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INVESTIGATION, FORMULATION AND EVALUATION OF ANTIDIABETIC TABLET OF *PUNICAGRANATUM* PEEL

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ABSTRACT

The present study was aimed to formulate & evaluate the antidiabetic tablet of Punicagranatum peels waste. Hyperglycemia is the most common metabolic endocrine disorder. It is the chronic condition in which blood glucose level is elevated than normal due to the improper insulin production in body or due to insulin resistance, high blood glucose level and low blood glucose level leads to diabetic condition. Allopathic treatment for diabetes mellitus is too costly so focus on herbal medicines is necessary. Pomegranate peels or rind are considered as an waste material these peels consists of numerous important active chemical constituents such as flavonoids, vitamins and minerals. The main principle active chemical constituents including punicalagin, punicalin, β-sitosterol and valoneic acid dilactone (VAD) from pomegranate peels powder shows potent antidiabetic activity Punicagranatum peels extract have stability problem than other dosage form by converting it into tablet dosage form. We enhance its acceptability, elegance and patient compliance. Manufacturing of tablets was done by using wet granulation method on lab level tablet press (CEMACH) by wet granulation method. Evaluations tests performed on tablets such as Hardness, Weight variation, friability, disintegration test etc

KEY WORDS

punicagranatum, antidiabetic, valoneic acid dilactone (VAD), herbal medicine

1.INTRODUCTION:

Diabetes mellitus is a metabolic disorder identified as increased in blood glucose level than normal. This is happened due to either insufficient insulin production or insulin resistance. High amount of lipids, free fatty acid and glucose in our body affects the B-cells function by various mechanisms such as generation of various reactive oxygen species (ROS). Generally, there are three types of Diabetes occurs one is the Insulin Dependence Diabetes Mellitus (IDDM) second is the (NIDDM) that is Non-Insulin Dependence Diabetes Mellitus and third one is the Gestational Diabetes.

1.1 Biological Sources: [17-20]

a} Botanical Name: *Punicagranatum*
b} Family Name: Puniacaceae
c} Common Name: Pomegranate**,** Anar
d} Part Used: Seeds, flowers, peels, roots etc.

1.2 Common Name: [17-20]

i. **Hindi:** Anar
ii. **English:** Pomegranate
iii. **Latin:** *Punicagranatum*
iv. **Sanskrit:** Dadimah
v. **Marathi:** Dalimba

2. MATERIALS:

Fresh Fruits of *punicagranatum* was collected from local market of Buldana, Maharashtra and transported to laboratory, authenticated from Center for Biodiversity Jijamata Mahavidyalaya, Buldana, Maharashtra. This authentification is done by Prof. Dr. S.V. Ambekar Sir. The fruits were washed with purified water, rinsed well and dried at room temperature for about 10min in open air. The peel from the fruit was removed carefully by knife and allowed to sun-drying. The dried material was

properly ground into powder. This powder material was separated according to particle size with the help of sieves no; #44, #60, #80, #85 to obtained different batches for further Preformulation Study.

Excipients: - Lactose, Starch & Amaranth obtained from Research Lab Akola.

Method: -

3. Preformulation study: -

3.1 Bulk Density: [22-39]

It refers to packing of particles. Bulk density is used to determine the amount of drug that occupies the volume in g/ml.

Procedure: Weighed quantity of tablet blend was transferred into 100ml measuring cylinder without tapping during transfer. The volume occupied by drug was measured. Bulk density was calculated by using formula

$$\textbf{Bulk Density} = \frac{\textbf{m}}{\textbf{Vi}}$$

Where, **m** = mass of the blend, Vi = Bulk volume

3.2 Tapped density: [22-39] Weighed accurate quantity of powder sample was into a graduated cylinder. Volume occupied by the drug was noted down. Then cylinder was subjected to 100, 200 & 300 taps in tap density apparatus.

