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Original Research Article

Transdermal patches of *Aegle marmelos* leaves for the management of diabetes

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ABSTRACT

The examination centers on an Enemy of diabetic movement of leaves concentrate of customary plant-Aegle Marmelos Linn, having a place with the group of Rutaceae, by and large known as Bael.[1] The treatment depends on transporter conveyance and the main reason for this detailing is to enhance the treatment of the sickness, increment the adequacy, decrease dosing recurrence, and improve tolerant consistence. The readied plan of HPMC-PEG gives preferable medication adequacy over the oral course. An HPMC-PEG transdermal fix can be utilized to stack a subterranean insect diabetic medication which makes it simpler for the stacked medication to infiltrate the skin film, bringing about higher blood focuses and in this manner better blood glucose level. Transdermal fix can assist with diminishing impurity when patients need to infuse insulin at the recommended time, particularly when they are in open zones and decrease needle fear also.

1. Introduction

Diabetes mellitus is a situation in which an excessively high level of glucose in the blood is the fundamental abnormality.[2] Diabetes is a condition, meaning a variation of signs and symptoms caused by hyperglycemia. WHO has given the guidelines for the diagnosis of diabetes which is called as *Glucose tolerance test.*[3] A condition in which tests results are higher than 100mg/dl but less than 126mg/dl is called Impaired fasting glucose while a condition in which blood glucose level exceeds than normal i.e. 140mg/dl to 199mg/dl 2 hours after glucose tolerance testing is called Impaired glucose tolerance,[4]

The drawback with insulin therapy is weight gain, so the search for alternate chemical agents to regulate diabetes that do Ayurveda is considered as one of the oldest and effective form of medicine and has potential to treat chronic diseases which are untreatable in modern medicine with no side effects. Ayurveda is based on two important principles- *Pareeksha* (tools of examination) and *Pramaana* (inspired from the philosophical term). The tool of examination consists of three concepts- *Pratyaksha* (the direct observation), *Anumana* (the inference), *Aptopadesha* (reliable evidence).[5]

Aegle Marmelos is most popular and ancient plant in Ayurveda and Siddha medicine systems. It is considered as sacred plant with spiritual powers in Charak Samhita and believed that it is an incarnation of Lord Shiva.[6]

1.1. Chemical compounds isolated from Plant[7]

1. *Leaf*-Skimmianine, Agelin, Rutin, Y-sit sterol, β-sitosterol, Flavones, Lupeol, Eugenol, Cineol, citral, Glycoside, O-isopentenyl, Halfordiol, Marmeline, Citronellal,
2. *Seed*- Essential oil: D-limonene, A-D-phellandrene, Cineol, Citronellal, Citral, P-cyrnene. not have side effects is important[4]

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2. Materials and Methods

2.1. Material, plant collection and authentication

Eudragit L, PVP, Ethyl cellulose, Pectin, Carbopol 934 and polyethylene glycol (PEG) were purchased from Sigma, Mumbai, India. In the present study, the chemicals in the laboratory except those used above in the study were analytical reagents grade.

The leaves of Aegle marmelos were collected in the month of November- December from the garden located near the laboratory and used without further purification. The plant was authenticated by our lab quality control team.

3. Preparation of Transdermal Patches

The solvent casting method was used to prepare the transdermal patch. The drug matrix was prepared using the Eudragit L, PVP, Ethyl cellulose, Pectin, Carbopol 934 (Table-1). The polymer was weighed to the required volume and the polymer solution (2.5% w / v) was prepared by dissolving the polymers in ethanol: water (1: 1) as a solvent. When the polymer is properly mixed, PEG as a plasticizer is added. Afterwards, the drug solution was added to the polymeric solutions and stirred for 45 minutes in a magnetic stirrer to achieve a homogeneous mixture. The mixture was kept at 60^{o}C for intermittent heating for few seconds and then poured into glass molds wrapped with aluminum foil at open ends. Kept this final mixture again at 60^{o}C for 6 hrs for drying.

