Volume 8, Issue 4, 2019, 692 - 697 **ISSN 2284-6808**

Letters in Applied NanoBioScience

https://nanobioletters.com/

https://doi.org/10.33263/LIANBS84.692697

Original Research Article **Open Access Journal**

Received: 19.09.2019 / Revised: 23.10.2019 / Accepted: 25.10.2019 / Published on-line: 28.10.2019

Formulation and evaluation of herbal tablet containing *Terminalia chebula* extract

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ABSTRACT

According to WHO, the prevalence of diabetes is likely to increase by 35%. Currently there are over 150 million diabetics worldwide and this is likely to increase to 300 million or more by the year 2025. International Diabetes Federation (IFD) estimates the total number of diabetic subjects to be around 40.9 million in India and this if further set to rise to 66.9 million by the 2025. In view of the above discussion this study was undertaken to investigate antidiabetic activity of herbal tablet of *Terminalia chebula* in alloxan induced diabetic rats. Solid pharmaceutical dosage formulations using a novel dry plant extract (*Terminalia chebula* fruits) using various excipients i.e.carbopol, lactose, gelatin, magnesium stearate and dicalcium phosphate by the wet granulation was reported to the statically significant. The present communication deals with the evaluation of formulated tablets (weight variation, friability and hardness and disintegration time). Diabetes was induced in Wistar albino rats (170-200g) by a single dose (I.P.) of alloxan monohydrate (150mg/kg) dissolved in normal saline, treatment were given orally for 21days and blood glucose level was estimated on Two different batches of herbal tablets of *Terminalia chebula* extract (carbopol & gelatin) were studied for blood glucose level in two different groups of animals. Oral administration of *Terminalia chebula* tablet having carbopol to diabetic rats at a dose of 200mg/kg body weight to wistar rats in a significant reduction in biochemical parameters in alloxan diabetic rats, and the best formulation according to disintegration time. Thus our investigation clearly shows that the *Terminalia chebula* tablet has antidiabetic effects.

Keywords: *Diabetes; Terminalia chebula; Antidiabetic activity; carbopol, gelatin; Herbal formulation.*

1. INTRODUCTION

Herbs are origins in ancient culture.Herbal medicinesas potential source of therapeutic purpose has a significant role to enhance general health all over the world for both humans and animals. India has approx. 45000 plant species and among them, several thousands have been demonstrated to possess medicinal properties. According to the report of WHO, 80% of the world population relies on the natural herbal drugs [1].

Herbal products may contain a single herb or combination of several different herbs believed to have complementary and/ synergistic effect. Some herbal products, including many traditional medicines formulations, also derived from animal or mineral origins. The fruits of plant *Terminalia chebula,* belonging family Combretaceae was used for the study of antidiabetic activity. This study is based on formulation and evaluations of the tablets made from methanolic extract of fruit of *Terminalia chebula* and alloxan is used to induce diabetes in rats [2]

Diabetes mellitus is a group of metabolic disorder characterized by hyperglycemia by improper secretion of insulin or insulin resistance, or both and associated with abnormalities in carbohydrate, fat and protein metabolism; and result in chronic complication including microvascular, macro vascular and neuropathic disorder [3]. The vast majority of diabetic patient is classified into two categories: Type 1 diabetes caused by an absolute deficiency of insulin, or type 2 diabetes defined by the presence of insulin secretion [4]. Women who develop diabetes due to the stress of pregnancy are have classified as having gestational diabetes [4].

Terminalia chebula (*T. chebula*), a natural plant found in India and South East Asia and is extensively cultivated in Taiwan. It is dried ripe fruit, has been traditionally been to treat different aliment in Asia. It is popular for folk medicine and also studied for its homeostatic laxative, purgative and cardio tonic activities [5]. *Terminalia chebula* has been reported to show a variety of pharmacological activities, anti-diabetic, anticancer, anti-mutagenic, and anti-viral activity, anti-nociceptive, anti-arthritic, molluscicidal etc [6].

