Formulation and Evaluation of *Lepidium Sativum* Seeds Extract as Diuretic Tablet dosage form

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Abstract

Purpose: The present study was undertaken to formulate solid consistency plant extract into tablet dosage form as diuretic and to evaluate the produced tablets (quality control tests).

Method: One formula was prepared by wet granulation method using microcrystalline cellulose, starch powder, starch paste, talc and magnesium stearate in the first formula and by using lactose , poly vinyl pyrrolidone, talc and magnesium stearate in the second formula.

Results: The evaluation of tablets was in accordance to (BP,2009) and (USP,2007). The formula passed weight variation test, percent deviations for formula were within the limit (less than 5%), Hardness test results for the formula were within the limits (more than 4kg and less than 10kg), Friability test results for the formula were within the limit (lost weight less than 1%), Content uniformity test for the formula was within the limits (not less than 85% and not more than 115%), and disintegration test was also with in the specified time.

Conclusion: The present study was undertaken to achieve the following goals:

- Formulation of selected extract into suitable dosage form (tablet).
- Evaluation of the produced tablets of formula (quality control tests)and accelerated stability study for the formula.

It can be concluded that, weight variation, content uniformity,friability,hardness,dissolution and disintegration tests for the formula was within the permitted limits from zero time of tablet production up to three months of accelerated stability studies at (40°C and 75% RH), which reflected the stability of the formula.

Key words: *Lepidiumsativum*, Furosemide, Diuretic Activity, Fractionated Methanolic Extract, Quality control tests.

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Introduction

The word pharmaceutics is used in pharmacy and pharmaceutical science to encompass many subject areas ,which are all associated with the steps to which a drug subjected towards the end of development –i.e. it's the stage that follow the discovery or synthesis, its isolation and purification ,and testing for advantageous pharmacological effects and the absence of serious toxicological problems.

Pharmaceutics converts a drug into a medicine ,pharmaceutics is concerned with the scientific and technological aspects of the design and manufacturing of drug delivery system (Aulton,2002).

The oral route is the most convenient route of administration and the one most commonly used. The oral route involves placing the drug in the mouth and swallowing it). Tablets, capsules, and liquids are all given orally. The drug is then absorbed from the stomach or small intestine into the blood. Compared to the other routes, the oral route is the simplest and safest mean of drug administration(Susan, 2010). over 80% of the drugs in the USA that are formulated to produce systemic effects are marketed as oral dosage forms. Compared to other dosage forms, tablets are the manufacturer's dosage form of choice because of their relatively low cost of manufacture, package, and shipment; increased stability; and virtual temper resistance (Banker and Rhodes, 2002).Tablets are solid dosage forms containing medicinal substances with or without suitable diluents. They may be classified , according to the method of manufacture, as compressed tablets or molded tablets(USP, 2009).Tablet dosage form has several advantages including that tablets are unit dosage form and offer the greatest capabilities of all oral dosage form for the greatest dose precision and the least content variability, cost is lowest of all oral dosage form, lighter and compact, easiest and cheapest to package and strip, easy to swallowing with least tendency for hang-up, sustained release product is possible by enteric coating, objectionable odor and bitter taste can be masked by coating technique, suitable for large scale production, greatest chemical and microbial stability over all oral dosage forms and product identification is easy and rapid requiring no additional steps when employing an embossed and/or monogrammed punch face is used (Anju, 2013).There are a lot of essential properties of tablet dosage form including tablets have accurate dosage of medicament, uniform in weight, appearance and diameter, have the strength to withstand the rigors of mechanical shocks encountered in its production, packaging, shipping and dispensing, a tablet should have elegant product identity while free of defects like chips, cracks, discoloration, and contamination, should have the chemical and physical stability to maintain its physical attributes over time, the tablet must be able to release the medicinal agents in a predictable and reproducible manner and must have a chemical stability over time so as not to follow alteration of the medicinal agents(Sahoo,2007).

Materials and Methods

First class freshly picked *L.sativum* seeds were purched from Omdurman market. The seeds were collected from west of the Sudan from Kurd fan; they were clean with brownish red color. The seeds were identified in Sudanese national Centre of research.