4. Experimental Detail

4.1. Physiochemical evaluation

Interaction Studies: Interaction study basically depends upon the compatibility of the drug and Excipient. Interaction studies are generally important to access the details of bioavailability and stability of the drugs. When new Excipient is used to formulate the formulation using active constituent, it is necessary to check the compatibility of the Excipient and new active constitute (Figure 1).The UV spectral analysis of compounds isolated from the ethanol fractions was recorded using UV spectroscopy was presented (Table 2).

Thickness of Patch: The thickness of the patches (with active constituent) was measured using a digital micrometer at different points of the patches (Figure 2). The thickness of the patches was calculated as average and standard deviation (Table 3).

Weight Uniformity: Weight uniformity of the patches were taken after dried at 60˚ C for 4 hours and recorded as average and standard deviation (Table 4). A particular area of the patches was cut in small parts and weighed in analytical weighing balance. The obtained weight for each patch was calculated for average and standard deviation (Figure 3).

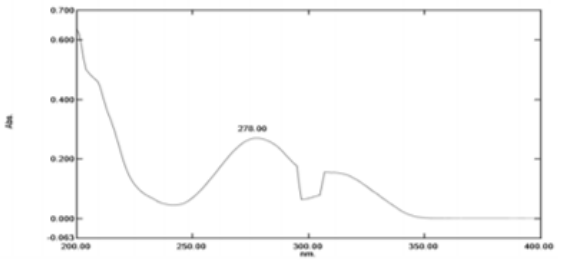

Fig. 1: Absorption spectrum value of isolated compound

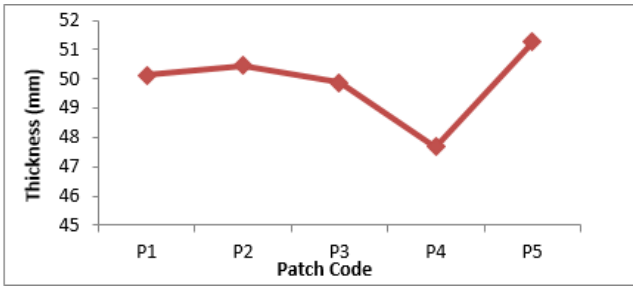

Fig. 2: Thickness of patches

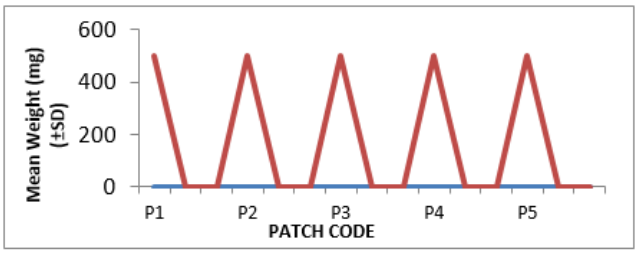

Fig. 3: Uniformity of weight

Folding Endurance: A single strip area is cut and folded repeatedly at the same position before it cracks. The number of times the film could be folded without breaking gave the significance of folding endurance. Folding endurance recorded as Table 5 and in Figure 4.

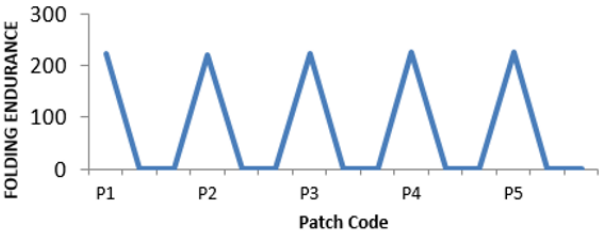

Fig. 4: Folding endurance

Percentage Moisture Content: The prepared patches must be kept at a room temperature in a Dessicator that contains fused sodium chloride. Patches shall be

Table 1: Formulation Table

Formulation Code	Drug	Matrix Forming Polymer 100MG	Solvent System (2.5mL)	Plasticizer (0.3 ml)	Penetration Enhancer 0.5ML	Water
F1	60 mg	Eudragit L 100	Chloroform: Methanol	Propylene Glycol	Tween 80 (0.5 ml)	3 ml
F2	60 mg	PVP	Chloroform: Methanol	Propylene Glycol	Tween 80 (0.5 ml)	3 ml
F3	60 mg	Ethyl cellulose	Chloroform: Methanol	Propylene Glycol	Tween 80 (0.5 ml)	3 ml
F4	60 mg	Pectin	Chloroform: Methanol	Propylene Glycol	Tween 80 (0.5 ml)	3 ml
F5	60 mg	Carbopol 934	Chloroform: Methanol	Propylene Glycol	Tween 80 (0.5 ml)	3 ml

