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Original Article

PREPARATION AND EVALUATION OF FAST DISSOLVING TABLETS OF PITAVASTATIN BY 3^2 FULL FACTORIAL DESIGN

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ABSTRACT

Objective: The objective of the present work was to prepare an optimized, fast dissolving tablet (FDT) of Pitavastatin to increase its dissolution by applying 3^2full factorial design.

Methods: Nine formulations (PF1 to PF9) with all possible combinations according to 3^2full factorial design by selecting two factors i.e. concentration of super disintegrant, Indion414 (5-15%) (A) and sublimating agent, camphor (40-60%) (B) as independent variables at three levels of-1, 0 and 1. The effect of these two variables on three dependent parameters, water absorption ratio (Y1), disintegration time (Y2) and *in vitro* drug release (Y3) was studied. All the powder blends were evaluated for precompression parameters, and the tablets were prepared by direct compression method which were further evaluated for post-compression parameters. The effect of change in concentration of two selected factors on dependent parameters was studied through 3D surface response plots and polynomial equations using Design expert software version11. Optimized formula was obtained by desirability and overlay plots for which compatibility stability was assessed.

Results: Precompression and post-compression parameters were satisfactorily within acceptable limits. Optimized formulation was prepared to prove the validity of the evolved mathematical model, which contained 6.75 mg of indion414(0.9) and 54 mg of camphor(0.9) with a disintegration time of 21 sec., water absorption ratio of 113 and 93% of drug release within 12 min. The compatibility between drugs and excipients was proved. The dissolution profiles of optimized formulation and commercially available conventional film-coated tablets of Pitavastatin were compared.

Conclusion: The optimized formulation showed significantly (P>0.05) increased drug release compared to commercially available film-coated tablets. No changes in disintegration time, drug content and in *in vitro* drug release from optimized formulation on storage for 3months at 40 °C±2 °C/75% RH±5% RH were observed during stability studies which confirmed the stability of the optimized formulation.

Keywords: Pitavastatin, Fast dissolving tablets, Indion 414, Direct compression, Factorial design

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INTRODUCTION

Nutritional and lifestyle changes in recent decades lead to many chronic diseases such as dyslipidemia. Dyslipidemia creates a serious problem all over the world as it was found as the primary factor for many heart illnesses resulting in mortality and expensive treatment. Dyslipidemia triggers various heart diseases such as atherosclerosis, cardiac infarction and ischemic heart diseases. Statins are one of the extensively prescribed medications to minimize the deaths due to Angina pectoris in hyperlipidemic patients [1]. All statins are available in conventional tablet formulations with very limited bioavailability. Pitavastatin comparatively novel derivative of statin family, it has unique pharmacological benefits in the reduction of low-density lipoprotein–cholesterol (LDL-C) and improvement of high-density lipoprotein-cholesterol (HDL-C) which is used in the treatment of many cardiovascular diseases [2]. Pitavastatin offered in film-coated tablets that cannot be crushed or chewed or swallowed easily by patients and is not available as liquid dosage forms. Pitavastatin is not useful in emergency clinical conditions of cardiovascular disease because of low solubility and slow onset of action. As there is an increased use of statins for the pediatric and geriatric population, there is a need to develop fast dissolving tablets of Pitavastatin for easy swallowing and fast onset of action.

The fast-dissolving tablets (FDTs) disintegrate and dissolve within seconds and are meant for administration to the patients who cannot swallow, such as elderly patients, stroke victims, bedridden patients, patients affected by renal failure, and patients who refuse to swallow, such as pediatric, geriatric, and psychiatric patients [3]. Hence, the present study was aimed at preparation of fast dissolving tablets of Pitavastatin using super disintegrant (Indion414) [4] and sublimating agent (camphor) [5] by direct compression method following 3^2 factorial design for the best-optimized formulation to increase dissolution of the drug, further to enhance absorption and bioavailability of drug for treating emergency clinical conditions of cardiovascular diseases.

MATERIALS AND METHODS

Materials

Pitavastatin was obtained as a gift sample from Aizant pharm labs (Hyderabad, India) Indion414 was purchased from Balaji drugs (Gujarat, India), microcrystalline cellulose, mannitol, magnesium stearate and aerosil were obtained from SD fine chemicals.

