

Anti-inflammatory activity of herbal tablet of *Phyllanthus emblica* on carrageenan-induced paw edema in wistar rats

ABSTRACT

Aim:In the current investigation, tablet dosage form of hydroalcohol extract of leaves of *P. emblica* was developed and evaluated for anti-inflammatory activities.

Methodology:Hydroalcohol extract of leaves of *P. Emblica* (HPE) was prepared and formulated tablet dosage form. The mechanical properties e.g. hardness, friability, disintegration, and dissolution of tablet were evaluated. Anti-inflammatory activities of HPE (150 mg/kg) and HPE (650 mg) tablets were performed in carrageenan induced hind paw edema in wistar rats.

Result:The anti-inflammatory activity was found to be significant in carrageenan induced paw edema. HPE (150 mg/kg) and HPE tablets (650 mg) were significantly ($p < 0.05$) reduced the carrageenan induced paw edema by 66.41% and 69.43% respectively as compared to carrageenan control. The % inhibition of standard drug (dichlorofenac sodium) was recorded to be 70.18% after 5 h.

Conclusion:The study standardised the development of HPE tablet and its anti-inflammatory effect.

Keywords: Phyllanthus emblica, dissolution, stability, carrageenan induced, anti-inflammatory activity

1. INTRODUCTION

Inflammation is a biological protective response of vascular tissues against external agents such as irritants, pathogens or damaged cells. It is characterised as increased movement of plasma and innate immune system cells such as neutrophils and macrophages from the blood into the injured tissues. Inflammatory symptoms such as increased blood flow, vasodilatation, and enhanced cellular metabolism, extravasation of fluids and release of soluble mediators are noticed [1-2]. In the presence of inflammatory substances, phospholipase A₂ get activated and release of inflammatory mediators such as prostaglandin, histamine, cytokines, leukotrienes, and serotonin occurs. As a result vascular permeability increases and excess accumulation of leukocytes takes place at the site of inflammation [3-5]. In light of these findings, studies on plants with proven folkloric anti-inflammatory properties are seen as a fruitful and reasonable research strategy in the search for new anti-inflammatory medications [6].

Phyllanthusemblica L. (family-Phyllanthaceae, synonym-*Emblica officinalis*) is commonly known as Indian gooseberry or amla an indigenous species to India. In traditional medicinal system this plant is used in the treatment in various diseases [7]. Every part of *P. emblica* is useful owing to its medicinal and pharmaceutical properties. This plant has been scientifically validated for anti-inflammatory, adaptogenic, anticancer, antioxidant, nootropic, antidiabetic, immunomodulatory, osteoporosis antimicrobial and hyperlipidemia activities [8]. Various parts of this plant possess phenolics, flavonoid, vitamin, amino acid, minerals and tannins which are responsible to elicit pharmacological activities [9]. In previous studies, anti-inflammatory activities of different extracts of fruit and leaf of this species have been performed in carrageenan induced edema. So, the present investigation is based on evaluation of anti-inflammatory activities of hydroalcohol extract of leaf of *P. emblica* and its tablet formulation in carrageenan induced paw edema in wistar rats.

2. MATERIALS AND METHODS

2.1. Material and reagents

All the solvents, chemicals and reagents were of analytical grade and purchased from Qualigenes Pvt. Ltd., India, Rankem Pvt. Ltd., India, S.D. Fine-Chem Pvt. Ltd., India.

2.2. Collection of plant material

The leaves of *P. emblica* were collected from Barunei forest, Khordha, Odisha. It was identified and authenticated by Dr. Priyanka Dash, Assistant Professor, Department of Pharmacognosy, Centurion University of Technology and Management, Bhubaneswar. The voucher specimen (7205/20/CUTM) was deposited at herbarium of Centurion University for future reference.

2.3. Preparation of plant extract

The collected leaves of *P. Emblica* were shade dried. The dried plant material (700 g) was grounded to coarse powder. The material was defatted with petroleum ether to remove oil, fats and then extracted with hydroalcohol (80:20) by percolation for 72 h. The extract was evaporated under reduced pressure in rotavapor (R-100, Buchi, Switzerland) to collect dried semisolid mass and it was kept in desiccator for further investigations [10].

2.4. Formulation of tablet

Excipients Selection

Excipients are important in the design of a drug delivery system as it directly affects quality and efficiency. In the selection of excipients, the following parameters such as compendial ingredients, compatibility, stability drug release and availability were considered [11].

