treated animals was significantly higher compared to the healing rate in both non-diabetic and the diabetic non-treated groups ($p<0.005$). On day 10 post-incision, a significant decrease in wound area was observed in both extract-treated and tablet-treated groups in comparison to control diabetic group and this was observed until the end of the experiment ($p< 0.01$). Mean wound area of tablet-treated group was significantly reduced compared to antibiotic–treated group ($p< 0.01$).

3.4. Toxicological study:

The behavior of rats was not affected by treatment with either the FDTs formulation or the plant extract in case of administration of either therapeutic or high doses. No reduction of locomotion, noise, or reaction to pinch was noticed in all tested doses. No death was recorded after administration of the tested preparations in all animals at both doses. Food consumption was not significantly affected for all treated rats (data not shown). Rats did not show any significant reduction in body weight during the experimental time **(Figure 2a)**. Organ-to-body weight ratio was calculated by dividing the weight (g) of each organ by the weight (g) of rat before sacrifice. The means of the organ-to-body weight ratios of rats that received both doses of the FDTs and the extract did not show a significant difference compared to the control group **(Figure 2b)**.

3.4.1. Histopathologic finding:

Histological examination of spleen, stomach and heart of control animals and animals receiving the therapeutic doses of plant extract and therapeutic doses of the formulated FDTs showed no remarkable microscopic lesions **(Figure 3)**. There was a mild cloudy swelling of the kidney in the group of rats receiving high dose of plant extract which is considered as mild form of cell injury. Mild fatty changes appeared in the liver of the groups receiving high dose of both the extract and the formulated tablets. The results indicate that the plant extract blend and the prepared tablets are safe in both therapeutic and high doses.

4. Discussion:

In spite of the promising biological activities of many natural active ingredients of herbal extracts, their poor stability and patient incompliance oppose their clinical application. Therefore, solid formulation of such therapeutically active herbal products may have an impact on enhancing their stability and therapeutic activity. Fast disintegrating tablets are usually addressed for the rapid absorption and enhanced bioavailability, Many previous studies have considered the formulation of suitable pharmaceutical dosage forms of combination of natural products for the treatment of various diseases [39]. In this study, a fast disintegrating tablet formulation of spray dried extract of blend of herbal plants of promising hypoglycemic and wound healing activity, has been optimized with. The optimized FDT formulation (F6) maintained the best preformulation parameters, especially compressibility index, and the least wetting time and disintegration time which guarantee better absorption.

Administration of either the herbal extract or the formulated tablets has resulted in a significant reduction of blood glucose levels and improvement of wound healing in STZ diabetic rats which can be explained based on the previously reported hypoglycemic effects of the components of our herbal mixture [11, 15-17, 40, 41]. The excellent wound healing effect of the extract and the formulated tablets may be attributed to their effect on reducing the blood glucose level of the diabetic rats **(Figure 1 a)** and subsequently enhancing angioneogenesis [42]. Since inflammation and circulating cytokines (TNF-α, IL-1β and IL-6) are among the mechanisms of retardation of diabetic wound healing [42], the anti- inflammatory effects of some plants of the herbal blend [43-46] may have a role in the promoted wound healing in the groups receiving the herbal extract or the tablet formulation.

Meanwhile, the more prominent enhanced hypoglycemic and diabetic wound healing effect of the optimized tablet formulation may be attributed to the instant absorption, accurate dosing and induced chemical and microbiologic stability of the prepared tablets compared to the aqueous extract solution [47, 48].

According to Allen et al., spray drying of the herbal blend have a positive role in the induced flowability of the pre-formulated tablet preparation [49]. Moreover, enhanced disintegration and wetting of the prepared formulation is believed to be attributed to the swelling of the added blend of superdisintegrants and the subsequent increased surface area of the formulation together with the enhanced distortion in the matrix of the blend allowing the Super disintegrating blend to pick up more water (combined swelling and pick up effect) [50].