The administration of drug by oral route is the important route for systemic delivery. It is probable that at least 90% drugs were delivered by oral route to produce systemic effects (Bentley and Rawlins).Compressed tablet is generally used pharmaceutical dosage forms for a number of reasons i.e. patient compliance, portable, and economically inexpensive than other oral dosage forms. They deliver a precise dose with a high degree of accuracy. Tablet can be made in a variety of shapes and sizes limited only by the ingenuity of the tool and die maker (i.e. round, oval, capsule-shaped, square, triangular, etc).

Compressed tablets are defined as solid-unit dosage forms made by compaction of a formulation containing the drug and certain fillers or excipients selected to aid in the processing and properties of the drug product. There are many types of tablets designed for specific uses or functions. These include tablets to be swallowed, per se; chewable tablets formulated to be chewed rather than swallowed, such as some antacid and vitamin tablets; buccal tablets designed to dissolve slowly in the buccal pouch; and sublingual tablets for rapid dissolution under the tongue. Effervescent caused by the reaction of citric acid with sodium bicarbonate or some other effervescent combination that produces effervescence in water. Suppositories can be made by compression of formulation using a specially designed die to produce the proper shape.

2. MATERIALS AND METHODS

The present work was designed at the formulation and evaluation of herbal tablets of *Terminalia chebula.*

Preparation of the extract: The fruits of *Terminalia chebula* were collected from local market of Saharanpur (U.P), India. Authentication of fruits was done by NISCAIR, New Delhi. Ref.no NISCAIR/RHMD/Consult/2014/2504/83.

Dried fruits were coarsely powdered in an electrical grinder. The powder was successively extracted with petroleum ether, ethanol and water by soxhlet apparatus. The residue obtained after extraction was concentrated using rotary evaporator under reduced pressure.

Formulation: For formulation of GRDSS polymers belonging to one group i.e. anionic (carbopol) were selected. The anti-diabetic herbal tablets were formulated by using wet granulation method. In this primarily a polymer solution was prepared with the suitable solvent. Then the remaining ingredients were mixed with the active constituents (drug) mass, which was passed through a proper sieve to form granules. The granules formed were further passed through a proper sieve, dried and mixed with lubricant and then compressed to form the desired oral tablet.

Designing of formulation of oral tablets.

Preparation of granules.

The granules of *Terminalia chebula* were prepared by wet granulation method (Subrahmanyam CVS second edition). The solutions were prepared in distilled water by taking appropriately quantities of starch & dicalcium phosphate and dissolving in 5% distilled water. This emulsion of starch along with preservatives was heated on a water bath until translucent semisolid mass was formed. The wet mass of gelatin/carbopol was prepared by using required quantity of water separately. The drug powder was transferred to motor and appropriate amount of lactose and magnesium stearate was added to it. The solution was added to the blend and mixed properly to make dough. This was passed through sieve no. # 22 (710µm). The granules so obtained were dried at 40.c for 1 hour. After drying granules were sized by sieving them through sieve no. # 20 and subjected to evaluation. Total six batches of granules were obtained. All quantity of drug and the other ingredients were kept constant [7].

Evaluation of powder blend.

The blend of powders was evaluated for the following parameters (Agarwal SP second edition):

Angle of Repose.

Angle of repose was determined by using fixed funnel method. The funnel was set perpendicular to the axis of symmetry and its tip was kept at a given height (h) above a graph paper that was placed on a left horizontal surfaces. The blend of powder was poured through the funnel and a maximum cone height (h) of powder blend was obtained [8]. The diameter (2r) of the base of the powder cone was determined and the tangent of the angle of repose was calculated by following given equation:

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

Bulk Density.

Apparent bulk density (ρb) of powder blend was determined by placing pre-sieve blend into a graduated cylinder and measuring the volume (V) and weight (M) [9]. Bulk density was calculated by using given equation:

$$\rho b = M/V$$

Tapped Density.

Tapped density was determined by pouring the accurately weighed quantity of powder blend into the graduate cylinder and the volume (V) was measured. Then the graduated cylinder was closed with lid, and tapped by using bulk density apparatus till a constant volume was maintained in the cylinder [10]. The tapped density was calculated by using given equation.

$$\rho t = M/V$$

Compressibility Index (Carr'sindex).

Compressibility index is also known as Carr's index and can be obtained by employing the poured density and tapped density values of a material. Theoretically it can be said that the less compressible a material the more flowable it is [11]. It can be determined by substituting the values of poured density and tapped density in the equation given below:

$$C = (\rho t - \rho b)/t \times 100$$

Where, ρt is tapped density and ρb is untapped density.

