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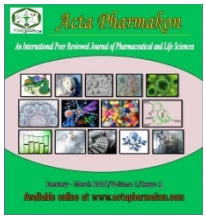
ACTA PHARMAKON

Acta Pharmakon

Issue 4, Vol. (1), Dec. 2015, 01-10
ISSN: 2455-8508



Research Article

Design, Development and Evaluation of Antidiabetic Herbal Tablet

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ARTICLE INFO

Received Aug 05, 2015
Revised Sept 02, 2015
Accepted Oct 10, 2015

Key Words:
- Antidiabetic activity
- Herbal tablet
- Decoction
- Synergistic action

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ABSTRACT

Medicinal plants have great importance to prepare herbal medicine are free from side effects, adverse effects and they are very low in cost, which will be beneficial for the people those are suffering from chronic diseases. Keeping this in view the plant *Gymnema salvestre*, *Tinospora cordifolia, Lawsonia inermis, Azadirachta indica* and *Ocimum sanctum* were selected according to having almost same Ayurvedic property as an antidiabetic action. These five plant extracts have showed synergistic antidiabetic activity. Main aim of this research work was to formulate herbal tablet from *Kwatha (decoction)* which was combination of these plant extracts and evaluate pre-compression parameters, post-compression parameters and stability studies.

1. INTRODUCTION

India has a very long, safe and continuous usage of many herbal drugs in the officially recognized alternative systems of medicine *viz*. Ayurveda, Yoga, Unani, Siddha, Homeopathy and Naturopathy. These systems have rightfully existed side-by-side with Allopathy and are not in 'the domain of obscurity'. [1]

The world health organization (WHO) estimates that 4 Billion people, 80 percent of the world population, presently use herbal medicine for some aspect of primary health care. WHO notes that of 119 plant-derived Pharmaceutical medicines, about 74 percent are used in modern medicine in ways that correlated directly with their traditional uses as plant medicines by native cultures. [2, 3, 4 & 5]

The plants *Gymnema sylvestre*, *Tinospora cordifolia, Lawsonia inermis, Azadirachta indica* and *Ocimum sanctum* were showed antidiabetic potential.[6] On the basis of Ayurveda these plants having same medicinal properties as antidiabetic action were selected.

The plant extracts of *Gymnema sylvestre*, *Tinospora cordifolia, Lawsonia inermis, Azadirachta indica* and *Ocimum sanctum* were converted into Kwatha (Decoction) and formulated as herbal tablet and evaluated its pre-compression, post compression parameters and stability studies.

2. MATERIALS AND METHODS

2.1 Collection and Authentication of Plants:

The *Gymnema sylvestre, Azadirachta indica* were purchased from local market and *Tinospora cordifolia, Lawsonia inermis*, *Ocimum sanctum* were collected from Jhalana forest, Jaipur (RAJ.). The plants were authenticated by Mr. P. G. Diwakar, Deputy Director, Botanical Survey of India, Pune, through comparing morphological features. The herbarium of the plant specimen was deposited at Botanical Survey of India having Ref. No. BSI/WRC/Tech/2010.

2.2 Excipients and Equipments:

The double distilled water prepared in laboratory was used for extraction and Kwatha formulation. Di-calcium phosphate, starch, Magnesium stearate, Methyl paraben, talc, Bronopol and Aerosil were purchased from Lobachem Laboratories, Pune for formulation of herbal tablet. Tablet compression machine (Karnavati Engineers, Ahmedabad), Hot air oven (Osworld, Mumbai), Stability Chambers (Thermolab, Mumbai), Weighing Balance (Sartorius, Germany), Homogenizer (Remi Motors Ltd., Mumbai), Disintegration apparatus (Electrolab, Mumbai), Roche Friabilator (Thermonik, Campbell electronics, Mumbai), Monsanto tablet hardness tester (Campbell electronics, Mumbai), Digital Vernier Calipers (Aerospace, China), Fluidized bed Dryer (Miniglat corporation).

2.3 Material Processing:

After collection of raw plant material washed with soaking high pressured water treatment (2 or 3 times) then dried at 60 to 80°C for two hours in hot air oven. Thereafter it was dipped in ethanol overnight then again dried in hot air oven and dried naturally. Finally useful part of plant material was cut with cutter mill and multi mill then obtained powdered material was prepared for extraction.