Methods

Factorial experimental design

Formulation of fast dissolving tablets (FDT) of Pitavastatin was designed according to 32 full factorial design using two independent variables, [6, 7] A (concentration of indion414, a super disintegrant) and B (concentration of camphor, a sublimating agent) at three (low, medium and high) levels of each variable (-1, 0 and 1) as given in table 1. The dependent parameters selected were water absorption ratio (Y1), disintegration time (Y2) and in vitro drug release (Y3). The software, design expert from Stat-Ease 11 version [8] was used for generating the experimental design from which the polynomial equations, surface response plots were obtained to find the impact of change in selected variables in three levels on Y1, Y2 and Y3. The desirability and overlay plots were generated to collect the composition of the best-optimized formulation along with the predicted values for Y1, Y2 and Y3 and calculated the validity of the design.

Formulation of FDT

Thus, a total of nine formulations of FDT of Pitavastatin was prepared by the direct compression method as per the composition shown in table 2. Pitavastatin, indion414, camphor, microcrystalline

cellulose and mannitol were accurately weighed and passed through sieve no 40 and were mixed well for 30 min to assure uniform distribution of the drug. Then, magnesium stearate and aerosil were added and mixed well [9, 10]. All materials were directly compressible, so the uniformly mixed blend was compressed into tablets using 7 mm punches on a twelve station tablet punching machine (Remek Minipress) [11]. All formulations were evaluated for different pre-compression and post-compression parameters.

Table 1: Coded and actual values of independent variables as per 3^2factorial design

Formulation code	Superdisintegrant (A) values		Sublimating agent (B) values	
	Coded	Actual (mg.)	Coded	Actual (mg.)
PF1	-1	2.5	-1	40
PF2	-1	2.5	0	50
PF3	-1	2.5	1	60
PF4	0	5	-1	40
PF5	0	5	0	50
PF6	0	5	1	60
PF7	1	7.5	-1	40
PF8	1	7.5	0	50
PF9	1	7.5	1	60
Optimized formula	0.9	6.75	0.9	54

Table 2: Composition of different pitavastatin fast dissolving tablets

Ingredients (mg)	PF1	PF2	PF3	PF 4	PF5	PF 6	PF7	PF8	PF 9	Optimized formula
Pitavastatin	4	4	4	4	4	4	4	4	4	4
Indion414	2.5	2.5	2.5	5	5	5	7.5	7.5	7.5	6.75
Camphor	40	50	60	40	50	60	40	50	60	54
Microcrystalline cellulose	49.5	39.5	29.5	47	37	27	44.5	34.5	24.5	31.25
Mannitol	50	50	50	50	50	50	50	50	50	50
Aerosil	2	2	2	2	2	2	2	2	2	2
Magnesium Stearate	2	2	2	2	2	2	2	2	2	2
Total weight	150	150	150	150	150	150	150	150	150	150

Evaluation methods

Precompression parameters

The powder blend was subjected to test the parameters before compression to tablets such as the angle of repose, bulk density, tapped density, Carr's index and Hausner's ratio using standard procedures [12].

Post compression parameters

Thickness, hardness and weight variation test

Thickness was determined for 20 pre-weighed tablets of each batch using a vernier calipers scale. Average of three readings were taken for each tablet and the results were tabulated. The hardness of five tablets was determined by Monsanto hardness tester then, the average hardness value was calculated and expressed in kg/cm^2. Randomly selected 20tablets of each batch were individually weighed using electronic balance, then, the average weight was calculated. The percentage deviation of each tablet weight from the average weight was tabulated.

Friability test

The friability of tablets was estimated using Roche friabilator. It was expressed in percentage (%) loss on friability. 10 tablets were pre-weighed and the weight was noted as initial weight and conveyed into friabilator, which was run at 25 rpm for 4 min. Then, the tablets were de-dusted, weighed again and the weight was noted as final weight. The percentage loss on friability was calculated with the difference in these weights which should be less than 4% for oral disintegrating and chewable tablets.

Wetting time and Water absorption ratio(R) (Y1)

Five circular tissue papers of 10 cm diameter were placed in a petri dish. 10 ml of water was added to petri dish, a tablet was carefully placed on the surface of each tissue paper. The time taken for water to reach the upper surface of the tablet was noted as wetting time.

The weight of the tablet before keeping in the petri dish was noted (Wb). Then the completely wetted tablet from petri dish was taken and reweighed (Wa). The water absorption ratio (R), was calculated by an equation: R=100(Wa-Wb)/Wb [13].