Hausner's Ratio

Hausner's ratio is an index of powder flow and was measured by the ratio of tapped density to the bulk density [12].

$$\text{Hausner's ratio} = \rho t / \rho b$$

Where, ρt is tapped density and ρb is untapped density.

Formulation of oral tablet.

Tablets were formulated as per the formulation is given in table no.I. Each tablet was of 300 mg containing 200 mg of the drug and rest excipients. The granules were mixed in appropriate quantities of magnesium stearate (as a lubricant &antiadherent) as given in table no.3.3. These were then compressed into tablets by using tablet punching machine employing 9.7mm of punch and die. Five batches of tablets were obtained and subjected to evaluation.

Evaluation of prepared tablets.

Prepared tablets were evaluated on the basis of following parameters

- **Thickness**

It can be determined by randomly selecting ten tablets from each batch using vernier calipers [13]. All readings were taken thrice.

- **Hardness**

It can be determined by randomly selecting ten tablets from each batch using a Monsanto Hardness Tester. The hardness of about 3-5kg/cm2 is considered to be satisfactory for uncoated tablets [14].

- **Friability:**

Friability of the sample was measured using a Roche Friabilator. Ten pre-weighed tablets were rotated at 25rpm for 4 minutes. The tablets were then dusted and reweighed. Friability is generally the loss of weight of tablet in the container due to the removal of fine particles from the surface [15].

- **Weight variation**

Ten tablets were randomly selected from each batch, individually weight; the average weight and percentage deviation from the average were calculated. It is done in order to ensure uniformity in the weight of tablets in a batch [16]

- **Disintegration time:**

Disintegration was determined USP basket type apparatus. To test for disintegration time one tablets were placed in each of the 6

tubes of the basket having a plastic disc over the tablets and the basket rack was placed in 1 L beaker of water. The temperature of water was maintained at 37±2^0 C. Tablets were subjected to the oscillation at a frequency of 28-32 cycles per minute. At the end of 15 minutes, lift the basket from the liquid and observe the tablets. The tablets pass the test if all tablets disintegrate at the end of 15 minutes. In case one or two tablets fail to disintegrate, repeat the test on 12 additional tablets. The tablets pass the test if not less than 16 of the total of 18 tablets has disintegrated [16].

Antidiabetic activity (*In-vivo study)*:

Experimental animals.

Albino rats weighing between 170-200 g were obtained from the Animal House, Department of Pharmacology, AVIPS, Gangoh (Saharanpur). The animals were placed at random and allocated to treatment groups in polypropylene cages with husk as bedding. Animals were housed at a temperature of 24±20 C 0 and relative humidity of 30-70 %. A 12:12 light: day cycle was followed. All animals were allowed to free access to water and fed with standard commercial pellet rat chaw. All the experimental procedures and protocols used in this study were reviewed by the Institutional Animal Ethics Committee (IAEC) and were in accordance with the guidelines of the IAEC. Animal handling protocol was performed according to Good Laboratory Practice (GLP) (17)

Induction of diabetes in rats.

Diabetes was induced in Wistar albino rats (150-200 g) by using a single intra peritoneal injection of alloxan monohydrate (150 mg/kg) dissolved in normal saline. One hour after administration of Alloxan administration, the animals were fed with standard laboratory diet and water ad libitum [4]. Three days after alloxan injection, the blood samples were collected from retro-orbital puncture using capillary tubes and blood glucose level was analyzed. Animals having blood glucose level range > 200 mg/dl were included for further study.

The selected diabetic rats were divided into five groups with six animals in each group.

Group I: Normal control.

Group II: Served as diabetic control group.

Group III: Standard drug glibenclamide (5 mg/ kg) *p.o* for 21 days gives to diabetic rats.

Group IV: Diabetic rats were given Carbopol containing herbal tablet of T.C 200 mg/kg *p.o* for 21 days.

Group V: Diabetic rats were given herbal tablet (Gelatin) of T.C 200 mg/kg *p.o* for 21 days.