2.4 Aqueous Extraction:

Firstly 50g dried plant material taken and extracted with distilled water at 80 to 90°C for 6 hours. After extraction, material was filtered with eight layer muslin cloth then taken filtrate and centrifuge at 5000 rpm for 15 min. then after supernatant was collected and heated at 70 to 95°C for six hours. Then dried extract was obtained. [7]

2.5 Kwatha Formulation:

The raw material was made into coarse powder and mixed with four times of distilled water in a stainless steel vessel, and then continuous mild heat was applied until it was reduced to ¼ of its initial quantity. During heating process, continuous stirring was done to facilitate the evaporation and avoid any deterioration due to burning of raw material. After desirable reduction in volume, the galenical was filtered through single folded cotton cloth and collected in a separate vessel for further processing. [8]

Observations in Kwatha preparation:

- Initially the liquid was light brownish green in color and bitter in taste.
- Initially the raw materials floated over the surface of the menstrum, which gradually settled down after 2 hours of heating evaporation started at 70 °C, which was aggravated on stirring.
- The menstrum was light brownish green in color in the initial stage, which was gradually turned to dark green in color
- The maximum temperature found in the liquid was in between 90-95°C.

2.6 Pre-formulation Studies: [11]

2.7 Physical character studies:

Physical study of extracts & Kwatha were carried out by organoleptic study like color, odor and taste inspection.

2.8 Physical compatibility studies:

The compatibility study of extracts & Kwatha were done with all the excipients used in the formulation. The extracts & Kwatha and the excipients were taken in 1:1 ratio and kept in a tightly closed vessel at 25ºC & 60% RH, 30ºC & 65% RH & 40°C & 75% of relative humidity (RH) for a total period of 1 month. Physical changes were noted down, if any.

2.9 Determination of solubility of extracts:

Solubility of extracts and Kwatha were determined with ethyl acetate, ethanol, methanol, isopropyl alcohol, chloroform, benzene, carbon tetrachloride, DMSO, phosphate buffer (pH 6.8, 7, 7.2), hot water and Sodium lauryl sulphate solution in water (0.5, 0.75,1% w/v).

2.10 Manufacturing Batch Formula

Table 1: Manufacturing Batch Formula

SN	Ingredients	Quantity- mg/Tab		
		F1 Batch	F2 Batch	F3 Batch
1	*Gymnema sylvestre*	35.78	35.78	35.78
2	*Tinospora cordifolia*	95.42	95.42	95.42
3	*Lawsonia inermis*	79.77	79.77	79.77
4	*Azadirachta indica*	80.36	80.36	80.36
5	*Ocimum sanctum*	54.87	54.87	54.87
6	Dicalcium phosphate	417.49	417.49	417.49
7	Starch	29.82	44.73	59.64
8	Magnesium stearate	7.45	7.45	7.45
9	Talc	14.91	14.91	14.91
10	Methyl paraben	7.45	7.45	7.45
11	Bronopol	0.74	0.74	0.74
12	Aerosil	3.72	3.72	3.72
	Total Weight	812	827	842

2.11 Pre-compression Parameters:[11, 12 &13]

2.12 Angle of Repose:

Flow properties of granules were determined by calculating angle of repose by fixed height method. The funnel was fixed in place 4 cm above the bench surface. About 10 g of sample was slowly passed along the wall of funnel till the tip of the pile formed touches the stem of the funnel, height of the granules forming the cone (h) and the radius (r) of the base were measured. A rough circle was drawn around the pile base and the radius of powder cone was measured. Angle of repose was calculated from three averages using following formula. Values of Angle of repose ≤30 usually indicate a free flowing material and angles ≥40 suggest a poorly flowing material. Results were only considered valid when a symmetrical

cone of powder was formed the angle of repose (θ) was calculated as follows:

$$\theta = \tan^{-1} h/r$$

Where, θ = angle of repose, h = height of powder cone, r = radius of the powder cone

2.13 Bulk Density:

Bulk density of granules was determined through a glass funnel into 100 ml graduated cylinder by pouring up to 40 ml of granules. Granules weight was observed and from which bulk density was calculated.

Bulk density = Weight of sample in g/ Volume occupied by the sample (g/ml).

2.14 Tapped Density:

Granules were poured gently through glass funnel into 100 ml graduated cylinder up to 40 ml. The cylinder was tapped gently from the height of 2 inches until a constant volume was obtained. Volume occupied by the sample after tapping were recorded and tapped density was calculated.

2.15 Compressibility (%):

It is also one of the simple methods to evaluate flow property of a powder by comparing the bulk density and tapped density. A useful empirical guide is given by Carr's compressibility.