2.4.1. Granulation

Hydroalcohol extract of leaves of *P. emblica* (HPE) was blended with lactose (I.P.) dry starch (I.P.) sodium starch glycolate (I.P.) and microcrystalline cellulose (I.P.) were individually passed through mesh no. 40 sieve and blended in a double cone blender for 15 minutes. The

powder blend was granulated with starch paste and passed through mesh no 12 sieve and dried at 50 ± 2 °C in a hot air oven for 15 h. The dried granules were checked for LOD (NMT 4%) and lubricated with the mixture of talc (I.P.) and magnesium stearate (I.P.) and compressed [12].

2.4.2. Compression

Each tablet(650mg) was compressed by using tablet compression machine eight station (Emtech, Ahmedabad, India). Theoretical average wt. 650mg were taken for compression into flat round tablets.Nine batches of 250 no. of tablets were prepared by wet granulation method using starch paste as granulating agent. The granules were dried after passing through 12 no. sieve for 18 h at 50 °C and finally passed through 16 no. mesh sieve, blended and lubricated[12].

2.5. Evaluation of tablet

2.5.1. Drug excipient compatibility study

The interaction of extract and excipient was analysed with KBr by using FT-IR (Perkin Elmer®, Model Spectrum 1, USA). IR spectrum of drug was measured at a modest scanning speed of 4000-400 cm^{-1} [11].

2.5.2. Test for Disintegration

The disintegration times (DT) of the tablets were determined in distilled water at 37 ± 0.5 °C using a digital disintegration testing apparatus (Electrolab, India) by following the standard method [12].

2.5.3. Dissolution Test

In vitro release study of the tablets was determined at 37 ± 0.5 °C in 900ml of 0.1M HCl using a dissolution test apparatus (Electrolab, India) with the paddle rotated at 100rpm. Samples (5ml) were withdrawn and replaced with fresh medium at fixed time (5, 10, 15, 30, 60, 90 and 120 min) intervals. The amount of drug released was determined at 314.8nm in UV-Vis (UV-1800 Shimadzu) spectrophotometer[13].

2.5.4. Stability

In accordance to ICH guidelines, the optimized batch no. B1 was subjected to three months of stability testing at 30 ± 2 °C/ 65 ± 5 % RH and 40 ± 2 °C/ 75 ± 5 % RH. Physicochemical parameters and active content were considered for stability of the drug[14-15].

2.6. Optimization through experimental design

To study the effect of variables, we applied the 32 factorial designs. The amount of SSG (X1) and MCC (X2) were kept as an independent variables and hardness, disintegration time, % drug release (Y1) were selected as dependent variables. The data analysis of values obtained from various batches for drug release and swelling were subjected to multiple regression analysis using statistical software (Design Expert, 8.0.7.1).The quadratic model fitted by carrying out multiple regression analysis as shown below

$$Y = \beta_0 + \beta_1 X_1 + \beta_2 X_2 + \beta_{11} X_1^2 + \beta_{22} X_2^2 + \beta_{12} X_1 X_2$$

Where Y: measured response; X: levels of factors; β : coefficient computed from the responses of the formulations. The levels of the two factors were selected on the basis of the preliminary studies carried out before implementing the experimental design. All other formulation and processing variable were kept constant throughout the study. The coefficients corresponding quadratic effects (β_{11} and β_{22}) are determined from the results of the experiment to identify statistically significant terms. Equation containing only statistically significant terms is then used to draw response surface plots (Design Expert, 8.0.7.1) to visualize the impact of changing variables at a glance[16].

2.7. *In vivo* studies of extract of leaves of *P. emblica* and tablet formulation

2.7.1. Experimental animals

Swiss albino mice (50-100 g) of both sexes purchased from **Imgenex India Pvt. Ltd., Bhubaneswar, Odisha**. All of the animals were kept in conventional laboratory conditions for

a week at temp of 25-30° C, relative humidity of 60-70%, and 12 h day-night period. Animals were fed with normal pellet diet (PranavAgro Industries Ltd., Pune) and given free access to water. The ethical clearance for animal handling was approved by Institutional Animal Ethical Committee (IAEC) of Centurion University of Technology and Management (Regd. No.2024/PO/Re/S/18/CPCSEA).