Blood samples were collected just prior to and on days 1,7,14 and 21 after the drug administration and the percentage of reduction in blood glucose, body weight changes were estimated and compared.

Table 1. Composition of unit dose of oral tablet of *Terminaliachebula.*

S.No.	INGREDIENTS	QUANTITY PER TABLET (mg)				
		F1	F2	F3	F4	F5
1	Plant extract	200	200	200	200	200
2	Carbopol	_	5%	_	5%	_
3	Gelatin	5%	_	5%	_	5%
4	Lactose	20	20	20	20	20
5	Starch	20	20	30	30	40
6	Di-calcium phosphate	50	50	40	40	30
7	Magnesium stearate	10	10	10	10	10
	Total weight	300	300	300	300	300

3. RESULTS

Extraction Yield of Drug:

The yield of methanol-water (50:50) extract was obtained 8.5 g.

Evaluation of granule:

The angle of repose was found to be range of 28.8- 30.3. Angle of repose was found to be best for formulation F1 which showed the excellent flow, and lowest for which showed the good flow, since the angle of repose for all formulation was less than 30˚ exhibited excellent to a good flow. (Table no. II and figure no. 1)

The bulk density was found to be in range of 0.36-0.42 as in table II. F2 possessed the greatest bulk density followed by F3 while F4. (Table no. II and figure no. 1).

The tapped density was found to be in range of 0.39-0.43 as in table II and figure no. I. It was observed that there was not much difference between the tapped and bulk densities. This result helps in calculating the% compressibility of the granule. Then % compressibility of granule was determined using Carr's compressibility index and was found to be range of 5.1-11.79 (Table II and figure 1). compressibility index below 15% is a characteristic of god flow but reading above 25% indicate poor flow ability, all formulation possess good flow characteristic in the order F2>F3>F1>F4>F5.

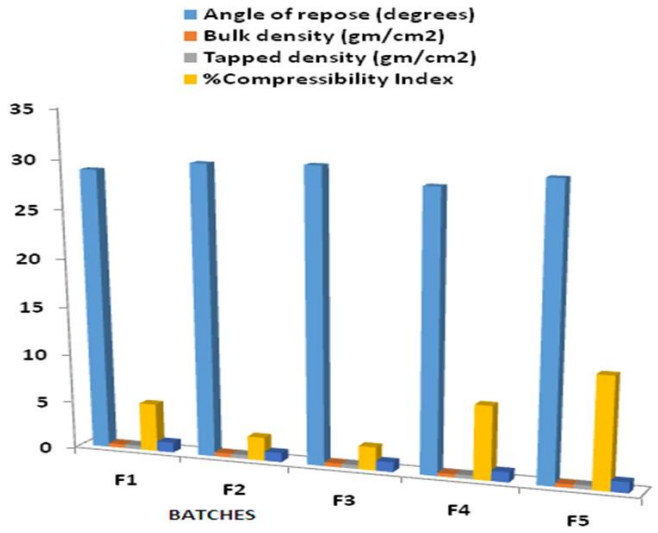

Figure 1. Showing Evaluation parameters of the granules.

The Hausner ratio found to be range of 1.1- 1.13. As the results were obtained within the limit so, granules will not cause any problem during tablet compression.

Evaluation of prepared tablets.

The tablets were described for their physical characteristic like general appearance, thickness, hardness, friability, weight variation, %drug content, disintegration time, in vitro drug release. The results of these studies are presented in Table III.

The tablets were elegant and standard concave in shape with the absence of any physical flaws or unpleasant odour. Tablets containing carbopol and magnesium stearet and pure form of TC were in greenish colour.

The thickness varied from 3.0±0.15-3.5±0.30 mm for various formulations and did not show much variation amongst each other of the same formulation.

The hardness varied from 4.1±0.10-4.6±0.17 kg^2/cm. The values of standard deviation indicate that the hardness of all the formulation was almost uniform and the tablets possessed good mechanical strength to withstand shocks of handling, packaging and shipping without having negative effect on disintegration.

The friability was found to be range of 0.58-0.66, the highest shown by formulation F5 and lowes formulation F1. All the values were below 1% indicating that all the tablets possessed good formulation, showing enough resistence to the mechanical, shock and abrasion.