Drug content

Ten tablets were selected randomly and crushed in a mortar and an accurately weighed amount of an average tablet was taken from the crushed blend. Then, the sample was transferred to the 100 ml volumetric flask and diluted up to the mark with p^H6.8 phosphate buffer. It was shaken and kept for 24 h for dissolving drugs completely. The drug content was estimated at λ max of 245 nm against p^H 6.8 phosphate buffer as a blank using a UV-Visible spectrophotometer after filtration and dilution. Then the average of triplicate measurements was taken and %drug content was recorded for all batches.

Disintegration time (Y2)

The disintegration test was carried out in a tablet disintegration test apparatus containing a basket rack assembly with six glass tubes and a 10 mesh sieve at the bottom. The basket was raised and lowered 28-32 times per minute in the medium of 900 ml of p^H 6.8 phosphate buffer was maintained at 37±2 °C. Six tablets were placed in each of the tubes and the time required for complete passage of tablet fragments through the sieve (# 10) was considered as the disintegration time of the tablet and the average disintegration time of FDTs was tabulated.

***In vitro* dissolution studies (Y3)**

In vitro drug release studies were carried out for all (PF1-PF9) formulations and commercial film-coated tablets of Pitavastatin using USP dissolution test apparatus II (paddle type) at 50 rpm. in 900 ml of p^H6.8 phosphate buffer maintained at 37±0.5 °C. A sample of 5 ml was withdrawn at specific time intervals (5, 10,15,20,25 and 30 min), filtered and the amount of drug released was estimated by UV-Visible spectrophotometer (Lab India, Mumbai) at 245 nm. 5 ml of fresh p^H6.8 phosphate buffer was replaced as soon as the drug samples were withdrawn. Percentage of drug dissolved and dissolution rate was determined in triplicate.

Optimized formulation

The optimized formula (table 2) was collected from the overlay plot and desirability plot obtained using the results of Y1, Y2 and Y3 of all formulations (PF1-PF9) by design expert software and the optimized

FDT (OFDT) formulation were prepared using the formula and evaluated by the same procedures. The design predicted and observed values of dependent variables (Y1, Y2 and Y3) of OFDT were compared and %error was determined. Dissolution profiles of prepared OFDT and conventional film-coated tablets of Pitavastatin were compared. OFDT was further evaluated for compatibility and stability [14, 15].

Drug and excipient compatibility studies

The compatibility between drug and excipients was estimated by recording Fourier Transform Infra-Red (FTIR) spectra on a FTIR spectroscopy (Bruker Germany,) with KBr disc technique in the scanning range of 4,000–400 cm−1and by Differential Scanning Calorimetric (DSC) thermograms for both pure drug and optimized formulation.

Stability studies

Stability studies were conducted for the optimized formulation as per International Council for Harmonisation (ICH) guidelines by placing in a glass container which was sealed in aluminum packaging and kept in stability chamber maintained at 40 °C±2 °C/75% RH±5% RH for 3 mo [16].

RESULTS AND DISCUSSION

3^2full factorial design was used in present research, in which the influence of two variables, percentage of super disintegrant, indion414 (A) and sublimating agent, camphor (B) each at three levels on water absorption ratio (Y1), disintegration time (Y2), and *in vitro* drug release (Y3) was evaluated by preparing FDT formulations at all nine possible combinations (PF1-PF9).

From the results of pre-compression parameters of powder blend (table 3), it was observed that all parameters were within the range of good flow properties and concluded that the powder blends possessed good flow properties and acceptable compressibility index; hence all were suitable for formulation development similar to the reports of Patel DM *et al.* [17].

Table 3: Results of pre-compression parameters of pitavastatin fast dissolving tablet (PF1-PF9) formulation blends