2.7.2. Acute toxicity study

Acute oral toxicity tests were carried out in accordance with the OECD-423 guidelines (Acute toxic class method). In this analysis, Swiss albino rat (both sex, 100-200 g) (n=3/each dose) were chosen using a random sampling technique. The animals were fasted for 4 h and only had access to water. The extract (suspended with 0.5% w/v, CMC) was given orally to different groups of mice at doses of 5mg/kg, 50mg/kg, 300mg/kg, and 2000 mg/kg, and any behavioural changes were observed every hour for 24 h, and then mortality was observed for three days. If mortality was observed in 2/3 or 3/3 animals, then the dose administered was considered as toxic dose. However, if mortality was observed in only one mouse out of 3 no. of animals then the same dose was repeated again to confirm the toxic effect. If mortality was not observed, the procedure was then repeated with higher doses such as 5, 50, 300, 2000 mg/kg. The general behaviours were observed for first one hour and after 24 h of test drug administration [17].

2.7.3. Experimental design for anti-inflammatory activity in carrageenan-induced paw oedema model

Anti-inflammatory activity was studied in carrageenan-induced edema animal model. The experimental animals were divided into 5 groups (n=6).

1. Group-I (Normal control): administered with CMC (1 ml of 1% w/v in NS)
2. Group-II (Negative control): administered with carrageenan (0.1 ml of 1% w/v in NS)
3. Group-III (Positive control): administered with carrageenan (0.1 ml of 1% w/v in NS) + standard drug (diclofenac sodium, 6 mg/kg bw, p.o.)
4. Group IV (HPE)-administered with carrageenan (0.1 ml of 1% w/v in NS) + HPE (150 mg/kg bw, p.o.)
5. Group V (HPE tablet)-administered with carrageenan (0.1 ml of 1% w/v in NS) + HPE tablet (650 mg/kg bw, p.o.)

In this model, acute inflammation was induced by sub-plantar injection of carrageenan suspension in normal saline in rat hind paw of groups II-V. Carrageenan was administered after 30 min of administration of test drugs and standard drug. The thickness of hind paw was measured by plethysmometric method. After 1, 3, and 5 h of carrageenan injection, inflammation was measured in animal. The % inhibition of inflammatory edema in test and standard groups animals was calculated by the formula, $i = 100\{1 - (a-x)/(b-y)\}$ where a = mean hind paw volume of test/standard group animals after carrageenan injection, b = mean hind paw volume of positive control animals after carrageenan injection, x = mean hind paw volume of test/standard group animals before carrageenan injection, y = mean hind paw volume of positive control animals before carrageenan injection [18].

2.7.4. Statistical analysis

The results of anti-inflammatory activity were expressed as mean \pm SD. One-way analysis of variance (One-way ANOVA) was used to compare the groups at $p < 0.05$, followed by Tukey's multiple comparison test using GraphPad software (Prism 7)

3. RESULT AND DISCUSSION

3.1. Drug excipient compatibility study

The peak values (wave number) and the possibility of the functional group are recorded (Fig. 1). The FTIR result shows (Table 1 and 2) that there is no significant change in the peak values of the extract when tested individually or collectively. Hence, the ingredients selected as an excipient are compatible with the extract.

Table 1. Formulation of different batches of HPEtablets

Ingredients	B1 (mg)	B2 (mg)	B3 (mg)	B4 (mg)	B5 (mg)	B6 (mg)	B7 (mg)	B8 (mg)	B9 (mg)
Extract	150	150	150	150	150	150	150	150	150
Lactose	327.2	337.2	317.2	317.2	327.2	307.2	307.2	317.2	297.2
Starch	34	34	34	34	34	34	34	34	34
Starch paste	28	28	28	28	28	28	28	28	28
Sodium starch glycolate	42	32	52	42	32	52	42	32	52
Talc	34	34	34	34	34	34	34	34	34
Magnesium stearate	6.8	6.8	6.8	6.8	6.8	6.8	6.8	6.8	6.8
MCC	28	28	28	38	38	38	48	48	48
Water	Q.S	Q.S	Q.S	Q.S	Q.S	Q.S	Q.S	Q.S	Q.S
Total weight	650	650	650	650	650	650	650	650	650