Tapped density was calculated.

$$\text{Tapped Density} = \frac{m}{Vt}$$

Where, m = mass of the blend, Vt = tapped volume

3.3 Carr's Index (Compressibility): [22-39] The compressibility index and Hausner's ratio was measures the property of powder to be compressed. The packing ability of powder material was evaluated from change in volume, which is due to rearrangement of packing occurring during tapping. It was indicated as Carr's compressibility index was calculated by following formula:

$$\text{Carr s index} = [TD-BD]/TD \times 100$$

3.4 Hausner s' Ratio: [22-39] **It** is measurement of frictional resistance of tablet blend. The ideal range should be 1.2-1.5. It was determined by the ratio of tapped density and bulk density.

$$\text{Hausner s' Ratio} = \frac{\text{Tapped Density}}{\text{Bulk Density}}$$

3.5 Angle of Repose (θ): [22-39] It is defined as the maximum angle that can be obtained between the free standing of powder heap and horizontal plane, which is determined by the equation;

$$\text{Angle of repose } (\theta) = \tan^{-1}(h/r)$$

Where, **θ** = Angle of repose; h = height of powder heap; r = Radius of the powder cone.

Procedure: Weighed quantity of the powder sample was passed through a funnel kept at a height 2cm from the base. The **powder** was passed till it forms a heap and touches the tip of the funnel. The radius was measured and angle of repose was calculated by using above formula.

3.6 Flow Rate [22-39]: -

1. Weighed accurate quantity of powder sample
2. Place a cotton plug at the neck of a clean and dry funnel of stem diameter 1-2.5cm.
3. Place powder sample in the funnel.
4. Remove plug from the neck & Record the total time required for all the powder to flow. Calculate flow rate by using formula.

$$\text{Flow Rate} = \frac{\text{Weight powder}}{\text{Time required to flow}}$$

3.7 Water Soluble Extractive: [19-21]**:**

Useful for the evaluation of a crude drug. Give idea about the nature of the chemical constituents present in a crude drug.

1. Weigh about 5gm of the coarsely powdered drug and transfer it to a dry 250ml conical flask.
2. Fill a 100 ml graduated flask with water and transfer into conical flask.
3. Cork the flask and set aside for 24 hours, shaking frequently. (Maceration).
4. Filter into a 50 ml cylinder. When sufficient filtrate has collected, transfer 25ml of the filtrate to a weigh thin porcelain dish.
5. Evaporate to dryness on a water- bath and complete the drying in an oven at 105^0C for 6 hours.
6. Cool and weigh immediately.
7. Calculate the percentage w/w of extractive with reference to the air-dried drug.

Calculation:

a) Weight of empty porcelain dish =.....(X).....gm

b) Weight of porcelain dish with residue =..... (Y).....gm

c) Weight of residue = ...(X –Y).....gm

$$\text{W.S.E.}(\%) = \frac{\text{Weight of residue X 100 X 100}}{\text{Weight of drug taken X Volume of filtrate (25 ml)}}$$

3.8 Alcohol Soluble Extractive: [19-21] Same as water soluble extractives only water is replacing with alcohol.

3.9 Moisture contents: [19-21] Weigh 1.5g of sample in a porcelain dish containing 6-8 cm diameter and 2-4 cm depth in it. Dry the sample in an oven at 105^0 C. cool & weigh. Calculate the moisture contents by using formula.

Moisture Contents(%)=Final weight-Initial weight×100

3.10 Total Ash Value: [19-21] Used to determine quality and purity of crude drug and to establish the identity of it.

Procedure:

1. Weigh 2gm of powder drug into the crucible
2. Ignite sample on burner (flame) until all the carbon is burned off.
3. Cool it and weigh the ash.
4. Calculate the percentage of total ash with references to the air-dried sample of crude drug.