Carr's index = [(Tapped density- Bulk density)/tapped density] x 100

2.16 Hausner Ratio:

It is very important parameter to be measured for flow properties of granules.

Hausner ratio = Tapped density / Bulk density

2.17 Moisture Content:

It is important factor of granules. It should be less than 5%. It was measured by Karl Fischer apparatus.

2.18 pH value:

Weighed and transferred accurately about 1.0 g of sample in a clean and dried volumetric flask, dissolved in carbon dioxide free water and made up the volume to 10 ml with same solvent and mixed. Determined the pH of freshly prepared solubility by using calibrated pH meter.

2.19 Optimization Condition and Sampling Plan:

1. FBD (Fluidellized Bed Drier)
   Temp. (Inlet) - 49ºC to 59ºC
   Temp. (Outlet) - 45ºC
   Time - 39 min.
2. Six time granulation done
3. Relative Humidity 40% to 48%

- Optimum temperature set to maintain the potency of tablet, avoid the thermal degradation.
- Instrument works at optimum temperature and time according to drying capacity of instrument to avoid sticky property and good flow property.

2.20 Technique and Procedure:

2.20.1 Compression Technique

This involves the compression of granules, which may be prepared by wet granulation or by dry granulation technique or direct compression of a blend of raw material to release the drug and other additives. In the present work wet granulation technique was employed. Wet granulation is pharmaceutical unit operation whereby a liquid or binder solution is sprayed onto a powder blend to improve the flow, compressibility and content uniformity of the blend, prior to preparation of tablet.

2.20.2 Procedure

a) Kwatha (Decoction) was taken in container and

mixed it in Dicalcium phosphate with slowly stirring. Kwatha (Decoction) was made a homogenous damp mass.

Table 2: Sampling Plan

During the manufacturing of tablets sampling carried out for in process analysis to measure and checks the response of every step which leads to effective and accurate tablet dosage form.

Sr. No.	Process stages	Variables	Justification	Sampling	Measured Response
1	Binding	Binder quantity	Uniform dough mass to form.	Physical verification	Uniform dough mass was formed.
2	Semi Drying	Temperature Time	Uniformly dry the granules.	samples taken to measure response after 5 min	LOD (loss on drying) of granules
3	Drying	Temperature Time	Uniformly dry the granules.	samples taken to measure response after 10 min	LOD (loss on drying) of granules
4	Lubrication	Time	Distribution of lubricants in homogeneous mixing with dry granules.	Unlubricated granules mixed with maize starch, talc and Magnesium stearate	Bulk density, tapped density, Angle of Repose.
5	Compression	Hopper level Speed of machine	All compressed core tablet comply with specification of core tablets.	Initial, middle, end of compression at selected speed 17 ± 5 RPM	Appearance Avg.wt. Dimension Hardness Friability Disintegration time

b) Damp mass was passed through sieve 10 and then formed granules.

c) All granules were kept in FBD for 39 min at 49˚C then dry granules was obtained.

d) Then again all granules were mixed with remaining Kwatha then again granulations done in optimize condition.

e) At the fifth time of granulation, add Bronopol and methyl paraben with granules. Then again granulation has done with the help of FBD and sieve.

f) At the sixth time of granulation, add magnesium stearate, talc, starch & aerosil.

g) Then check all pre-compression parameters and kept in hopper of compression machine. Then got F1 batch tablets.

h) Then checked all post compression parameters mainly hardness and disintegration time for checking the physical stability.

i) Then add 100gm starch with granules and then F2 batch was obtained. Check all post

compression parameters then hardness and disintegration time parameters.

j) Then again add 100gm starch with granules and then F3 batch was obtained.

k) Check all post compression parameters then hardness and disintegration time parameters were proper. Then F3 batch was finalized.

2.21 Post Compression parameters [11, 12 & 13]

2.21.1 General Appearance of Tablets

Tablets were examined under a lens for the shape and color of the tablet, its overall elegance, uniformity, consistency, surface texture, odor, taste, etc.

2.21.2 Diameter

Three tablets from each batch were used and the average value was calculated. The diameters of the tablets were determined by digital vernier calipers.

2.21.2 Thickness

It was determined by digital vernier calipers. Three tablets from each batch were used and the average value was calculated.

2.21.3 Average Weight and Uniformity of Weight

Twenty tablets were selected randomly and weighed. Average weight was calculated.