MCC- microcrystalline cellulose, Q.S- quantity sufficient

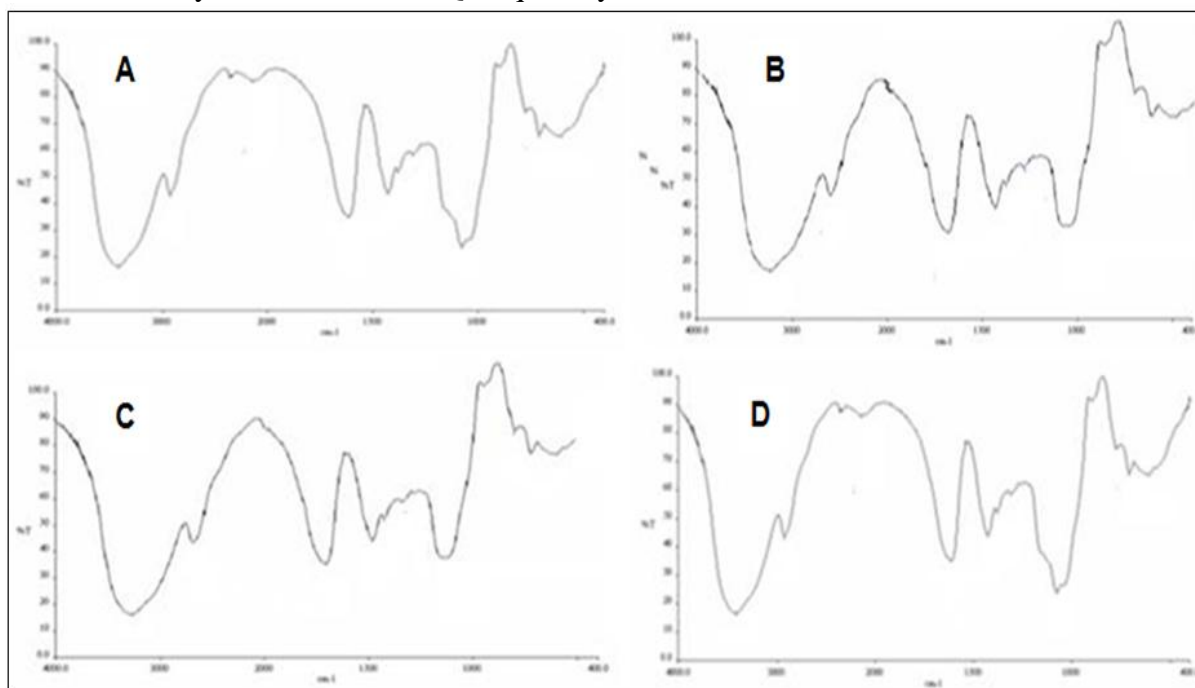


Fig. 1. (A) Hydroalcohol extract of leaves of *P. emblica* (B) Hydroalcohol extract of leaves of *P. emblica* + sodium starch glycolate (C) Hydroalcohol extract of leaves of *P. emblica* + microcrystalline cellulose (D) Hydroalcohol extract of leaves of *P. emblica* + other usual excipients

Table 2. Drug excipient compatibility

Peaks (cm ⁻¹)				Probable functional group	Normal range (cm ⁻¹)
HPE	HPE + MCC	HPE + SSG	HPE + excipients		
3408.86	3406.45	3419.0	3416.45	O-H stretch	3300-3600
2925.07	2921.45	2920.85	2920.24	C-H stretch	2700-3500

2139.94	2140.36	2131.23	2146.86	C=C	2100-2400
1611.72	1620.32	1616.20	1631.12	C=O	1600-1900
1426.22	1422.35	1412.23	1422.32	O-H Bending	1200-1500
1380.64	1375.54	1375.75	1378.23	C-H Bending	900-1400
1306	1304.54	1301.32	1312.21	C-H Bending	900-1400
1074.91	1075.23	1074.10	1068.10	C-O Stretch	900-1300

MCC- microcrystalline cellulose, SSG-starch glycolate sodium

3.2. Physicochemical tests

All the batches of the formulated tablet were subjected to evaluation concerning hardness (kg/cm^2), thickness (mm), diameter (cm), friability (%), disintegration time (sec), and dissolution time (%). The obtained result of the evaluation parameters are given below (**Table 3**). All the fabricated batches displayed the necessary hardness of more than 5 kg/cm^2 along with friability value of less than 1%, ultimately representing the required strength and resistibility of the formulations. The tablet fabrication was done employing the punch to produce dimensions of 5 mm \times 1.3 cm. The results confirmed that the produced tablets were detected to be free from any problems like capping, picking, and chipping.