Calculation:

a) Weight of the empty dish = x
b) Weight of the drug taken = y
c) Weight of the dish with ash = z
d) Weight of the ash = (z - x)

$$\text{Total ash} = \frac{100(Z-X)}{y}$$

3.11 Antimicrobial test: Antimicrobial test Perform against *Escherichia coli* & *Staphylococcus aureus* culture medium.

1. Weigh accurately all the ingredients & prepared nutrient broth and agar medium.
2. Used nutrient brouth for sub-culturing of phathogen (freshly prepared bacterial culture).
3. Take petri plate and test tube wash it properly with tap water & autoclave it (at 121^0C 15 lb pressure for 15-30 minute).
4. Prepared aceptic area in aceptic room.
5. Dilute the testing sample in test tube in a range of 10^{-1}, 10^{-2}, & 10^{-3} respectively.
6. Transfer the agar medium in Petri plate in aceptic condition allowed it cool & solidify.
7. Then transfer the microbial culture which is required (*E. coli & S.aureus*) with the help of sterile disposable syringe.
8. Shake it properly 2-3 times for proper mixing.
9. Then transfer the sample which is diluted with the help of disc or bohr plate technique.
10. Then incubate the plate for 24-48 hours in Incubator.
11. Calculate the zone of inhibition by comparing with standard.

3.12 Drug Excipient Compatibility study: [33-38]
Compatibility of the drug with excipients was determined by FT-IR spectral analysis, this study was carried out to detect any changes on chemical constitution of the drug after combining it with the excipients. The samples were taken for FT-IR study

3.13 Formulation Designing:

Table 1 Formulation Designing

Sr.no	Ingredients in (mg)	F1	F2	F3	F4	F5	F6
01	Pomegranate powder	20	40	60	80	100	120
02	Lactose	100	100	80	80	50	60
03	Starch	130	110	110	90	100	70
04	Amaranth	q.s	q.s	q.s	q.s	q.s	q.s
Total		250mg	250mg	250mg	250mg	250mg	250mg

3.14 Wet Granulation Method: [33-36]

1. Starch was weighed and made into an emulsion and cooked well on a water bath until translucent semisolid mass was formed.
2. The Amaranth solution was prepared by using required quantity of water separately.
3. The weighed quantities of excipients were mixed thoroughly with powder drug, the cooked starch and Amaranth solution were added slowly till the powder became a damp mass.
4. This damp mass was passed through sieve number 22# and dried in an oven at a temperature of 105°C, until granules were dried properly.
5. Then the dried granules subjected to compression.

6. Finally, the tablets were compressed with 8 mm punches by using multiple punch Tablet press machine (CEMACH).

4. Evaluation of prepared tablets:

4. 1 General appearance: [22-39] Physical examination is done by visual inspection, Color, Odor Size, Shape Unique Identification Marking etc.

4.2 Thickness: [22-39] Ten Tablets were selected randomly from individual formulations and thickness was measured by using vernier caliper scale, which permits accurate measurement. The average of 3 readings was taken as thickness of the tablet.

4.3 Weight variation: [22-39] Twenty tablets were taken randomly, weigh individually and average weight was determined. The individual tablet weight was compared with average tablet weight.

4.4 Hardness: [22-39] Tablets require certain amount of strength or hardness, to withstand mechanical shocks of handling in manufacture, packaging, and shipping. The most widely used apparatus to measure tablet hardness (strength) is the pfizer hardness tester.

Method: Ten tablets were randomly selected and hardness was measured in Pfizer hardness tester. The average of 3 readings was taken as hardness of the tablet.

4.5 Friability: [22-39] **Friability** is related to the ability of tablet to withstand both shocks and abrasion without crumbling during manufacturing, packing, transportation and consumer handling. Friability can be evaluated by means of friability test apparatus friabilator. Compressed tablets that loose less than 0.5% to 1.0% in weight are generally considered as acceptable.

Method: Ten tablets were randomly select and weighed (initial wt.) and then transfer into friabilator. It was subjected to 100 revolutions in 4 minutes. The tablets were dedusted and reweighed (final wt). These two weights (i.e. initial and final) were applied to calculate the friability.

$$\%\text{Friability} = \frac{(\text{Initial Weight} - \text{final weight})}{(\text{Initial weight})} \times 100$$

4.6 Disintegration test: [22-39] In vitro disintegration time was measured using USP disintegration test apparatus. For DT test randomly one tablet were selected from each batch and test was performed in 900 ml distilled water at 37 ± 0.5 °C temperature and at the rate of 30 ± 2 cycles/min.