Formulation code	Angle of repose (θ)	Bulk density (gm./cm²)	Tapped density (gm./cm²)	Carr's index	Hausner's ratio
PF1	29.5±0.8	0.64±0.4	0.78±0.5	17.9±0.9	1.21±0.7
PF2	29.1±1.2	0.68±0.3	0.76±0.5	10.5±1.0	1.11±1.1
PF3	27.2±0.1	0.61±1.0	0.73±0.9	16.4±0.9	1.19±0.8
PF4	32.5±0.7	0.58±0.7	0.70±0.5	17.1±1.1	1.21±0.9
PF5	28.7±1.0	0.66±0.3	0.76±0.4	13.1±0.6	1.15±0.8
PF6	23.8±0.2	0.65±0.2	0.74±0.3	12±0.3	1.13±0.5
PF7	30.2±0.6	0.70±0.8	0.78±0.8	10.2±0.8	1.11±1.0
PF8	26.5±0.3	0.69±0.9	0.78±0.8	11.5±0.9	1.13±1.1
PF9	27.7±0.2	0.73±1.0	0.81±1.1	9.8±0.7	1.10±0.9

n=3, all values represent mean±SD

Table 4: Post compression parameters of Pitavastatin fast dissolving tablets

Formulation code	[a]Thick ness (mm)	[b]Hardness (kg/cm²)	[c]Weight variation %	[d]% Friability	[a]Wetting time (sec)	[a]Water absorption ratio	[e]Disintegration time(sec)	[a]Assay (%)
PF1	3.4±0.2	2.6±0.1	0.133±0.5	0.74±1.1	35±1.0	45±0.5	80±0.3	98.5±0.5
PF2	3.3±0.1	2.4±0.2	0.066±0.006	0.94±0.6	31±1.0	65±1.0	53±0.5	99.3±0.3
PF3	3.6±0.2	2.5±0.1	0.266±0.01	0.84±0.8	28±1.0	63±0.6	68±0.6	99.7±0.1
PF4	3.5±0.1	2.7±0.3	0.266±0.01	0.75±1.2	39±1.0	72±0.8	58±1.2	98.7±0.2
PF5	3.2±0.4	2.8±0.5	0.123±0.02	0.99±1.0	29±1.0	76±1.2	45±0.8	98.6±0.5
PF6	3.3±0.1	2.8±0.2	0.136±0.05	0.11±1.1	22±1.0	93±0.8	38±0.7	99.5±0.6
PF7	3.5±0.1	2.5±0.3	0.210±0.08	0.83±0.6	26±1.0	80±1.2	76±0.4	98.5±0.3
PF8	3.2±0.3	2.1±0.2	0.064±0.001	0.66±0.9	23±1.0	88±0.6	28±0.5	98.8±0.5
PF9	3.3±0.1	2.6±0.2	0.124±0.01	0.84±1.0	21±1.0	135±0.8	20±1.2	99.4±0.4

[a]n=3, [b]n=5,[c]n=20,[d]n=10,[e]n=6, all values represent mean±SD

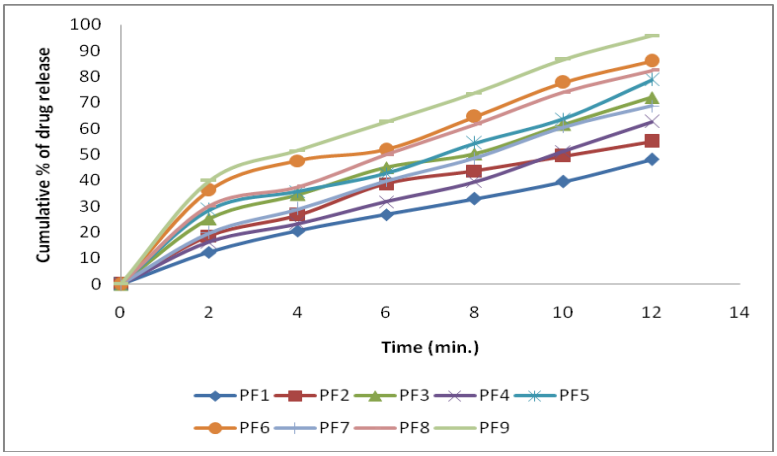


Fig. 1: *In vitro* drug release profiles of pitavastatin fast dissolving tablets, n=3

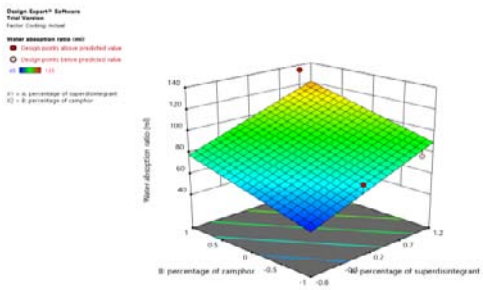
The results of post-compression parameters (table 4) indicated that the hardness, weight variation, friability of all the formulations were within the range of IP limits. Wetting time of all the formulations was found to be in the range of 21 to 39

seconds, less wetting time of formulation is an indication of fast disintegration, water absorption ratio was in the range of 45 to135 and disintegration time was 20 to 80 seconds. The PF9 formulation consisted of high levels of super disintegrant and sublimating agent has shown the least disintegration time and the highest water absorption ratio might be due to remarkable moisture absorbing and swelling properties of indion 414 and volatilization of camphor caused creation of pores and absorption of more water through pores which were supported by the results of Salch AER [18]. The drug content of all formulation was within 98.5 to 99.7%.