Table 3. Evaluation of different batches of HPE tablets

Parameters	Specification	B1	B2	B3	B4	B5	B6	B7	B8	B9
Hardness(kg/cm^2)	3-6	4	4	3	2.5	2.5	3.7	3.5	2	3
Thickness (mm)	5	5	5	5	5	5	5	5	5	5
Diameter (cm)	1.3	1.3	1.3	1.3	1.3	1.3	1.3	1.3	1.3	1.3
Friability (%)	NMT1.5%	0.4	1.32	1.3	1.64	1.75	1.45	1.53	1.6	1.4
Disintegration time (sec)	15-120	15	60	17	60	45	25	22	80	65
Dissolution time (%)	NLT 90%	97.3	73.3	95.1	76.1	81.3	67.2	92.8	58.4	70.5
Assay %	95 \pm 5	100	84	98	96	98	95	95	96	95

3.3. Dissolution study

At the end of 30 min, it was revealed % drug release (DR) of batch no B1; 97.4%, batch no B2; 73.3%, batch no B3; 95.1%, batch no B4; 76.1%, batch no B5; 81.3%, batch no B6; 67.2%, batch no B7; 92.8%, batch no B8; 58.4% and batch no B9; 70.5%. The sequence of drug release is shown in **Table 4**. In the present study, the dissolution rate of batch no. B1 was greater than other batches. Also, the drug released from nine batches of formulations adopted zero-order kinetics (**Fig.2**). The results identified tablets of batch no. B1 as compatible formulation and investigated for further studies.

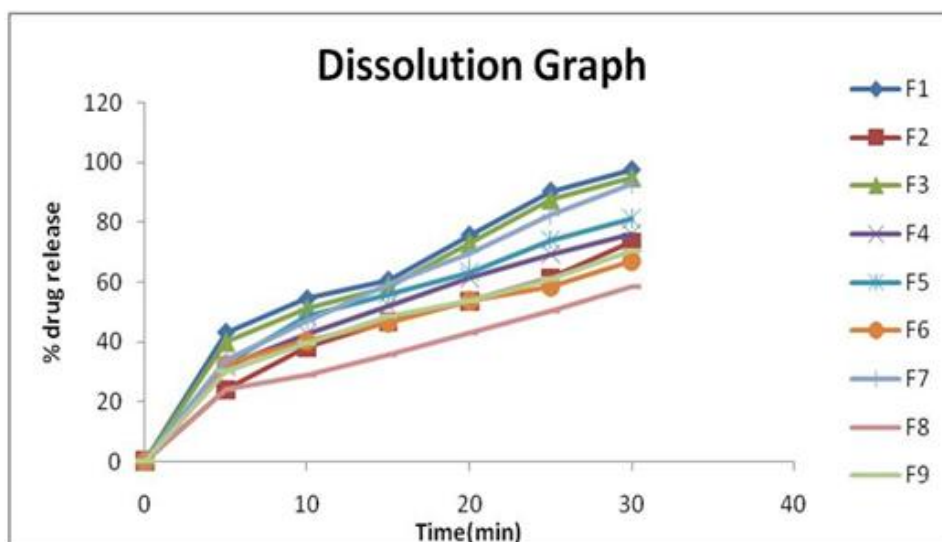


Fig. 2. *In vitro* dissolution studies of different batches of HPE tablets

Table 4. Drug release study of different batches of HPE tablets

Time (min)	B1	B2	B3	B4	B5	B6	B7	B8	B9
5	43.1	23.9	39.9	31.8	32.8	32.6	33.9	23.9	30.1
10	54.3	38.2	51.3	42.7	48.6	40.3	46.7	28.6	39.6
15	60.5	46.7	58.7	52.2	56.1	46.4	59.2	35.7	48.5
20	75.6	53.7	73.3	61.5	63.4	53.7	69.6	42.9	53.6
25	90.2	61.4	87.6	69.3	74.1	58.6	82.4	50.1	61.2
30	97.4	73.3	95.1	76.1	81.3	67.2	92.8	58.4	70.5

3.4. Stability studies

Sample tablets of the optimized formulation i.e. batch no. B1 was kept for stability studies. Stability studies for the tablet revealed good physical stability and organoleptic properties of tablets. The results suggested that the developed tablet formulation is stable for duration of three months with no loss of properties (Table 5).

