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Original Article

FORMULATION AND EVALUATION OF FLOATING TABLET OF *ECLIPTA ALBA* EXTRACT FOR HEPATIC DISORDERS

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ABSTRACT

Objective: The aim of the present study was to design and estimate gastro retentive floating tablet of *Eclipta alba* extract to increase the efficacy by extending the release of extract. *Eclipta alba* is reported to be useful in liver ailments and has been shown to possess hepatoprotective activity.

Methods: The floating tablet extract of *Eclipta alba* was prepared by using kollidon SR as floating and release retarding polymer. The effect of various additive excipient was also studied and optimized using 3^2full factorial design to alter the floating behaviour and extract release from the floating tablet.

Results: The polymeric structure of Kollidon® SR possesses appreciable porosity during the compression process. Results of multiple regression analysis show that the amount of stearic acid and lactose has significant influence on Q2, Q6 and Q10.

Conclusions: From the desirability function, the levels of the optimized batch were selected as -1 for the X1 and 1 for the X2 which correspond to batch F3 of factorial design. This study can open the avenues for the *In-vitro* dissolution testing of herbal extracts by simple UV method for the determination of extract release in extended release formulations.

Keywords: Floating tablet, *Eclipta alba,* Hepatoprotective, Kollidon® SR.

INTRODUCTION

Herbal medicine also called botanical medicine or phytomedicine - refers to using a plant's seeds, berries, roots, leaves, bark, or flowers for medicinal purposes. Herbalism has a long tradition of use outside of conventional medicine [1]. Nearly one-third of Americans use herbs. Unfortunately, a study in the New England Journal of Medicine found that nearly 70% of people taking herbal were reluctant to tell their doctors that they used complementary and alternative medicine [2].

Due to increased frequency of alcohol drinking and change of diet construction, such as the increase of fat content, there is an increase of an incidence of liver diseases which is becoming another important risk factor for morbidity and mortality in addition to viral hepatitis. The spectrum of alcoholic liver disease ranges from fatty liver to alcoholic hepatitis and ultimately fibrosis and cirrhosis [3].

It is therefore necessary to search for effective alternative drugs for the treatment of liver diseases to replace currently used drugs of doubtful efficacy and safety. Herbal-based therapeutics for liver disorders has been in use in India for a long time and has been popularized the world over by leading pharmaceuticals. Despite the significant popularity of several herbal medicines in general, and for liver diseases in particular, they are still unacceptable treatment modalities for liver diseases. A large number of plants and formulations have been claimed to have hepatoprotective activity. Nearly 160 phyto constituents from 101 plants have been claimed to possess liver protecting activity. In India, more than 87 plants are used in 33 patented and proprietary multi-ingredient plant formulations [4].

Eclipta alba Hassk. (Bhringaraja, Fam: Compositae) is a herb which grows widely in moist tropical countries. Different uses have been reported for this herb. It is used as anthelmintic, expectorant, antipyretic, antiasthmatic, tonic, deobstruent in hepatic and spleen enlargement. It is good for the diseases of the spleen, stomatitis, toothache, hemicrania, fever, pain in liver and cures vertigo. Its juice in combination with honey is administered for Catarrh and Jaundice [5]. Hepatic diseases are much prominent in the tropical countries including Africa, mexico south-western Asia and under developed countries [6]. The aim of the present investigation was to optimize gastro retentive floating tablet of selected hepato protective herbal drugs to increase the efficacy and stability of the drug using 3^2 full factorial design.

MATERIALS AND METHODS

Materials

Eclipta alba was purchased from sanjivani aushadhalay, Bhavnagar. Kollidon SR was received as a gift sample from BASF, USA; lactose, Stearic acid and dicalcium phosphate (DCP) was purchased from SD Fine chemicals, India.

Methods

Extraction of powdered plant

The coarsely powdered plant was extracted with 50% v/v ethanol by cold maceration (I. P. 1985). Solvent was removed at 50°C and reduced pressure. The dried extract was stored in a refrigerator for further use [7].

Analytical method development

UV Spectroscopic method was carried out at 207 nm for estimation of extract release.