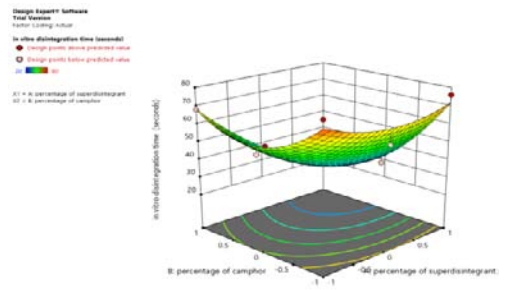
The *in vitro* drug release studies of all formulation batches (PF1-PF9) (fig. 1) shown significantly enhanced drug release (PF7-PF9 as compared to PF1-PF3) with the increased concentrations of super disintegrant (indion414) and camphor (sublimating agent). Among all the formulations, PF9 has shown the highest percentage drug release (95%) within 12 min.

Factorial design–data analysis

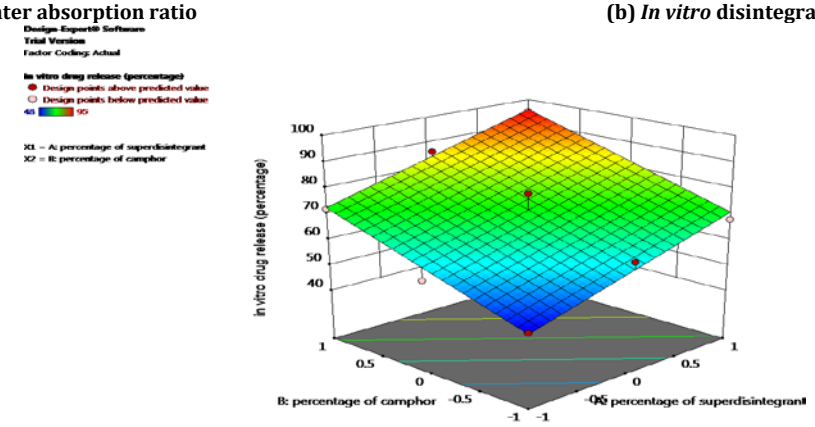
The polynomial equations (linear equations) were generated by design (table 5) and 3D response surface plots resulting from equations were obtained by design expert software (fig. 2).



(a) Water absorption ratio



(b) *In vitro* disintegration time



(c) *In vitro* drug release studies

Fig. 2: 3D surface response plots for a) Water absorption ratio (Y1) b) Disintegration time (Y2) c) *In vitro* drug release (Y3) of pitavastatin fast dissolving tablets

Table 5: Polynomial equations for selected responses generated by design

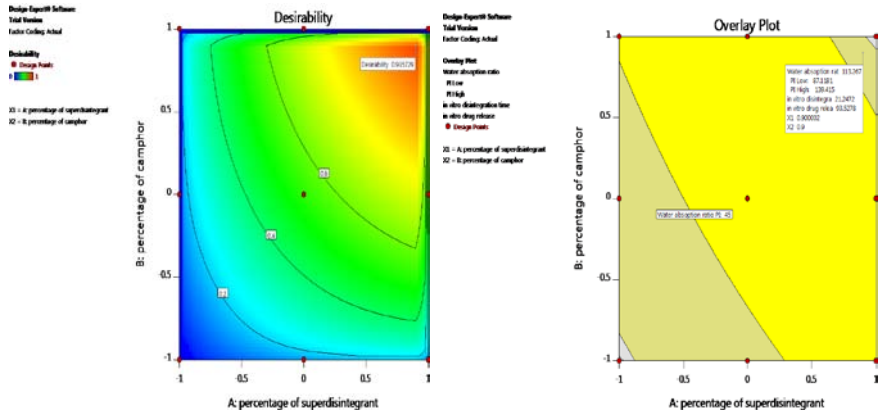
Eq. No.	Name of response	Polynomial Equation
1	Water absorption ratio (Y1)	$Y_{1=}$+79.67+21.67A+15.67B
2	Disintegration time (Y2)	Y_2=37.22-12.83A-14.67B
3	*In vitro* Drug release (Y3)	Y_3=71.78+11.67A+12.50B