Table 5. Stability study of optimized batch no. B1 HPE tablets

Duration (days)	Observations							
	Weight (mg)	Hardness (N)	Moisture (%)	Disintegration time (Sec)	Color	Odor	Stickiness	Active content (%)
30°C ± 2°C and 65% ± 5% RH								
Initial	650	4	2	30	Light Brown	Mixed odour of Aq. extract	No Stickiness	97.4
30	652	3.8	3	35	No Changes	No Changes	No Changes	96.8
60	649	4.1	3.2	35	No Changes	No Changes	No Changes	95.3
90	653	3.9	3.0	30	No Changes	No Changes	No Changes	96.8

40°C ± 2°C and 75% ± 5% RH								
Initial	650	4	2	30	Light Brown	Mixed odour of Aq. Extract	No Stickiness	97.4
30	652	3.9	3.1	35	No Changes	No Changes	No Changes	96.9
60	654	4.2	4	40	No Changes	No Changes	No Changes	96.3
90	648	3.8	3.4	35	No Changes	No Changes	No Changes	96.2

3.5. Optimization through factorial design

Optimization of tablet formulations of HPEwas performed by using 3² full factorial designs. The comparison of the experimental and expected values of the responses is performed to determine the model's reliability. To determine simplicity of the experiment, two-variable analysis at three experimental levels were performed. A total of 9 no. of batches of tablet were prepared and these batches were evaluated for hardness, disintegration time and % drug release (Table 6). The dependent variables values of the formulations were calculated to generate polynomial equations for the dependent variable in Design expert software.

Table 6. Experimental runs and observed responses for 3² factorial design

Batch	Code		Hardness (kg/cm ²) (Y1)	Disintegration time(sec) (Y2)	% Drug release (Y3)
	X1	X2			
B1	0	-1	4	20	97.4
B2	-1	-1	4	60	73.3
B3	+1	-1	3	17	95.1
B4	0	0	2.5	60	76.1
B5	-1	0	2.5	45	81.3
B6	+1	0	3.7	25	67.2
B7	0	+1	3.5	22	92.8
B8	-1	+1	2.0	80	58.4
B9	+1	+1	3	65	70.5

Response 1: Hardness

For Hardness, the following equation was obtained from the design model,

$$Y1 = 3.10 + 0.20X1 - 0.42X2 + 0.50X1X2 - 0.30X1^2 + 0.35X2^2$$

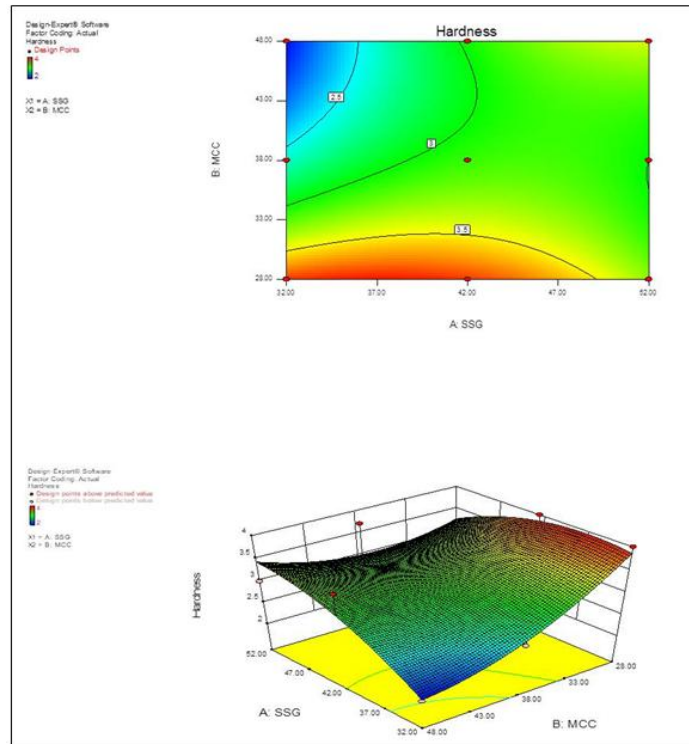


Fig. 3. Contour plot and response surface plot showing the effect of factorial variables on hardness

The positive coefficient of X1 indicated an increase in hardness with an increase in SSG, in the same way, the negative coefficient of X2 indicates a decrease in (Y1) i.e. hardness with an increase in MCC concentration. The mean hardness of tablet was calculated as 3.10. The surface responses plot for hardness shows that SSG (X1) effect was positive on hardness. As the concentration of SSG increased (from -1 to +1) i.e. from 32-52 then increase in hardness of tablet was observed. MCC also shows a negative effect on response Y1. As we increased MCC concentration from 28-48 then decrease in hardness was noticed but to a slight extent. Contour plot and Response surface plot showing the effect of factorial variables on hardness is depicted in **Fig.3**.