Hot continuous extraction (soxhelt)

20gm of the coarse powder of the dried seeds of *Lepidium sativum* was weighed using sensitive electric balance, transferred to a soxhelt containing 200mL of petroleum ether (defatting), and allowed for 10 hrs. The defatted powder of the seeds was transferred to a soxhelt containing 200mLof different concentration of methanol and allowed for 18 hrs. The methanolic extract was filtered and evaporated to reduce the solvent volume using rotary evaporator under reduced pressure at 40ºC, placed in a Petri dish and left to dry to constant weight.

Fractionation of methanol extract

10 gram of methanol extract was dissolved in 10 ml of methanol then sufficient amount of ethyl acetate was added until white precipitate formed.

Preparation of tablets

A specified amount of the dry fractionated methanolic extract was weighed precisely, put in a beaker and labeled (A). A specified amount of mixture of lactose and starch was put in another beaker and labeled (B). Both (A) and (B) were mixed together to form a wet mass by using Poly vinyl pirolidine aqueous solution. This mass was forced manually through a No. 10 mesh screen to form granules, which were placed in a hot air oven at 40ºC for complete drying. The dried granules were resized using No. 32 mesh screen to get uniform- sized granules. The external phase composed of magnesium stearate, and talc were added to dried granules. The above mixture was transferred to the hopper of a single- punch tableting machine, using 12 mm die. The weight and the pressure of the machine were adjusted to obtain the tablets.

Table (1) Ingredients of the formula

Material	Quant./tablet mg	Quant. For 500 tab(g)
Extract	300	150
Lactose	200	100
Starch	60	30
PVP	10	5
Talc	3	1.5
Magnesium stearate	2	1

Quality control of prepared tablets

Weight variation test

According to USP (2007), 20 tablets were weighed individually. The average weight of these tablets was calculated, the deviation of each tablet from the mean was calculated, from which the standard deviation, and percentage deviation were calculated and compared with standard.

$$\text{The Calculated Standard Deviation } (SD) = \sqrt{\frac{\sum(X - \bar{X})^2}{n - 1}}$$

$$\% D = \frac{SD \times 100}{\text{averageweight}}$$

In which:

Tablet weight (×) ,Mean ($\bar{X}$),Deviation from the Mean (X- $\bar{X}$).

Friability test

According to USP (2009), a sample of 20 tablets was taken and carefully dedusted prior to testing. The tablet sample was accurately weighed and placed in the drum of the apparatus. The drum was rotated 100 times, removed the tablets, the loose dust from the tablets was removed as before, and accurately reweighed. The test was repeated three times, and the mean of the three tests was determined. A maximum mean weight loss from the three samples of not more than 1.0% is considered acceptable for most products.

Hardness test

10 tablets were placed individually in hardness tester and the data collected was used to calculate the mean tablets hardness according to BP (2009).

Disintegration test

According to BP (2009), one tablet was placed in each of the six tubes of the basket of the disintegrator, a disk was added to each tube, and the apparatus was operated, using distilled water as medium. The medium was maintained at 37 ± 2ºC. At the end of the test., the basket was lifted from the fluid, and the disintegration time was recorded.

Dissolution test

Dissolution test of sample

The dissolution tester was filled with distilled water as medium, and allowed to warm up to 37± 0.5º C. Tablets were individually introduced into dissolution tester. Then the machine was operated adjusting the rotational speed to 100 rpm. 20 ml of sample was withdrawn after (45 minutes), filtered and assayed using UV method with reference to the standard.

Dissolution test of standard

The dissolution tester was filled with distilled water as medium, and allowed to warm up to 37± 0.5ºC.a specified amount of the dry methanolic extract was introduced into the dissolution tester. Then the machine was operated adjusting the rotational speed to 100 rpm. 20 ml of sample was withdrawn after (45 minutes), filtered and assayed using UV method, taking the highest beak as the Finger print.

Stability test

Tablets of each formula were packed in a glass container and placed into stability chamber under controlled temperature (40°C ± 2°C) and relative humidity (75% RH ± 5% RH), for three months. Weight variation test, dissolution test, disintegration test and content uniformity test were done at zero time, after one month, after two months and after three months. In addition friability test and hardness test were carried out for both formulae at zero time.