Preparation of the tablets of *Eclipta alba* by 3^2 factorial design

As shown in table 1 the amount of stearic acid, (X1) and the amount of lactose (X2) were chosen as independent variables and % extract released at 2 h (Q2), 6 h (Q6) and 10 h (Q10) were taken as dependent variables.

$$Y = bo + b1X1 + b2X2 + b12X1X2 + b12X12 + b22X22$$

Where Y is the measured response associated with each run, bo is the arithmetic mean response of the total 9 runs, bi is the regression coefficient for factor Xi computed from the observed response Y. The main effects (X1 and X2) represent the average result of changing one factor at a time from its low to high value. The interaction term X1X2 show how the response changes when two factors are simultaneously changed. The polynomial terms X12 and X22 represent the nonlinearity in the model [8, 9].

The 3^2 factorial design consisting of 9 batches was formulated to evaluate the effect of independent factors i.e. amount of stearic acid and lactose. The calculated amount of stearic acid and lactose was mixed homogenously and heated to 75 ^{0} C i.e. above the melting point of stearic acid. The mixture was cooled to room temperature and passed through 30 # seive. Each tablet containing 100 mg powdered extract of *Eclipta alba* and the excipient listed in table 1 below were punched in rotary tablet press by direct compression using 10 mm flat punches with the hardness of not more than 3.5 and not less than 3.0.

Evaluation parameters for floating tablet of *Eclipta alba* extract

Compressed tablets were evaluated for assay, hardness, weight variation and friabilityaccording USP 28. For assay, 20 tablets were crushed and the powder equivalent of 100 mg extract was transferred to 1000 ml of 0.1 N HCl in the volumetric flask. The solution was analyzed by using double beam UV/VIS spectrophotometer after suitable dilution.

***In vitro* buoyancy study**

The *in vitro* buoyancy was characterized by floating lag time (FLG) and total floating time (TFT). The test was performed using USP 24 type II paddle apparatus using 400 ml of 0.1 N HCl at 50 RPM and 37 + 0.5^{0}C.

***In vitro* dissolution study**

Dissolution studies were conducted using standard USP paddle dissolution apparatus. In all the dissolution studies, the paddles were rotated at a speed of 50 rpm in 400 ml simulated gastric fluid at 37±0.5^{0}C. A series of samples (5 ml each) was withdrawn at predetermined intervals for a period of up to 12 h. The samples were filtered and then analyzed.

Stability study of tablets of promising batch

In order to determine the change in performance of dosage form on storage, stability study of optimized batch was carried out at 40°C in a humidity jar having 75 % RH according to ICH guidelines. Samples were withdrawn after three months and evaluated for change in buoyancy characteristics and extract release pattern. The similarity factor (f_2) was applied to study the effect of storage; optimized batch was evaluated for the floating lag time, total floating time [10].

RESULTS AND DISCUSSION

Lactose and stearic acid was added as release modulating excipients in the kollidon SR tablet of *Eclipta alba* and the concentration of these excipients optimized by 3^2 full factorial design. The polymeric structure of Kollidon® SR possesses appreciable porosity during the compression process. The floating ability of the Kollidon SR is highly dependent on the compression force of the tablet punching machine.

It was noted that when the compression force was higher so as to yield the hardness of the tablet more than 3.5, the density of the tablet was increased and the sinking of the tablet was observed, as shown in table 2.

Table 1: Composition of factorial batches

Batches	Herbal extract	Kollidon SR	Stearic acid	Lactose
F1	100	260	20	20
F2	100	240	20	40
F3	100	220	20	60
F4	100	240	40	20
F5	100	220	40	40
F6	100	200	40	60
F7	100	220	60	20
F8	100	200	60	40
F9	100	180	60	60

*All the values are in mg.