The % weight variations for all formulation were given in table III. The entire formulation passed weight variation test since the results obtained were within the pharmacopoeia limits and hence they passed weight variation test.

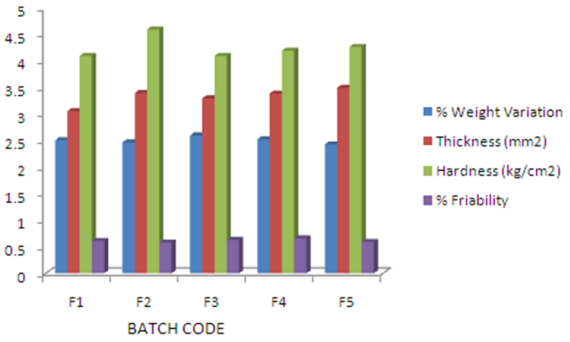

Figure 2. Showing Evaluation of prepared tablets.

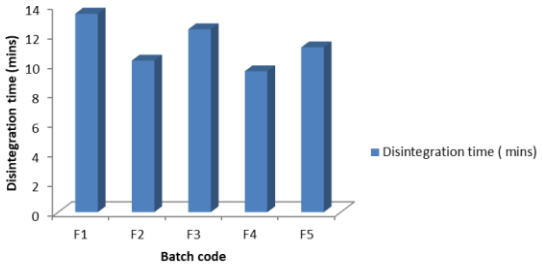

Figure 3. Showing disintegration time of tablet.

Anti-diabetic activity.

Two different batches of the herbal tablets of *Terminalia Chebula* extract (Carbopol& Gelatin) were studied for blood glucose level in two different groups of animals. Both groups showed an extremely significant decrease in blood glucose level in alloxan induced diabetic rats when compared to *diabetic* control group. The initial readings of blood glucose level of Carbopol and Gelatin were 262.66±8.26 and 270.16±8.20 respectively. Both doses produced consistent reduction in the blood glucose levels after 7 days (144.50±5.92, 156.66±2.45) and marked reduction in 21 days (108.33±5.58 and 117.33±4.86). However Carbopol has shown maximum effect than Gelatin. In standard group initial blood glucose level was 263.66±12.49 and on 21 day was 93.00±5.47 which showed that the standard drug produced maximum hypoglycemic effect and the statistical analysis was extremely significant and slightly higher than that of test groups. Diabetic rat group which left untreated shows gradually increases in blood glucose level. Initially blood glucose level of untreated diabetic control group was 258.50±8.06 and after 21 days of the blood glucose level was increased to 297.66±4.13.

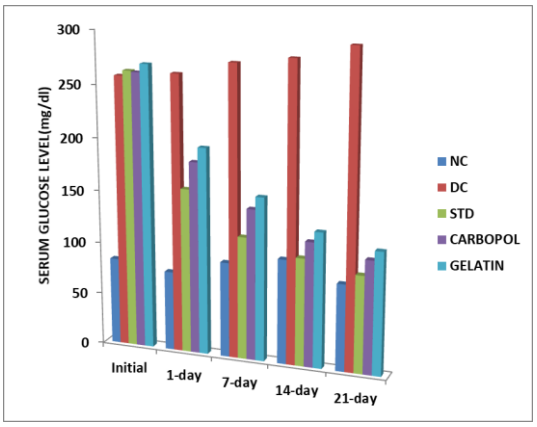

Figure 4. Effect of *Terminalia chebula* herbal tablets on serum glucose level of rats.

NC- Normal control, **DC-** Diabetic control, **STD-** Glibenclamide (5 mg/kg), **CARBOPOL-** *Terminalia chebula* extract (200 mg/kg) with carbopol binder, **GELATIN-** *Terminalia chebula* extract (200 mg/kg) with gelatin binder. **The data collected from various groups were statistically analyzed using one-way ANOVA followed by Tukey's Multiple Range Test. $p< 0.05$, is considered statistically significant.**

Anti-diabetic activity evaluation it was observed that there was an extremely significant reduction in blood glucose level by herbal tablets of *Terminalia chebula* extractsin alloxan induced diabetic rats. The maximum result obtained by the herbal tablet contains carbopol shows maximum effect compare to herbal tablets contain gelatin. The declined trend was observed at a constant level. The anti-diabetic activity of *Terminalia chebula* may be due to the increased release of insulin from beta cells of pancreas or it may potentiate the effect of insulin. Treatment of *Terminalia chebula* in diabetic rat also showed the highly significant weight gain property which favors the beneficial effect of *Terminalia chebula* extract. Also, the maximum effect shown by tablet containing carbopol is because of low binding property of carbopol which disintegrate tablet faster in stomach and provides better availability then tablet containing gelatin.