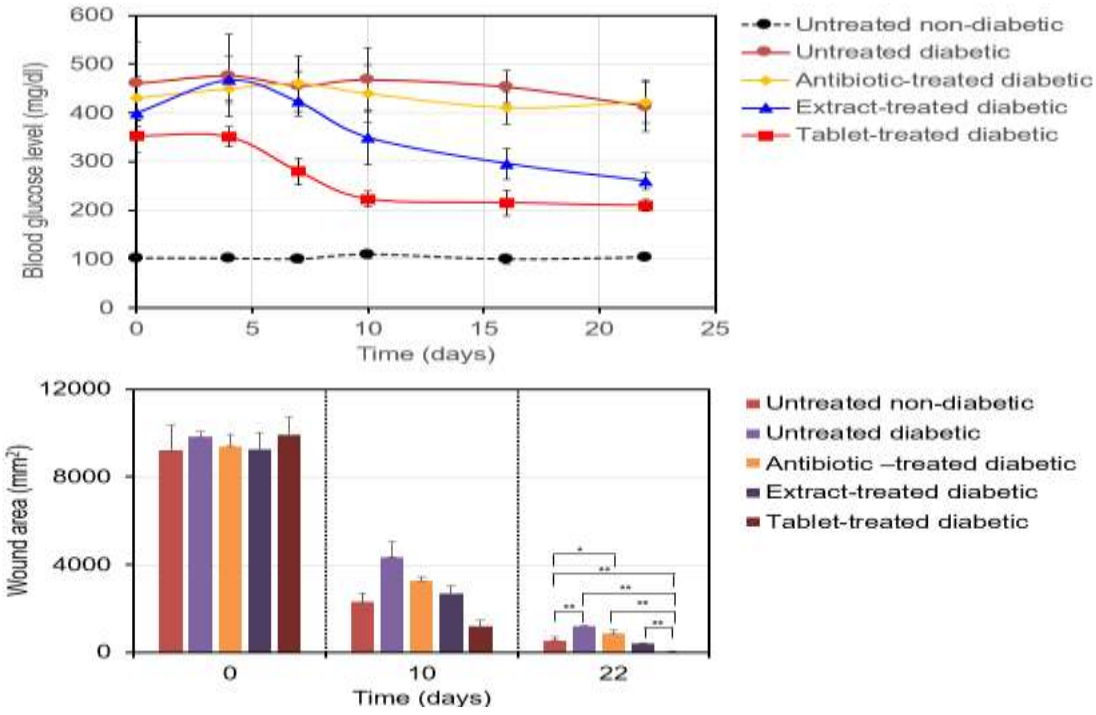

Figure (1): a) Plasma glucose levels in control diabetic rats, antibiotic-treated diabetic rats, tablet-treated diabetic rats and extract-treated diabetic group along 22 days post-induction of diabetes.

b) Wound area (mm^2) by a specific image analysis computer program (IACP) on days (0, 10, 22) in control non-diabetic, control diabetic, antibiotic-treated diabetic rats, tablet-treated diabetic rats and extract-treated diabetic rats.