4.7 Stability Study: [33&37] The purpose of stability testing is to provide evidence on how the quality of a drug substance or drug product varies with time under the influence of a variety of environmental factors such as temperature, humidity and light, enabling recommended storage conditions, re-test periods and shelf-lives. The International Conference on Harmonization (ICH) Guidelines titled "Stability Testing of New Drug substance and Products" (QIA) describes the stability test requirements for drug registration applications in the European Union, Japan and the United States of America.

Stability conditions: (ICH guidelines)

25°C / 60%RH Long term Testing for 12 months

30°C / 65% RH Intermediate condition if significant change occurs due to accelerated testing

40 ºC / 75% RH Accelerated testing for 06 month

Method:

The selected formulation was exposed to different storage condition. As per ICH guidelines for 3 months and evaluated.

5. RESULTS & CONCLUSION:

Table no 2: Preformulation Study of Powder Sample

Sr.no:	Parameters	Sieve no: #44	Sieve no: #60	Sieve no: #80	Sieve no: #85
01	Colour	Light Brown	**Light Brown**	Light Brown	Light Brown
01	Bulk Density (gm/ml)	0.645	**0.56**	0.476	0.454
02	Tapped Density (gm/ml)	0.772	**0.64**	0.638	0.556
03	Carr's Index (%)	16.45	**12.29**	17.39	18.34
04	Hausner's ratio	1.19	**1.14**	1.24	1.22
05	Porosity (%)	25	**16.66**	23.80	19.047
06	Angle of Repose (θ)	33^0 42"	**29^0 98"**	26^0 56"	31^0 29"

07	Moisture contents (%)	10	**09**	10	20
08	Flow Rate (gm/sec)	0.78	**0.66**	0.44	0.33
09	Ash value (NMT4%)	0.32	**0.32**	0.32	0.32
10	Water Soluble Extractive (%)	45.6	**45.6**	45.6	45.6
11	Alcohol Soluble Extractive (%)	49.6	**49.6**	49.6	49.6
12	Antimicrobial Test *(E. coli & S.aureus)*	+ve	**+ve**	+ve	+ve

From above preformulation data powder from Sieve no: #60 shows acceptable angle of repose, Bulk density, Tapped density, Carr's index and Hausner's ratio, Flow rate, Moisture contents. The batch shows good data as compared with other batches. Therefore, it was concluded that the Powder from Sieve no: #60 consider as an optimized batch.

Table No 3: Antimicrobial test

		Zone of Inhibition in mm diameter			
Sr. no	**Name of Pathogens**	**Dilutions**	**Sample A**	**Sample B**	**Std. Ciprofloxacin**
01	*Escherichia coli*	10^{-1}	17	16	15
		10^{-2}	14	12	12
		10^{-3}	12	11	10
02	*Staphylococcus aureus*	10^{-1}	15	14	14
		10^{-2}	13	12	12
		10^{-3}	10	11	10

Sample A = Pomegranate peel powder, Sample B = Pomegranate Tablet

From the above evaluation details it can be concluded that *punicagranatun* peel powder shows +ve antimicrobial activity against *E.coli* & *S.aureus*, shows more potency than that of Standard Ciprofloxacin.