Table 2: Physiochemical properties of factorial batches

Batches	Hardness Kg/cm^2 (n=3)	% Friability	Average weight of tablet (n=20)	% extract per tablet
F1	3.2 ± 0.3	0.67	392	97.86 ± 0.18
F2	3.4 ± 0.2	0.71	396	97.18 ± 0.34
F3	3.4 ± 0.4	0.73	402	100.2 ± 0.26
F4	3.1 ± 0.5	0.81	398	102.78 ± 0.64
F5	3.4 ± 0.1	0.76	394	102.36 ± 0.48
F6	3.3 ± 0.2	0.79	404	98.04 ± 0.42
F7	3.4 ± 0.3	0.84	406	97.96 ± 0.48
F8	3.2 ± 0.5	0.86	404	106.56 ± 0.74
F9	3.3 ± 0.4	0.78	398	99.56 ± 0.56

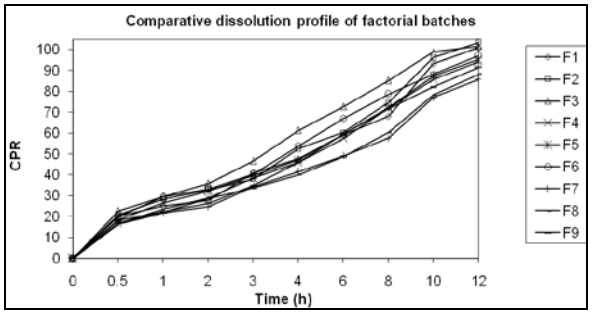


Fig. 1: *In vitro* dissolution profile of factorial design batches

In-vitro extract release data were subjected to multiple regression analysis (table 3) the results are depicted in table 3.

Low density excipients in higher levels were related to a lower density and thus improved floating behaviour. During the dissolution process drug starts to dissolve, whereas the water insoluble matrix former Kollidon® SR will begin to relax and swell. In all the batches, tablets floated on the surface till 12 hours dissolution study. In order to evaluate the performance of the formulation, *in vitro* extract release data is an important parameter. The results of in vitro drug release study are depicted in fig. 1.

Tablets of each batch had complied with the assay, weight variation and friability test according to USP 28. Tablets of factorial batches have practically no floating lag time. Tablets of each batch constantly floated on dissolution medium for more than 12 h. The dependent variables studied were the release of extract at 2, 6 and 10 hours representing the extract release at initial, intermediate and terminal part of the study. The value of the correlation co-efficient indicated a good fit. Results of multiple regression analysis show that, the amount of stearic acid and lactose have significant influence on Q2, Q6 and Q10 $P<0.05$ (table 4).

Table 3: Layout of 3^2 factorial design batches

Batches	Real values (%w/w)		Transformed values		Responses		
	Stearic acid	Lactose	X_1	X_2	Q2	Q6	Q10
F1	5	5	-1	-1	27.75	59.03	93.16
F2	5	10	-1	0	32.9	60.22	96.12
F3	5	15	-1	+1	35.82	72.63	97.74
F4	10	5	0	-1	29.02	57.4	85.63
F5	10	10	0	0	32.31	59.37	87.25
F6	10	15	0	+1	33.18	67	87.97
F7	15	5	+1	-1	24.63	48.98	76.9
F8	15	10	+1	0	28.59	48.54	78.38
F9	15	15	+1	+1	26.28	59.48	82.08

Q2 = 32.717 -2.828X1 +2.313X2 -2.175X11 - 1.820X22 - 1.605X12

Q6 = 58.117 -5.813X1 +5.617X2 - 3.110X11 + 4.710 X22 - 0.775X12

Q 10 = 86.952 - 8.277X1 + 2.017X2 + 0.447X11 -0.003X22 + 0.150X12

It was observed that as the amount of stearic acid was increased there was the decrease in the drug release represented by the negative sign in the equations of Q2, Q6 and Q10. This may be due to its lipophilicity and particle coating of the lipid on the other particles of the tablet. When the amount of lactose was increased it led to increase in the release of the extract from the tablet as represented in the equations by the positive sign. In the equation generated by multiple regression analysis for the Q2 and Q6, all the terms have p value less than 0.05 indicating the all the interaction terms and polynomial terms are significant except the interaction term for Q6 which displays the p value greater than 0.05. For the dependent factor Q10 the overall p value is significant but the p value of the interaction terms and polynomial term is greater than 0.05 indicating that release at 10 hour is dependent only on X1 and X2. The above discussion clearly shows that as the dissolution time increase from 2 hr to 10 hr, influence of the interaction terms and polynomial term decreases. The probable reason may be that as the dissolution media enter deeper in the tablet resulting in the relaxation and swelling of the polymer which facilitates the easy diffusion of the dissolution media in this relaxed tablet front thereby decreasing the influence of the interaction terms.