Results

The results of the evaluation carried out on both formulae are listed in tables below.

Quality control tests at zero time

Table(2)Weight variation test (1), at (0) time

No. of tablet	Tablet wt. in gram(X)	Deviation form mean $(X- \bar{X})$	$(X- \bar{X})^2$
1	0.598	0.014	0.000196
2	0.586	0.002	0.000004
3	0.590	0.006	0.000036
4	0.595	0.011	0.000121
5	0.586	0.002	0.000004
6	0.580	-0.004	0.000016
7	0.590	0.006	0.000036
8	0.589	0.005	0.000025
9	0.586	0.002	0.000004
10	0.595	0.011	0.000121
11	0.590	0.006	0.000036

12	0.580	-0.004	0.000016
13	0.586	0.002	0.000004
14	0.571	0.013	0.000169
15	0.582	-0.002	0.000004
16	0.578	-0.006	0.000036
17	0.573	-0.011	0.000121
18	0.577	0.007	0.000049
19	0.575	-0.009	0.000081
20	0.573	-0.011	0.000121
Mean	**0.584**		$\sum$ **0.0012**

The Calculated Standard Deviation (SD) $= \sqrt{\frac{\sum(X-\bar{X})^2}{n-1}} = \sqrt{\frac{0.0012}{19}}$ **= 0.0080**

D% = (SD/average weight)× 100 = 1.39%

Table(3) Friability test, at (0) time

Test No.	Wt. of 20tablet in gram before test (X1)	Wt. of 20tablet after test (X2)	Difference (X1-X2)	Weight loss %
T1	11.27	11.225	0.045	0.399
T2	11.20	11.18	0.02	0.178
T3	11.23	11.20	0.03	0.267
Mean				**0.281**

Table(4) Hardness test, at(0) time

Tablet No.	Test No1	Test No2	Test No3
1	3.8	5.5	4.0
2	3.8	4.8	3.4
3	4.5	3.9	4.6
4	4.7	4.0	5.0
5	4.7	5.4	3.8
6	4.8	4.2	5.2
7	4.9	5.0	3.5
8	5.0	4.3	4.4
9	5.0	4.4	5.2
10	5.0	5.3	4.5
Mean	**4.62**	**4.68**	**4.36**

Table(5) Disintegration test result, at (0) time

Tab. No.	Time	Tab. No.	Time	Tab. No.	Time
1.	2.71	**1.**	1.98	**1.**	3.36
2.	3.15	**2.**	2.17	**2.**	1.89
3.	3.28	**3.**	3.12	**3.**	2.72
4.	1.50	**4.**	2.15	**4.**	3.88
5.	2.05	**5.**	3.07	**5.**	1.70
6.	3.09	**6.**	2.10	**6.**	3.25
Mean	**2.63**	**Mean**	**2.43**	**Mean**	**2.8**

Dissolution test of standard

Concentrations of tablets were obtained from the following equation:

Concentration= (sample Absorbance)/ Standard Absorbance)X100

Table(6) Absorbance of standard(selected extract)

Time/min.	Absorbance
10	0.356
20	0.365
30	0.375
40	0.378
45	0.388
50	0.390

Dissolution test, at (0) time

Table(7) Absorbance, at (0) time

Tab. No.	Absorbance					
	10 min	20 min	30 min	40 min	45 min	50 min
1.	0.103	0.141	0.258	0.310	0.355	0.372
2.	0.121	0.130	0.231	0.299	0.343	0.369
3.	0.100	0.125	0.311	0.341	0.350	0.366
4.	0.088	0.139	0.219	0.303	0.357	0.371
5.	0.123	0.137	0.305	0.369	0.349	0.360
6.	0.091	0.122	0.352	0.278	0.352	0.367
Mean	**0.104**	**0.132**	**0.279**	**0.317**	**0.351**	**0.368**

Table(8) Concentration %, at (0) time

Tab. No.	Concentration %					
	10 min	20 min	30 min	40 min	45 min	50 min
1.	28.93	38.63	68.80	79.90	91.49	95.38
2.	33.99	36.52	61.60	79.10	88.40	94.62
3.	28.09	35.11	82.93	90.21	90.21	93.85
4.	24.72	39.04	58.40	80.16	92.01	95.13
5.	34.55	37.53	81.33	97.62	89.85	92.31
6.	25.56	33.42	93.87	73.54	90.92	94.10
Mean	**29.31**	**36.71**	**74.49**	**83.42**	**90.50**	**94.23**