2.21.4 Hardness

The hardness of a tablet is defined as the force required breaking a tablet in diametric compression test. Monsanto hardness tester was used for determining the hardness of the tablets.

2.21.5 Friability

Twenty tablets were weighed and placed in the Roche friability test apparatus. The tablets were exposed to rolling and repeated shocks, resulting from free falls within the apparatus. After 100 revolutions the tablets were re-dusted and weighed again. The friability was determined as the percentage loss in weight of the tablet.

% Friability = [(1- Weight of tablets after test) / Weight of tablets before test] x 100

2.21.6 Disintegration Time

Six tablets were taken in glass tube of tablet disintegration tester. The time was noted when all tablets were disintegrated.[15]

2.21.7 Stability Studies:

The stability studies were performed on the most promising tablet formulation batches. The study was performed by keeping the prepared tablets in air tight polyethylene bottles at 25°C & 60% RH, 30ºC & 65% RH, 40ºC & 75% RH. Herbal tablets were estimated after 1 and 2 months.[9]

3 RESULT AND DISCUSSION:

3.1 Screening of herbal extracts:

Percentage yield of plant extract obtained after extraction of useful part of plant material that was important for quantification of extract of bulk raw material for batch formulation development then identified extracts color as description.

3.2 Pre-formulation Studies

Physical Character Studies Physical characters (Organoleptic properties) of plant extracts and Kwatha were determined by visual inspection complies.[6]

3.3 Solubility Studies

- Completely soluble in water, phosphate buffer (ph 6.8, 7, 7.2).
- Partially soluble in organic solvent like ethyl acetate, ethanol, methanol, isopropyl alcohol, chloroform and 0.5, 0.75 or 1% w/v SLS (sodium lauryl sulphate) solution in water.

Table 3: Summary of Extraction & Extract

Sr.	Medicinal plants material	Part used	Quantity (Kg)	% Yield	Total Extract (g)	Description
1	*Gymnema sylvestre*	Whole (Panchang)	2.5	9.6%	240	Dark green
2	*Tinospora cordifolia*	Stem	9.0	12.8%	640	Dark brown
3	*Lawsonia inermis*	Leaf	2.5	21.4%	535	Dark black
4	*Azadirachta indica*	Leaf	9.0	15.4%	539	Brown
5	*Ocimum sanctum*	Leaf	3.0	9.2%	368	Light black

Table 3: Physical Character Studies:

SN	Plant Extract	Color	Odor	Taste
1	*Gymnema sylvestre*	Light green	Characteristics	Bitter
2	*Tinospora cordifolia*	Dark brownish	Characteristics	Bitter
3	*Lawsonia inermis*	Blackish	Characteristics	Bitter
4	*Azadirachta indica*	Brownish	Characteristics	Bitter
5	*Ocimum sanctum*	Brownish	Aromatic	Astringent
6	Kwatha	Brownish-Blackish	Characteristics	Bitter

Table 4: Physical Compatibility Studies:

SN.	Decoction: Excipients	Ratio	25ºC, 60%RH	30ºC, 65%RH	40ºC, 75%RH
1	Decoction: DCP	1:1	No Color Change	No Color Change	No Color Change
2	Decoction: Starch	1:1	No Color Change	No Color Change	No Color Change
3	Decoction: Mag.St.	1:1	No Color Change	No Color Change	No Color Change
4	Decoction: Talc	1:1	No Color Change	No Color Change	No Color Change
5	Decoction: Meth.parab.	1:1	No Color Change	No Color Change	No Color Change
6	Decoction: Bronopol	1:1	No Color Change	No Color Change	No Color Change
7	Decoction: Aerosil	1:1	No Color Change	No Color Change	No Color Change

- Insoluble in nonpolar solvents like as benzene, carbon tetrachloride.

3.3 Formulation Studies:

3.3.1 Pre-compression Parameters:

Pre-compression Parameters of three tablet batches granules were carried out. It was observed that angle of repose complies as good flow property according to standard values ($30^0 – 35^0$), % Carr's index complies as excellent flow property according to standard values (5 – 15%), Housner ratio complies as good flow property according to standard values (below 1.25), Bulk density, tapped density, moisture content and pH values were determined. So it is concluded that F3 Batch formulation has good flow property as compare to F1 and F2 batch formulation.[14]

3.3.2 Optimization of Formulation:

Optimization of formulation was done post compression parameters such as hardness and disintegration time before batch formulation. It is observed that hardness and disintegration time values of F3 formulation was complies with standard values according to pharmacopoeia. F3

batch formulation (842 mg tablet) is optimize and acceptable formulation, because it have optimize hardness and disintegration time according to pharmacopoeia.[15]

3.3.3 Post Compression Parameters

Post compression parameters such as weight variation, thickness, hardness, friability and disintegration time of three batch formulation was carried out. Results shown that F3 batch formulation has optimize post compression parameters that it was acceptable as compare to others (F1 and F2 Batch).[14,16]

3.4 Stability Studies (F3 batch)

The stability studies were carried out after one and two months resulted data showed that these minor changes were acceptable according to ICH Guidelines.