❖ **Drug Excipient Compatibility study**

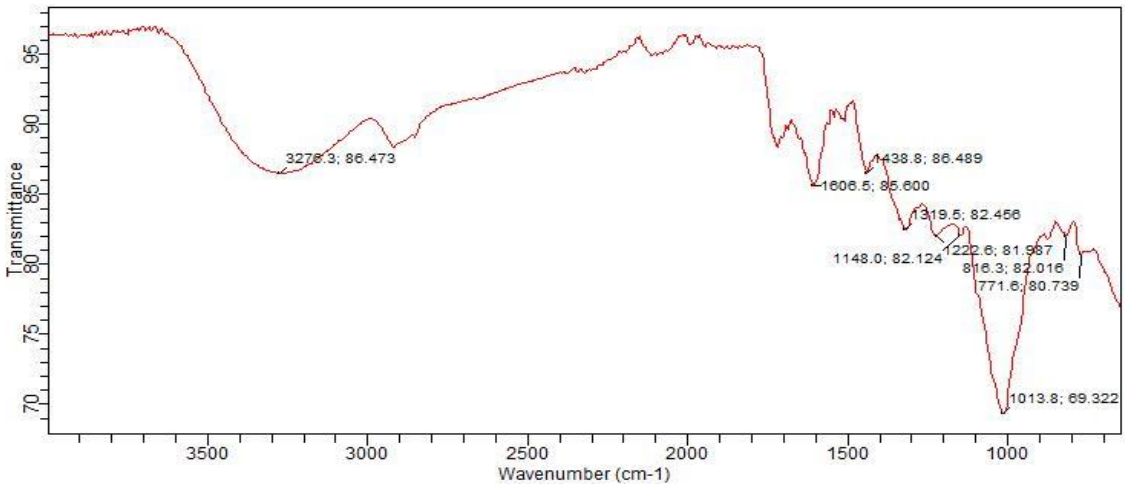

Figure 1: FTIR Spectra of pomegranate peel powder

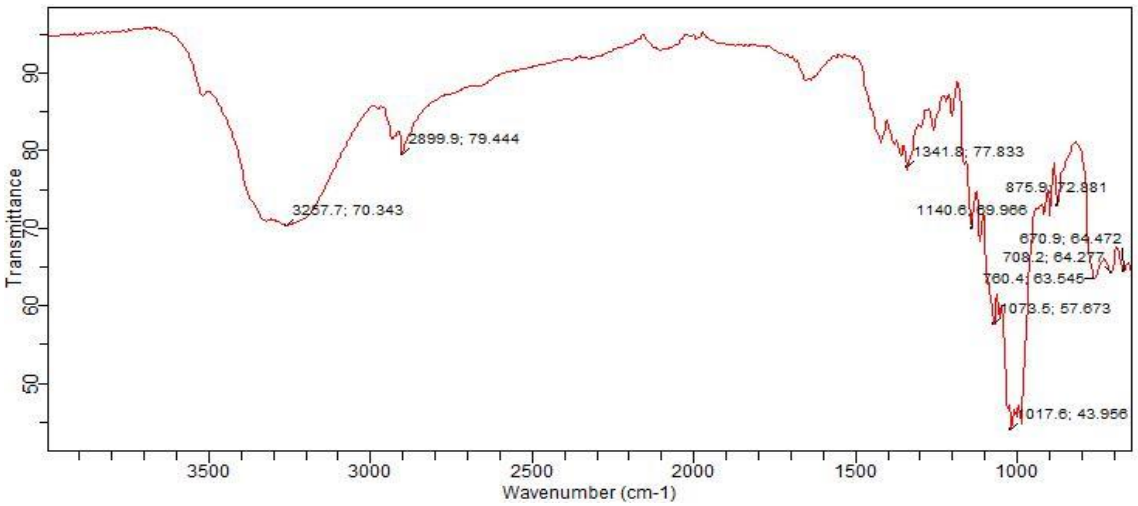

Figure 2: FTIR Spectra of pomegranate peel tablet

Table No 4: Preformulation Study of Granules

Sr.No:	Parameters	F_1	F_2	F_3	F_4	F_5	F_6
01	Bulk Density (gm/ml)	0.645	0.640	0.540	0.769	0.689	0.740
02	Tapped Density (gm/ml)	0.952	0.740	0.689	0.833	0.740	0.866
03	Carr's Index (%)	33.24	13.51	21.62	7.68	6.89	14.54
04	Hausner's ratio	1.475	1.156	1.275	1.083	1.074	1.170
05	Porosity (%)	10	32.25	9.37	13.33	25	6.896
06	Angle of Repose (θ)	$35^0 52''$	$36^0 02''$	$34^0 59''$	$33^0 69''$	$34^0 13''$	$33^0 69''$
07	Moisture contents (%)	07	09	08	06	09	08
08	Flow Rate (gm/sec)	0.77	0.44	0.66	0.33	0.85	0.75

From above preformulation study of granules, F_4 and F_5 batch shows acceptable angle of repose, Bulk density, Tapped density, Carr's index and Hausner's ratio, Flow rate, and Moisture contents.