Table 2: Absorption spectrum value

S. NO	Wavelength	Absorbance
1.	278	0.278
2.	310	0.160

Table 3: Thickness of the patches

Patch Code	Individual Thickness	Mean Weight (mm) (±SD)
	51.11	
P1	49.12	50.14±1.0
	50.18	
	49.46	
P2	51.35	50.45±0.9
	50.53	
	50.28	
P3	49.54	49.87±0.4
	49.8	
	47.1	
P4	47.98	47.69±0.5
	47.99	
	50.51	
P5	52	51.27±0.7
	51.3	

Table 4: Uniformity of weight

Patch Code	Individual Weight	Mean Weight (MG) (±SD)
	501.11	
P1	499.12	500.14±1.0
	500.18	
	499.11	
P2	501.35	500.33±1.1
	500.53	
	501.28	
P3	499.54	500.21±0.9
	499.8	
	499.1	
P4	498.98	499.36±0.6
	499.99	
	500.51	
P5	502.2	501.34±0.8
	501.3	

NOTE: Imp- Implant, Sd- Standard Deviation, Mg- Milligram

Table 5: Folding endurance

Patch Code	Individual Folding Endurance	Folding Endurance Mean±SD
P1	225 223 224	224±1.00
P2	220 219 221	225±1.00
P3	222 223 221	226±1.00
P4	226 225 224	227±1.00
P5	226 227 225	228±1.00

reweighed after completion of 24h. Moisture content shall be determined by the following formula (Table 6).

Percentage moisture content (%) = [Initial weight - Final weight / Final weight] ×100

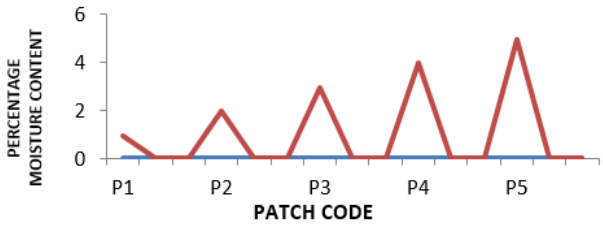

Fig. 5: Percentage moisture content

5. Fw-Final Weight, Iw- Initial Weight

Percentage Moisture Uptake: Patches shall be weighed individually and stored in desiccators which contain saturated potassium chloride solution to maintain 84% Rhesus factor (RH) (Table 7),(Figure 6).

Percentage moisture uptake (%) = (Final weight - Initial weight / initial weight) × 100

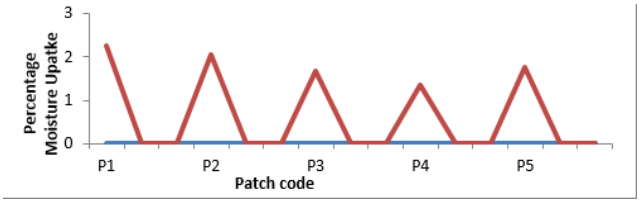

Fig. 6: Percentage moisture uptake

Percentage Elongation Test: The percentage elongation tests were estimated and calculated from the formula by observing the length just before the break point (Table 8, Figure 7).

Elongation percentages = L1 - L2 / L2 × 100.

Where L1 = final length of each strip L2 = initial length of each strip.

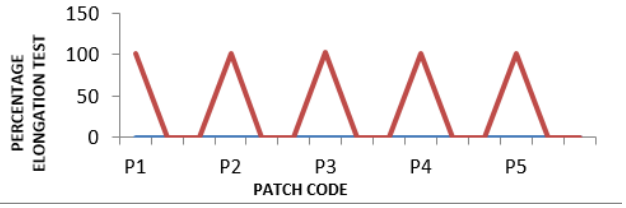

Fig. 7: Percentage elongation test

Percentage Drug Diffusion Test: The drug diffusion data present in Table 9 and graphically represented in Figure 8 and the best result of p4 data presented as mean SD in Table 10 and Figure 9.