Table 2. Data of different parameters of granules.

Batch code	Angle of repose (degrees)	Bulk density (gm/cm^2)	Tapped density ($gm/cm^{2)}$	% Carr's Index	Hausner ratio
F1	28.9±0.66	0.38±0.06	0.40±0.15	5	1.05
F2	30.0±0.45	0.42±0.02	0.41±0.25	3	1.1
F3	30.3±0.05	0.40±0.03	0.41±0.03	3	1.025

Batch code	Angle of repose (degrees)	Bulk density (gm/cm^2)	Tapped density ($gm/cm^{2)}$	% Carr's Index	Hausner ratio
F4	28.8±1.11	0.36±0.05	0.39±0.5	7.69	1.08
F5	30.1±0.79	0.38±0.02	0.43±0.2	11.62	1.13

Table 3. Data of various tests of oral tablet of *Terminalia chebula tablets.*

Batch code	% Weight variation	Thickness (mm^2)	Hardness (kg/cm^2)	% Friability	Disintegration Time
F1	2.51±0.21	3.06±0.15	4.1±0.5	0.61±0.03	13 min 45sec
F2	2.47±0.12	3.4±0.21	4.6±0.17	0.58±0.05	10 min 27sec
F3	2.60±0.11	3.3±0.15	4.1±0.30	0.63±0.15	12 min 39sec
F4	2.53±0.16	3.3±0.25	4.2±0.25	0.66±0.04	9 min 55 sec
F5	2.43±0.25	3.5±0.26	4.2±0.21	0.59±0.14	11 min 17sec

4. CONCLUSIONS

Herbal products may contain a single herb or combination of several different herbs believed to have complementary and/ synergistic effects. Some herbal products, including many traditional medicine formulations, also include animal products and minerals. The fruits of plant *Terminalia chebula*, belonging family Combretaceae was used for the investigation anti-diabetic activity.

Therefore, in the present study, efforts have been made to develop herbal tablet of *Terminalia chebula extract* by wet granulation technique by involving the polymer anionic (carbopol). Five formulations (F1, F2, F3, F4, F5) were designed in which F1, F3, F5 contains carbopol and F2, F4 contains gelatin. In all formulation the drug was present in 150 mg quantity and lactose as a diluents, di-calcium phosphate as a glidant, and magnesium stearate as a lubricant and anti-adherent. The granules prepared by wet granulation were evaluated for their flowability, % compressibility and hausner ratio. All the formulation exhibited good to excellent flow and were compressed into tablets of 250 mg. The phyiso-chemical properties thickness range from 3.1± 0.02 to 3.5±o.33 (mm), hardness from 2.1± 0.30 to 2.5± 0.31(kg/cm^2), friability ranges from 0.57± 0.03 to 0.66± 0.04(%) and drug content was found to 93.62± 6.2 to 97.91± 0.03. From these five batches two batch f1 and f4 were best in terms of disintegration time.

The anti-diabetic activity of fruits found to be significant. Anti-diabetic activity evaluation was observed from the data that there was an extremely significant reduction in blood glucose level by herbal tablets of *Terminalia chebula extracts* in alloxan induced diabetic rats. The maximum result obtained by the herbal tablet contains carbopol shows maximum effect compare to herbal tablets contain gelatin. The declined trend was observed at a constant level. The anti diabetic activity of *Terminalia chebula* may be a result of increased release of insulin from beta cells of pancreas or it may potentiate the effect of insulin. Treatment of *Terminalia chebula* in diabetic rat also showed the highly significant weight gain property which favors the beneficial effect of *Terminalia chebula extract*. Also, the maximum effect shown by tablet containing carbopol is because of low binding property of carbopol which disintegrate tablet faster in stomach and provides better availability then tablet containing gelatin.

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