Response 2: Disintegration time

For Disintegration time, the following equation was obtained from the design model,

$$Y2 = 33.56 - 13.00 X1 + 11.67 X2 + 7.00 X1X2 + 14.67 X1^2 + 0.67 X2^2$$

The negative coefficient of X1 indicated a decrease in disintegration time with an increase in SSG, in the same way, a positive coefficient of X2 indicates a decrease in (Y2) i.e. disintegration time with an increase in MCC concentration. Also positive coefficient of the combination of both X1 and X2 indicates an increase in disintegration time with an increase in SSG and MCC. Mean disintegration time of tablet was calculated as 33.56.

Surface responses plot for disintegration time showed that SSG (X1) effect was negative on disintegration time, as the concentration of SSG increased from (-1 to +1) i.e. from 32-52 and increased in disintegration time. MCC showed a positive effect on response Y2, as we increased the MCC concentration from 28-48 and that resulted in increase in disintegration time. The combination of SSG and MCC showed a positive effect on response Y2. The effect of factorial variables on disintegration time is depicted in the contour plot and response surface plot (**Fig.4**).

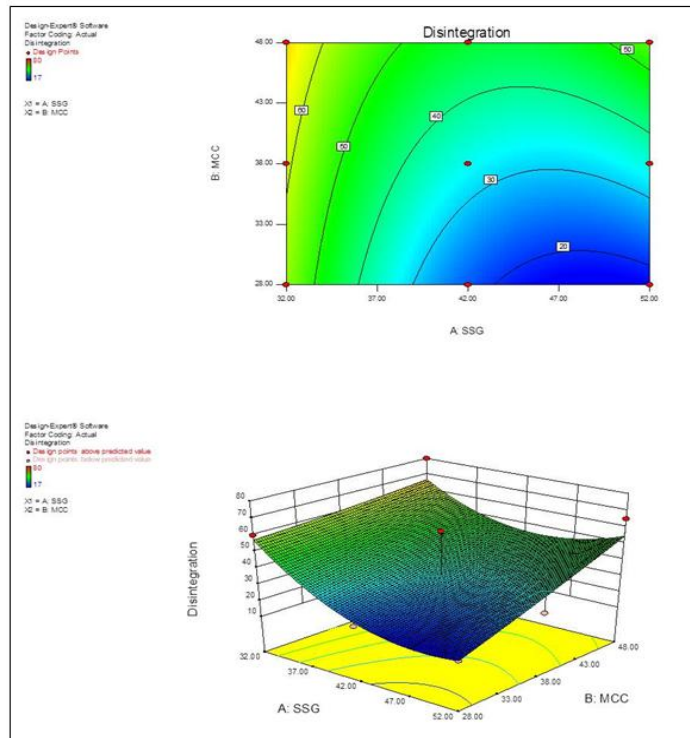


Fig. 4. Contour plot and response surface plot showing the effect of factorial variables on disintegration time

Response 3: Percent drug release

For % drug release, the following equation was obtained from the design model,

$$Y2 = 84.51 + 3.30 X1 - 7.35 X2 - 2.43 X1X2 - 14.47 X1^2 + 6.38 X2^2$$

The positive coefficient of X1 indicated an increase in % drug release with an increase in SSG, in the same way, a negative coefficient of X2 indicated a decrease in (Y1) i.e. % drug release with an increase in MCC concentration. The mean % drug release of the tablet was found to be 84.51.