Stability test result, after one month

Table(9)Weight variation test, after one month

No. of tablet	Tablet wt. in gram (X)	Deviation form mean $(X- \bar{X})$	$(X- \bar{X})^2$
1	0.580	-0.002	0.000004
2	0.585	-0.003	0.000009
3	0.590	-0.008	0.000064
4	0.580	-0.002	0.000004
5	0.575	-0.007	0.000049
6	0.585	-0.003	0.000009

7	0.590	-0.008	0.000064
8	0.575	-0.007	0.000049
9	0.580	-0.002	0.000004
10	0.570	-0.012	0.000144
11	0.585	-0.003	0.000009
12	0.590	-0.008	0.000064
13	0.592	0.01	0.0001
14	0.580	-0.002	0.000004
15	0.575	-0.007	0.000049
16	0.570	-0.012	0.000144
17	0.585	-0.003	0.000009
18	0.593	0.011	0.000121
19	0.580	-0.002	0.000004
20	0.570	-0.012	0.000144
Mean	**0.582**		**∑0.0010**

The Calculated Standard Deviation (SD) $= \sqrt{\frac{\sum(X-\bar{X})^2}{n-1}} = \sqrt{\frac{0.0010}{19}}$ **= 0.0073**

D% = (SD/average weight)× 100 = 1.27%

Table(10) Friability test, after one month

Weight of 20 tablet before test	**Weight of 20 tablet before test**	**Difference (X1-X2)**	**Weight loss %**
11.173	11.141	0.032	0.286

Table(11) Hardness test, after one month

Tablet No.	Hardness
1	4.4
2	5.7
3	3.2
4	5.1
5	5.2
6	3.2
7	5.7
8	5.2
9	3.9
10	5.3
Mean	**4.7**

Table(12) Disintegration test, after one month

Tab. No.	Time/min
1	3.31
2	2.29
3	1.93
4	1.14
5	2.99
6	3.18
Mean	**2.47**

Dissolution test, after one month

Table(13) Absorbance, after one month

Tab.No.	Absorbance					
	10 min	20 min	30 min	40 min	45 min	50 min
1.	0.110	0.140	0.241	0.307	0.363	0.379
2.	0.128	0.144	0.260	0.320	0.365	0.375
3.	0.109	0.138	0.225	0.368	0.361	0.370
4.	0.087	0.147	0.320	0.303	0.350	0.383
5.	0.127	0.145	0.355	0.300	0.352	0.377
6.	0.093	0142	0.310	0.349	0.360	0.380
Mean	**0.109**	**0.143**	**0.285**	**0.325**	**0.359**	**0.377**

Table(14) Concentration %, after one month

Tab.No.	Concentration %					
	10 min	20 min	30 min	40 min	45 min	50 min
1.	30.90	38.36	64.27	79.12	93.56	97.18
2.	35.96	39.45	69.33	84.66	94.07	96.15
3.	30.62	37.81	60.00	97.35	94.04	94.87
4.	24.44	40.27	85.33	80.16	90.21	98.21
5.	35.67	39.73	94.67	79.37	90.72	96.67
6.	26.12	38.90	82.67	95.24	92.78	97.44
Mean	**30.62**	**39.09**	**76.05**	**85.98**	**92.56**	**96.75**

Stability test result, after two months

Table(15) Weight variation test , after two months

No. of tablet	Tablet wt. in gram (X)	Deviation form mean $(X- \bar{X})$	$(X- \bar{X})^2$
1	0.596	0.013	0.000169
2	0.592	0.009	0.000081
3	0.582	-0.001	0.000001
4	0.586	0.003	0.000009
5	0.596	0.013	0.000169
6	0.575	-0.008	0.000064
7	0.596	0.013	0.000169
8	0.582	-0.001	0.000001
9	0.586	0.003	0.000009
10	0.592	0.009	0.000081
11	0.565	-0.018	0.000324
12	0.596	0.013	0.000169
13	0.575	-0.008	0.000064
14	0.570	-0.013	0.000169
15	0.582	-0.001	0.000001
16	0.581	-0.002	0.000004
17	0.586	0.003	0.000009
18	0.570	-0.013	0.000169
19	0.565	-0.018	0.000324
20	0.580	-0.003	0.000009
Mean	**0.583**		**∑0.0020**