Stability studies were carried out of F3 batch formulation after one and two months in different environmental condition such as 25ºC & 60% RH, 30ºC & 65% RH, 40ºC & 75% RH. It is observed that color, size, shape, weight variation, thickness, hardness and disintegration time data shown minor changes occurred were acceptable according to ICH Guideline.

Table 5: Pre-compression Parameters

Sr. No.	Parameters	F1 Batch	F2 Batch	F3 Batch
1	Angle of Repose	31.66	32.65	34.45
2	Bulk density (gm/ml)	0.46	0.49	0.52
3	Tapped density (gm/ml)	0.55	0.57	0.59
4	% Carr's index	16.36%	14%	11.10%
5	Housner Ratio	1.19	1.16	1.13
6	Moisture content	3.03%	3.59%	3.79%
7	pH	9.77	9.67	9.50

Table 6: Optimization of Formulation

Batch	Starch Qty.	Hardness Kg/Cm^2	Disintegration Time
F1	200g	10.5	16.30 min
F2	300g	4.8	10.20 min
F3	400g	3.1	4.15 min

Table 7: Post Compression Parameters

S.NO.	Batch	Weight variation	Thickness (mm)	Diameter (mm)	Hardness Kg/Cm^2	Friabi-lity	D.T.* (Min.)	Result
1	F1	865 mg	4.2	12.0	10.5	0.16%	16.3	Reject
2	F2	844 mg	4.1	12.0	4.8	0.14%	10.2	Reject
3	F3	842 mg	4.0	12.0	3.1	0.12%	4.15	Accept

*= Disintegration time

Table 8: One Month Stability Data

Sr. No.	Parameters	Description	Weight variation	Thickness	Hardness Kg/Cm^2	D.T.* Min.
1	25ºC/60% RH	Brown, Circular, Flat	842.3mg	4.30 mm	3.07	4.6
2	30ºC/65% RH	Brown, Circular, Flat	842.4mg	4.27 mm	3.06	4.5
3	40ºC/75% RH	Brown, Circular, Flat	842.5mg	4.26 mm	3.05	4.4

*= Disintegration time

TABLE 9: TWO MONTH STABILITY DATA

Sr. No.	Parameters	Description	Weight variation	Thickness	Hardness Kg/Cm^2	D.T.* Min.
1	25ºC/60% RH	Brown, Circular, Flat	842.8 mg	4.28 mm	3.04	4.4
2	30ºC/65% RH	Brown, Circular, Flat	842.9 mg	4.26 mm	3.02	4.2
3	40ºC/75% RH	Brown, Circular, Flat	843.0 mg	4.24mm	3.00	4.1

*= Disintegration time

4 CONCLUSION:

The plants *Gymnema sylvestre*, *Tinospora cordifolia, Lawsonia inermis, Azadirachta indica* and *Ocimum sanctum* were selected according to having same Ayurvedic property as an antidiabetic action. The plant extracts of *Gymnema sylvestre*, *Tinospora cordifolia, Lawsonia inermis, Azadirachta indica* and *Ocimum sanctum* were converted into Kwatha (Decoction) and formulated as herbal tablet and evaluated its pre-compression, post compression parameters and stability studies. For the purpose of our study 3 batches of polyherbal tablets were formulated. From our study we found that polyherbal tablet formulation F3 batch was found to be significant optimized formulation on the basis of pre-compression parameters and post compression parameters. F3 batch polyherbal tablets were achieved stable on basis of stability studies.

Acknowledgements:

The authors thanks to Mr. Jairam Mutreja, proprietor of "biotech", Herbal Industry, MIA, Jaipur (Raj.) for providing infrastructure facility and technical guidance. The author also thanks to Dr. M. L. Jaiswal, Associate Professor, National Institute of Ayurveda, Jaipur (Raj.) for scientific guidance as a co-guide.

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