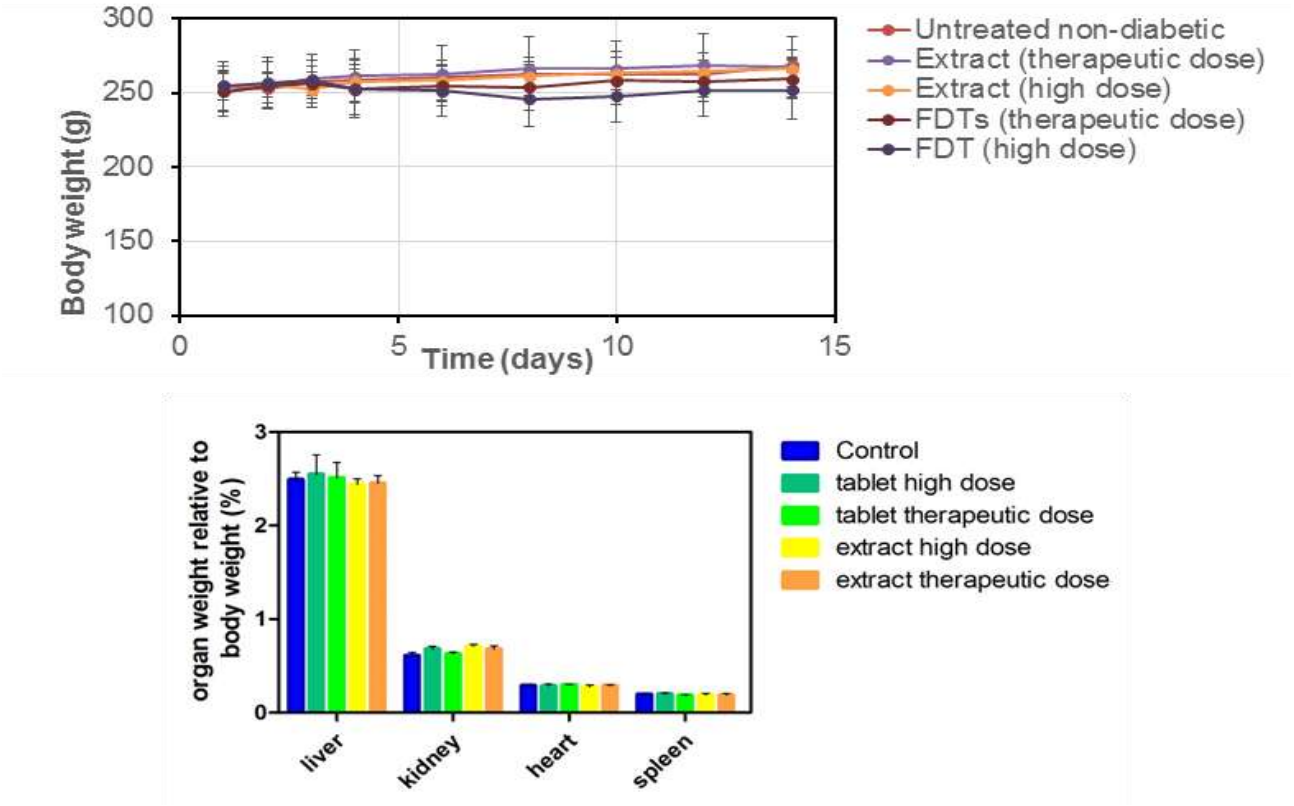

Figure (2): a) Body weight of rats of the control group, rats receiving high dose FDTs, rats receiving therapeutic dose FDTs, rats with high dose extract and rats with therapeutic dose extract.
b) Organ weight relative to body weight of rats of the control group, rats receiving high dose FDTs, rats receiving therapeutic dose FDTs, rats with high dose extract and rats with therapeutic dose extract.

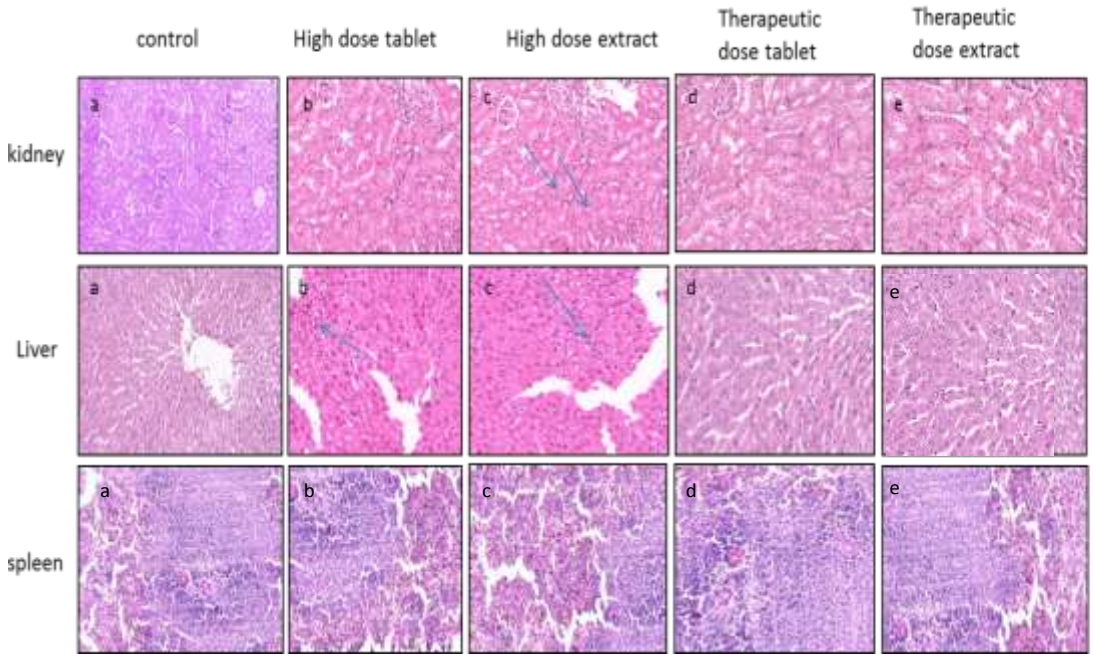

Figure (3): Histopathologic analysis of organs of control rats (a), rats treated with high doses of tablets (b), rats treated with high doses extract (c), rats treated with therapeutic doses of tablets (d) and rats treated with therapeutic doses of extract (e).

All these combined factors maintained the wettability, dispersibility, disintegration and improved bioavailability of the optimized formulation [51].

5. Conclusion

In this study, fast dissolving tablets containing a blend of spray dried extracts of seven herbs that are known for their hypoglycemic, antibacterial, anti-inflammatory and blood flow improvement actions were prepared and evaluated. The tablets show improved hypoglycemic and wound-healing activity in diabetic rats with full thickness injuries, compared to both extract-treated rats and antibiotic-treated rats. It is believed that spray drying of the powder prior to tablet compression and the using a blend of super-disintegrants in the preparation of the tablets have improved the bioavailability of the herbal extract compared to unformulated extracts. The extract and the prepared fast disintegrating tablets were safe enough so that no remarkable toxicity was observed in either the extract-treated or the tablet-treated rats, even at high doses. This new natural blend of pharmacologically active herbs shows promise in treating peripheral injuries of the foot in diabetic patients (diabetic foot) and controlling blood glucose levels, and the improvement of activity following its formulation in FDTs carries high potential towards clinical translation.

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