The Calculated Standard Deviation (SD) $= \sqrt{\frac{\sum(X-\bar{X})^2}{n-1}} = \sqrt{\frac{0,0020}{19}} = 0.0103$

D% = (SD/average weight)× 100 = 1.79%

Table(16) Friability test after two months

Weight of 20 table before test	Weight of 20 tablet before test	Difference (X1-X2)	Weight loss %
11.260	11.220	0.040	0.355

Table(17) Hardness test, after two months

Tablet No.	Hardness
1	3.5
2	5.2
3	4.7
4	3.0
5	4.3
6	5.2
7	5.0
8	3.5
9	5.3
10	4.5
Mean	**4.4**

Table(18) Disintegration test, after two months

Tab. No.	Time/min
1	1.16
2	3.7
3	2.67
4	3.19
5	1.79
6	2.8
Mean	**2.55**

Dissolution test, after two months.

Table(19) Absorbance, after two months

Tab. No.	Absorbance					
	10 min	20 min	30 min	40 min	45 min	50 min
1.	0.100	0.135	0.260	0.320	0.360	0.375
2.	0.091	0.138	0.239	0.312	0.344	0.372
3.	0.075	0.146	0.315	0.344	0.352	0.370
4.	0.087	0.144	0.222	0.315	0.364	0.373
5.	0.094	0.137	0.310	0.358	0.355	0.369
6.	0.105	0.140	0.353	0.275	0.358	0.378
Mean	**0.092**	**0.140**	**0.283**	**0.321**	**0.356**	**0.373**

Table(20)Concentration %, after two months

Tab.No.	Concentration %					
	10 min	20 min	30 min	40 min	45 min	50 min
1.	28.09	36.99	69.33	84.66	95.24	96.15
2.	25.56	38.81	63.73	82.54	88.66	95.38
3.	21.07	40.00	84.00	91.01	90.72	94.87
4.	24.44	39.45	59.20	83.33	93.81	95.64
5.	26.40	37.53	82.67	94.71	91.49	94.62
6.	29.49	38.36	94.13	72.75	92.27	96.92
Mean	**25.84**	**38.52**	**75.51**	**84.83**	**92.03**	**96.60**

Stability test result, after three months

Table(21) Weight variation test , after three months

No. of tablet	Tablet wt. in gram (X)	Deviation form mean $(X- \bar{X})$	$(X- \bar{X})^2$
1	0.594	0.012	0.000144
2	0.591	0.009	0.000081
3	0.593	0.011	0.000121
4	0.594	0.012	0.000144
5	0.591	0.009	0.000081
6	0.588	0.006	0.000036
7	0.591	0.009	0.000081
8	0.594	0.012	0.000144
9	0.564	-0.018	0.000324

10	0.593	0.011	0.000121
11	0.588	0.006	0.000036
12	0.575	-0.007	0.000049
13	0.594	0.012	0.000144
14	567	-0.015	.0000225
15	0.593	0.011	0.000121
16	567	-0.015	.0000225
17	0.564	-0.018	0.000324
18	0.575	-0.007	0.000049
19	567	-0.015	.0000225
20	0.564	-0.018	0.000324
Mean	**0.582**		**∑0.0030**

The Calculated Standard Deviation (SD) = $\sqrt{\frac{\sum(X-\bar{X})^2}{n-1}} = \sqrt{\frac{0.0030}{19}}$ **= 0.0126**

D% = (SD/average weight)× 100 =2.19%

Table(22) Friability test, after three months

Weight of 20 table before test	Weight of 20 tablet before test	Difference (X1-X2)	Weight loss %
11.227	11.076	0.051	0.452

Table(23) Hardness Test, after three months

Tablet No.	Hardness
1	4.0
2	3.5
3	5.1
4	4.9
5	4.0
6	5.0
7	3.5
8	5.3
9	4.9
10	5.4
Mean	**4.56**