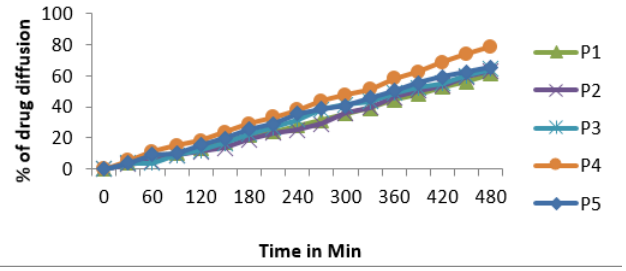

Fig. 8: Percentage drug diffusion

Surface pH Test: The patches were allowed to swell by keeping them in contact with 1 ml of distilled water for 2 h at room temperature and pH was noted down by bringing the electrode in contact with the surface of the patch, allowing it to equilibrate for 1 min (Table 10,Figure 9).

Table 6: Percentage moisture content

Patch Code	Final Weight	Initial weight	% Moisture Content=IW-FW/IW*100	% Moisture Content (Mean±SD)
	506.12	510.82	0.92	
P1	507.11	511.23	0.81	0.96±0.18
	506.17	512.11	1.16	
	506.21	510.22	0.79	
P2	505.12	510.43	1.04	1.02±0.22
	504.9	511.22	1.24	
	503.7	508.28	0.90	
P3	504.43	508.32	0.77	1.01±0.31
	502.2	509.11	1.36	
	501.23	507.54	1.24	
P4	501.12	506.78	1.12	1.04±0.26
	500.32	504.11	0.75	
	503.23	510.43	1.41	
P5	504.21	510.21	1.18	1.05±0.14
	504.13	510.01	1.15	

Table 7: Percentage moisture uptake

Patch Code	Final Weight (mg)	Initial weight (mg)	% Moisture Content=FW-IW/IW*100	% MoistureUptake (Mean±SD)
	510.82	501.11	1.94	
P1	511.23	499.12	2.43	2.25±0.3
	512.11	500.18	2.39	
	510.22	499.11	2.23	
P2	510.43	501.35	1.81	2.06±0.2
	511.22	500.53	2.14	
	508.28	501.28	1.40	
P3	508.32	499.54	1.76	1.67±0.2
	509.11	499.8	1.86	
	507.54	499.1	1.69	
P4	506.78	498.98	1.56	1.36±0.5
	504.11	499.99	0.82	
	510.43	500.51	1.98	
P5	510.21	502.2	1.59	1.77±0.2
	510.01	501.3	1.74	

FW-Final Weight, IW- Initial Weight

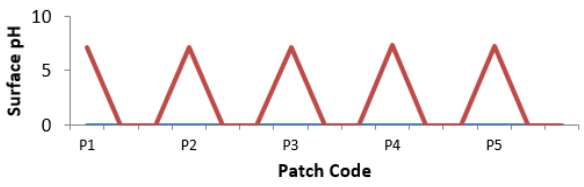

Fig. 9: % of drug diffusion (P5)

6. Results and Discussion

1. *Thickness:* The results indicate that the thickness with the formulations was not much distinct and was in the range from 47.69±0.5mm to 51.27±0.7 (Table 3, Figure 2).
2. *Weight Uniformity:* The weight of the patch has been measured by Sartorius electronic balance by taking three different patches of individual batch of the formulations. The average weight and standard deviation of three patches were calculated. The weight of the patches was ranged from 499.36±0.6mg 501.34±0.8mg (Table 4, Figure 3).
3. *Folding endurance:* The folding durability of the films has been measured by repeated folding of the patch at the same position before it breaks. Folding endurance was performed to check the durability of the patch, once it get folded and comes in the same position shows the endurance of the folding.
4. It was found that the prepared patch ranges between 224±1.00 to 228±1.00 (Table 5, Figure 4).