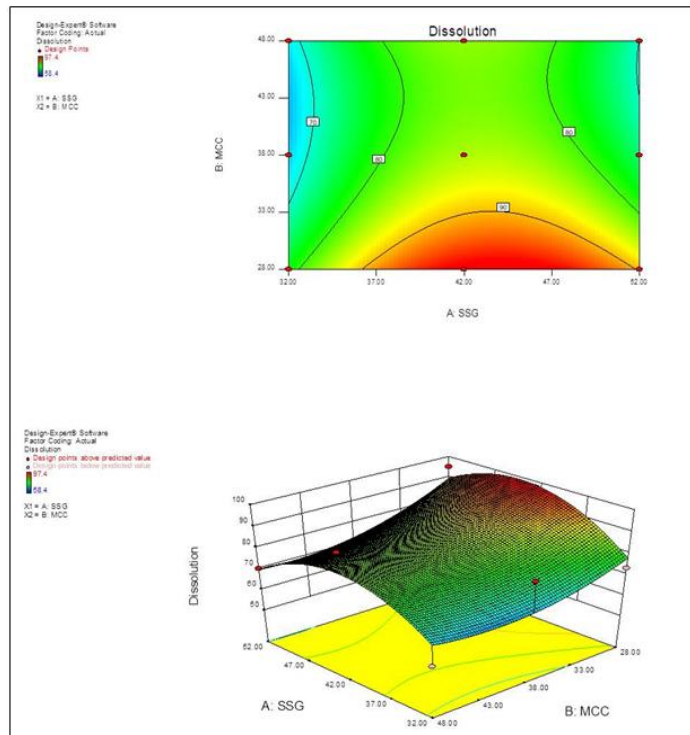


Fig. 5. Contour plot and response surface plot showing the effect of factorial variables on drug release

13	Lacrimation	+	+	+	+	+	+	+	+	+	+	+	+
14	Salivation	-	-	-	-	-	-	-	-	-	-	-	-

3.7. Anti-inflammatory activity

Inflammation is a part of vascular tissues' complex biological reaction to adverse stimuli like pathogens, damaged cells, or irritants. Redness, swollen joints, joint discomfort, stiffness, and loss of joint function are all symptoms. NSAIDs are currently used to treat inflammation. Unfortunately, these medications raise the risk of blood clots, which can lead to heart attacks and strokes. As a result, the development of potent anti-inflammatory medications from natural ingredients is currently being considered. The carrageenan-induced acute inflammation test is one of the best ways to find anti-inflammatory agents[20].

Table 9.Anti-inflammatory activities of HPE and HPE tablet

Group	Dose	Paw volume after carrageenan injection					
		1 h		3 h		5 h	
		EV	EI	EV	EI	EV	EI
Normal control	CMC (1 ml)	-	-	-	-	-	-
Negative control	Carrageenan (0.1 ml)	2.40±0.03	-	2.58±0.03	-	2.65±0.02	-
Positive control	Diclofenac sodium (10 mg/kg)	1.32±0.03	45.00	1.05±0.02*	59.30	0.79±0.03***	70.18
HPE	150 mg/kg	1.51±0.02	37.08	1.17±0.03*	54.65	0.89±0.04 ***	66.41
HPE tablet	650 mg/kg	1.48±0.06	38.33	1.11±0.03*	56.97	0.81±0.03**	69.43

Values are given in mean ± SD (n=6). Statistical significance differences were represented as * p< 0.05, ** p< 0.01, and *** p< 0.001

ED-edema volume, EI-edema inhibition, HPE-hydroalcohol extract of leaves of *P. emblica*

On the basis of the results of acute toxicity studies, HPO (150 mg/kg) was selected and effective dose for treatment of edema and tablet (650 mg/kg) of batch no. B1 were opted for evaluation of anti-inflammatory activities in carrageenan induced animal model. The animals were observed for 5 h for change in their paw edema. In negative control group, administration of carrageenan caused inflammation and after 5 h, the degree of edema was observed to be maximum (2.65±0.02). However, on administration of HPE (150 mg/kg) and tablet (650 mg) caused significant reduction in edema (HPE, 66.41% and tablet, 69.43%) after 5 h and the results were found to be similar to that of standard drug (diclofenac sodium, 70.18%). The anti-inflammatory effect of HPE was attributed to the presence of bioactive compounds in it which may inhibit the secretion of inflammatory markers such as COX-1 and COX-2 and inhibit synthesis of prostaglandins (Table 9).

4. CONCLUSION

In the present study, the results and discussions proved the potential anti-inflammatory activity of *P. emblica* in tablet formulation. The selection of excipients and methodologies adopted to manufacture tablet formulation of hydroalcohol extraction of *P. emblica* (HPO) were found to be result-oriented as it is evidenced by various investigation of the current research work. Currently, the regular used NSAIDs are associated with many unwanted complications. Henceforth, the developed formulation of HPO warrants further investigations on anti-inflammatory mechanism of action of drug at molecular level in various inflammatory diseases. Furthermore, extensive research work is needed to develop different dosage forms of HPO with reduced toxicity and value-added clinical utility.

AUTHOR'S CONTRIBUTION

All the authors have contributed equally.

CONFLICT OF INTEREST

Authors have no conflict of interest.

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