Table(24) Disintegration test, after three months

Tab. No.	Time/min
1	3.12
2	2.50
3	1.82
4	3.35
5	3.05
6	2.1
Mean	**2.65**

Dissolution test, after three months

Table(25) Absorbance, after three months

Tab. No.	Absorbance					
	10 min	20 min	30 min	40 min	45 min	50 min
1.	0.106	0.145	0.260	0.315	0.346	0.375
2.	0.119	0.139	0.235	0.301	0.358	0.364
3.	0.098	0.128	0.313	0.306	0.347	0.367
4.	0.090	0.136	0.220	0.344	0.350	0.372
5.	0.129	0.133	0.304	0.280	0.355	0.368
6.	0.120	0.130	0.351	0.366	0.351	0.359
Mean	**0.144**	**0.135**	**0.281**	**0.319**	**0.351**	**0.368**

Table(26) Concentration %, after three months

Tab.No.	Concentration %					
	10 min	20 min	30 min	40 min	45 min	50 min
1.	29.78	39.73	69.33	83.33	89.18	96.15
2.	33.43	38.08	62.67	79.63	92.27	93.33
3.	27.53	35.07	83.47	80.95	89.43	94.10
4.	25.28	37.26	58.67	91.01	90.21	95.38
5.	36.24	36.44	81.07	74.07	91.49	94.36
6.	33.71	35.62	93.60	96.83	90.46	92.05
Mean	**31.00**	**37.03**	**74.80**	**84.30**	**90.51**	**94.23**

Clinical study results of the formula

Table(27) Effect of the formula on urine excretion

Treatment	1 hour	2 hour	3 hour	4 hour	5 hour	6 hour
Control	0	0	0.1	0.2	0.3	0.3
Furosemide 20mg/kg	3.3*±0.7	4.4***±0.5	5.3***±0.3	5.6***±0.3	5.7***±0.4	5.8***±0.5
The formula	2.8***±0.1	3.1***±0.1	3.6***±0.1	3.7***±0.1	4.2***±0.2	4.7***±0.2

*p < 0.05 and ***p < 0.001 compared with the control group (Bonferroni Multiple Comparisons Test). (Data are expressed in mean± standard error of mean)

Table(28)Effect of the formula on sodium and potassium excretion in urine and pH

Treatment	Na+conc. (meq./L)	K+conc. (meq./L)	pH
Control	28.26±0.7	7.13±0.2	6.30±0.04
Furosemide 20mg/kg	66.95***±0.5	15.38***±0.4	7.35***±0.04
The formula	68.71***±1	7.82±0.1	6.35±0.06

*p < 0.05 and ***p < 0.001 compared with the control group (Bonferroni Multiple Comparisons Test).

Discussion

The evaluation of tablets was in accordance to (BP,2009) and (USP,2007).The formula passed weight variation test, percent deviations for the formula were within the limit (less than 5%), Hardness test results for the formula were within the limits (more than 4kg and less than 10kg), Friability test results for the formula were within the limit (lost weight less than 1%), Content uniformity test for formula was within the limits (not less than 85% and not more than 115%), and disintegration test was also with in the specified time.

Weight variation, content uniformity and disintegration tests for formula were within the permitted limits from zero time of tablet production up to three months of accelerated stability studies at (40°C and 75% RH), which reflected the stability of the formula. The formula exhibited an increase in urine excretion. The formula also produced a significant increase in the Na+ excretion when compared to that produced by the reference diuretic furosemide and they had advantage of a potassium-conserving effect. There was no significant change in pH of urine after administration of the tablets.

Conclusion

The present study was undertaken to achieve the following goals:

- Formulation of selected extract into suitable dosage form (tablet).
- Evaluation of the produced tablets of the formulae (quality control tests)and accelerated stability study for the formula.

It can be concluded that, weight variation, content uniformity,friability,hardness,dissolution and disintegration tests for the formula were within the permitted limits from zero time of tablet production up to three months of accelerated stability studies at (40°C and 75% RH), which reflected the stability of the formula.

This study was able to highlight the importance of these tablets which formulated from *L. sativum* extracts for the management of hypertension (as diuretic) and the need for further clinical studies and scale up of the bench scale methods.

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