Table 8: Percentage elongation test

Patch Code	Initial Length of Patch	Increase in Length of Patch	% Elongation	% Elongation (Mean±SD)
	87.21	88.23	101.17	
P1	86.32	87.23	101.05	101.42±0.53
	87.21	88.98	102.03	
	89.43	90.21	100.87	
P2	88.7	89.43	100.82	101.07±0.39
	85.4	86.7	101.52	
	87.32	89.29	102.26	
P3	87.01	88.78	102.03	101.9±0.44
	89.07	90.32	101.40	
	88.61	89.23	100.70	
P4	87.6	89.45	102.11	101.03±0.73
	88.92	89.9	101.10	
	88.32	89.5	101.34	
P5	88.01	89.01	101.14	101.12±0.23
	89.23	90.01	100.87	

Table 9: Percentage of drug diffusion

Sn.	Time (Min)	% of Drug Diffusion				
		P1	P2	P3	P4	P5
1	0	0	0	0	0	0
2	30	3.98	3.01	3.80	5.6	4.11
3	60	8.67	5.21	4.13	11.3	9.32
4	90	10.08	9.02	8.90	15.4	10.21
5	120	13.78	11.23	11.87	18.4	15.67
6	150	17.45	13.56	16.70	23.5	19.90
7	180	21.56	18.93	22.39	28.9	25.40
8	210	23.98	23.30	26.76	33.5	29.20
9	240	27.80	25.32	31.89	37.8	35.60
10	270	31.21	28.89	38.43	43.7	38.67
11	300	35.54	35.87	41.21	47.6	40.55
12	330	39.09	39.44	43.23	51.1	45.78
13	360	44.43	46.09	48.65	57.8	50.11
14	390	47.89	50.24	52.31	62.5	55.40
15	420	52.67	53.32	54.72	68.6	58.98
16	450	56.21	58.95	59.83	74.0	62.13
17	480	60.89	63.09	64.11	78.6	65.40

Table 10: Surface "pH" of all baches of transdermal pach

Patch Code	Surface pH	Surface pH Mean±SD
	7.2	
P1	7.1	7.2±0.06
	7.2	
	7.2	
P2	7.1	7.1±0.06
	7.1	
	7.3	
P3	7.1	7.2±0.012
	7.1	
	7.2	
P4	7.3	7.3±0.06
	7.2	
	7.2	
P5	7.2	7.2±0.06
	7.3	

5. *Moisture Content:* The prepared patches percentage mean moisture content for batch p1,p2,p3,p4 and p5 is 0.96±0.18, 1.02±0.22, 1.01±0.31, 1.04±0.26 and 1.05±0.14 respectively (Table 6, Figure 5)
6. *Moisture Uptake:* The moisture uptake was found be in the range of 1.36±0.5to 2.25±0.3 (Table 7, Figure 6).
7. *Percentage Elongation Test:* The percentage elongation tests were estimated and calculated from the formula by observing the length just before the break point (Table 8, Figure 7)
8. *Percentage Drug Diffusion:* The effective permeation area calculated was: 3.18cm^2. The drug release was slower at the beginning and then it increases gradually. The percentage of drug release was found significant in the P5 formulation (Table 9, Figure 8).
9. *Surface pH:* The result was found in the range between7.1 to 7.3 (Table 10, Figure 9).

7. Conclusion

The mixture of formulation parameters, drug-polymer ratio and have been designed to make thin, clear, smooth, stable, and highly stable transdermal patches. From the clarify, the best formula were select based on physio-chemical analysis and in-vitro drug dispersion learn.

As a plasticizer, 0.3ml of propylene glycol has been applied to form a stretchy patch without have any significant effect on its diffusion properties. The film losses its versatility and becomes rigid when the amount exceeds. The plasticizer diffuses the polymer particles into the patch and softens them. Such softening favors confluence of latex and patch forming.

All the six lots have been accessed for thickness, folding endurance, flatness, drug content, determination of weight, moisture content, and in-vitro study of patches. No major variations in drug content were observed among the six formulated transdermal patches.

The results of the constancy studies show that there was substantial deviation from its first existence until the time of three month.

8. Source of Funding

None.

9. Conflict of Interest

None.

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