Table 4: Observed response parameter for 3^2 factorial design batches

Observed responses		b0	X1	X2	X11	X22	X12	F Significance	R^2
Q2	p value	0.0000	0.0032	0.0057	0.0305	0.0479	0.0273	0.00773	0.9912
	coefficient	32.717	-2.828	2.313	-2.175	-1.820	-1.605		
Q6	p value	0.0000	0.0019	0.0021	0.0479	0.0162	0.3367	0.00438	0.9940
	coefficient	58.117	-5.813	5.617	-3.110	4.710	-0.775		
Q10	p value	0.0000	0.0003	0.0189	0.5950	0.9967	0.7966	0.00230	0.9961
	coefficient	86.952	-8.277	2.017	0.447	-0.003	0.150		

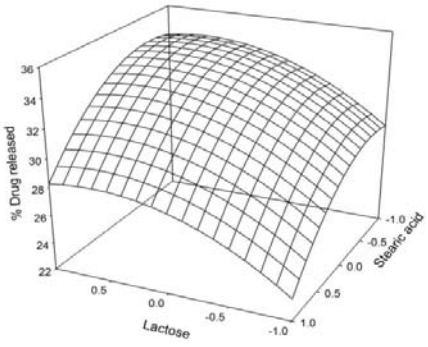


Fig. 2: Response surface plot for Q2

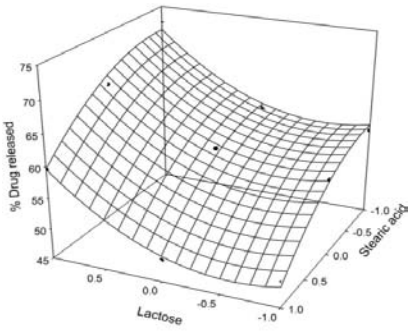


Fig. 3: Response surface plot for Q6

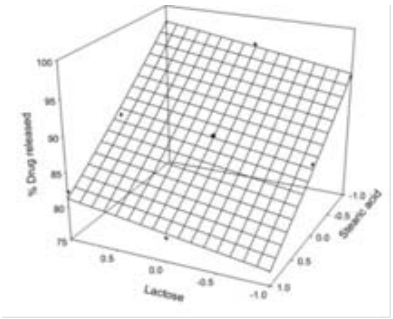


Fig. 4: Response surface plot for Q10

The surface response plots of the factorial design are displayed in the fig. 2, 3 and 4. It can be observed from the surface response plot that all the levels of X1, when the level of X2 was increased there was increase in the extract release, while at all the levels of X2, when the level of X1 was increased there was decrease in the extract release.

Statistica®8.0 software was used to validate the factorial design and simultaneously selection of the optimized batch was done using the desirability function. Constrain for the extract release at 2, 6 and 10 hours were defined in table 5. The standard deviation was calculated by conducting *in vitro* dissolution of this batch in triplicate. The result of the unpaired Student's t test for the single mean exhibited that there was no significant difference between the actual values and the estimated values derived from the factorial design. Thus the given model was validated and F3 was concluded as the optimized batch. Optimized batch shows agreement with the Higuchi and korsmeyer peppas model.