Table No 5: Evaluation of Formulation

Sr.No:	Parameters	Formulation Batch					
	General appearance	**F_1**	**F_2**	**F_3**	**F_4**	**F_5**	**F_6**
01	a) Colour	Pink	Pink	**Pink**	Pink	Pink	**Pink**
	b) Odour	None	None	**None**	None	None	**None**
	c) Taste	None	None	**None**	None	None	**None**
	d) Size (Diameter)	1.7mm	1.8mm	**1.7mm**	1.8mm	1.7mm	**1.7mm**
	e) Shape	Round	Round	**Round**	Round	Round	**Round**
02	Hardness (kg/cm^2)	3.5	5	**3.5**	3	3.5	**4**
03	Thickness (mm)	3	3.2	**3**	3	3	**3.5**
04	Friability (%)	0.79	0.85	**0.50**	0.70	0.85	**0.16**
05	Weight variation test	Pass	Pass	**Pass**	Pass	Pass	**Pass**
06	Dis. time (sec.)	20	25	**20**	15	30	**25**
07	Antimicrobial Test	+ve	+ve	**+ve**	+ve	+ve	**+ve**
08	Moisture content (%)	7	8	**6**	9	8	**9**

From the above evaluation parameter like thickness, average weight, hardness, friability, disintegration time etc. It can be concluded that the F_1 and F_4 batch show all parameter within acceptable limit, as compared to other batches therefore it is considered as a good formulation.

Table No 6: Comparative Study

Sr.no	Parameters	Batch		
	General appearance	**F1**	**F4**	**MF**
01	a) Color	Pink	Pink	White
	b) Odor	None	None	None
	c) Taste	None	None	Bitter
	d) Size (Diameter)	1.7mm	1.8mm	1.5mm
	e) Shape	Round	Round	Round
02	Hardness (kg/cm^2)	3.5	3	3.5
03	Thickness (mm)	3	3	3
04	Friability (%)	0.79	0.70	0.49
05	Weight variation test	Pass	Pass	Pass
06	Dis. time(sec.)	20	15	280
07	Antimicrobial Test	+ve	+ve	+ve
08	Moisture content (%)	7	9	8

Stability Study of optimized batch: -

The effects of temperature and humidity, on the physical characteristics of the tablets, were evaluated for assessing the stability (40 ^{0}C ± 2 ^{0}C/ 75 % ± 5% RH) of the prepared formulation.

Table No 7: Stability Study of Optimized Formulation

Duration (Months)	General Appearance	Hardness (kg/cm^2)	Weight Variation	Friability (%)	Disintegration Time (sec)
1 Month	No change	3.5	249	0.70	20
2 Months	No change	3	248	0.60	15
3 Months	No change	3	250	0.79	25

Stability study of the tablets at 40^{0}C ± 2^{0}C/ 75% ± 5% RH for 3 months showed no significant changes in the mechanical strength or in disintegration time of the tablets.

Figure 3 Pomegranate Fruit

Figure 4 Pomegranate Peel

Figure 5 Pomegranate peel powder

Figure 6 Pomegranate Tablet

7. DISCUSSION AND CONCLUSION:

Herbs plays major role in the treatment than the allopathic medicines because of less side effects, low cost and easy availability. The research work done on that basis and the selected plant for the formulation was proved for the use of antidiabetic purpose. The *Punicagranatum* peel powder were used to formulate tablets and evaluated for physical parameters and standardize as per pharmacopoeial standards. Preformulation study and Physical Parameter revealed that all the values were within acceptable limit shown in table no 5. The herbal formulation showed significant antidiabetic activity and the tablet standardize as per Pharmacopoeial standards. From the above evaluation parameters, it can be concluded that overall batches the F1 & F4 batch show all parameter in acceptable limit. Therefore, it is considered as a good Formulation.

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