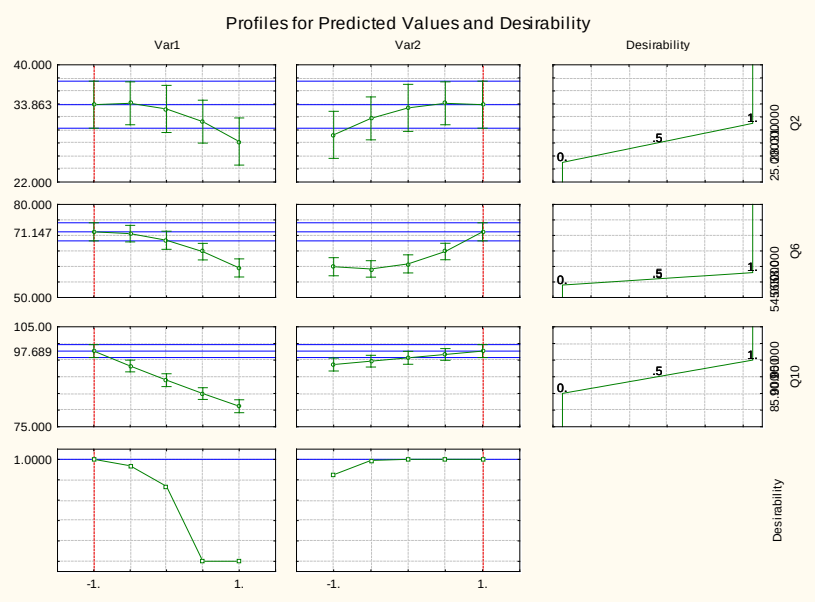


Fig. 5: Profile for predicted values and Desirability

Table 5: Variables in factorial design

Variables in factorial design	Level			Constraints			
Independent variables	**Low**	**Medium**	**High**	**Low**	**Medium**	**High**	**Goal**
X1Stearic acid (% w/w)	5	10	15				
X2 Lactose (% w/w)	5	10	15				
Dependent Variables							
Y1 drug release at 2 hour				25	28	31	Maximum
Y2 drug release at 6 hour				54	56	58	Maximum
Y3 drug release at 10 hour				85	90	95	Maximum

The graph displaying the levels of the optimized batch is shown in fig. 5 i. e. -1 for the X1 and 1 for the X2. This batch coincides with the batch F3 of the factorial batches which was selected as optimized batch. The actual and the predicted values of the dependent variables are given in table 6.

Table 6: Observed response for selected values

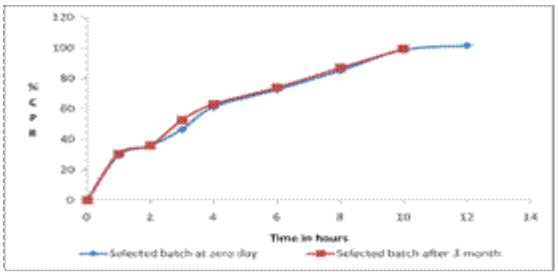
	Q2	Q6	Q10
Actual	35.82	72.63	97.74
Std deviation	5.26	3.58	1.38
Predicted	33.863	71.147	97.689
T cal	0.644	2.56	0.064
T tab (2 0.05)	4.3	4.3	4.3

Table 7: Model fitting of optimized batch

Model	R2
Zero order	0.9835
First order	0.941
Higuchi	0.994
Korsmeyer (n value=0.502)	0.991

The value of dissimilarity factor (*f1*) was found to be 3.71 and similarity factor (*f2*) was found to be 80.33 for dissolution profile of tablets after three month of storage compared with the dissolution profile of freshly prepared formulation.

As shown as in fig. 6 and the values of dissimilarity and similarity factor it can be observed that there was no significant change in the dissolution profile of the Batch F3 before and after stability studies for 3 months as per ICH guidelines. The tablets had no floating lag time and total floating time obtained was more than 12 hr which indicated no change in buoyancy characteristic upon storage.



6: Drug release data after 3 month stability study

CONCLUSION

The floating tablet of extract of *Eclipta alba* was prepared by using kollidon SR as floating and release retarding polymer. The effect of lactose and stearic acid was also studied by 3^2 full factorial design to alter the floating behaviour and drug release from the floating tablet. The data clearly indicated that the dependent variables are strongly dependent on independent variables. The value of the correlation co-efficient indicated a good fit. Results of multiple regression analysis show that the amount of stearic acid and lactose has significant influence on Q2, Q6 and Q10. Statistica® 8.0 software was used to validate the factorial design and simultaneously selection of the optimized batch was done using the desirability function.

From the desirability function, the levels of the optimized batch were selected as -1 for the X1 and 1 for the X2. This batch coincides with the batch F3 of the factorial batches which was selected as optimized batch. This optimized batch shows agreement with the Higuchi and korsmeyer peppas model. This study can open the

avenues for the *In-vitro* dissolution testing of herbal extracts by simple UV method for the determination of extract release in extended release formulations.

CONFLICT OF INTERESTS

Declared None

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