The formulations were analysed for three selected critical parameters for which three polynomial equations were generated according to the results of parameters from software (table.5). The magnitude and sign of coefficients of two variables in three equations indicated the extent and trend of influence of two variables (A and B) on three responses (Y1, Y2 and Y3). A positive sign implicated a synergistic effect and negative sign indicated an antagonistic effect of the variable on responses.

The overall conclusion of influence of A and B variables (Concentration of Indion414 and camphor)was positive on Y1 (water absorption ratio) and Y3(*in vitro* drug release) indicated that increased concentrations of two variables enhanced the water absorption and drug release due to its high moisture absorption and fast disintegration capacity of tablets. The effect of two variables was negative on Y2 (disintegration time) indicated that disintegration time was decreased with an increase in concentrations of A and B due to same reason. Among two variables, the magnitude of A in equation 1was highest implied the more influence of concentration of Indion (A) on water absorption ratio than on all other responses.

Further numerical and graphical optimization of variables were obtained by desirability and overlay plots (fig. 3)

As per numerical optimization, the overall desirability of optimized formulation was found to be near to one (0.99) in the desirability plot (fig. 3a.). Then the optimized tablets were prepared according to composition obtained in overlay plot (fig. 3b) as per the design and evaluated for three dependent parameters, water absorption ratio, disintegration time and *in vitro* drug release in 12 min. and the results were 113, 21 sec. and 93% respectively which were compared with the model predicted values. The high water absorption ratio of OFDT is contributed for its least disintegration time and more drug release. The % prediction error was less than 5% (table 6), hence the validity of the design and optimized formulation was confirmed.



a) (b)

Fig. 3: a) Desirability plot b) Overlay plot of pitavastatin fast dissolving tablets by 3²full factorial design

Table 6: The model suggested an optimum formula with predicted and observed values of responses

Independent variables	Optimum values		Dependent variables	Observed values	Predicted Values mean±SD	% of prediction error
	Coded	Actual (mg.)				
A	0.9	6.75	**Y1**	113.26	[a]125.5±0.5	-10.4
B	0.9	54	**Y2(sec.)**	21.24	[b]18.21±1.0	-14.2
			Y3(%)	93.52	[a]96.68±0.3	3.32

[a]n=3, [b]n=6

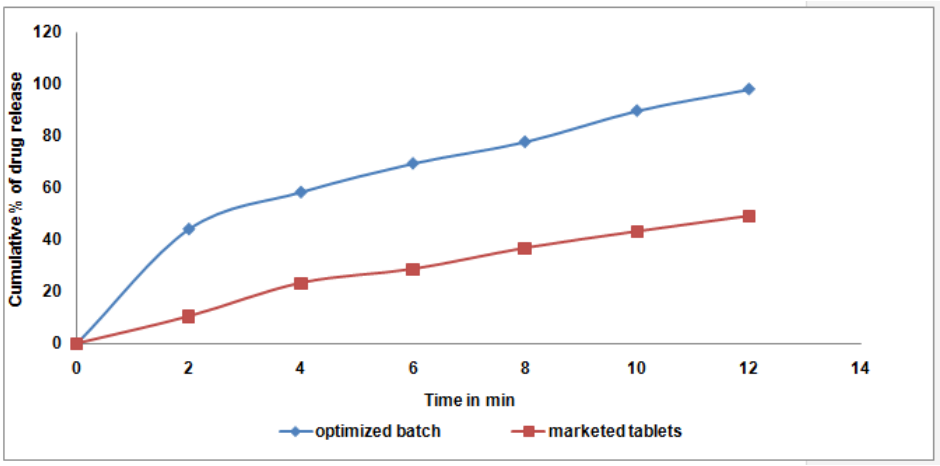


Fig. 4: Comparative *in vitro* dissolution profiles of marketed and optimized pitavastatin fast dissolving tablets, n=3

Drug release profiles of optimized formulation and commercially available film-coated tablets of Pitavastatin, (fig. 4) were compared. Drug release from optimized formulation was significantly enhanced ($p \geq 0.05$) compared to the commercial formulation.

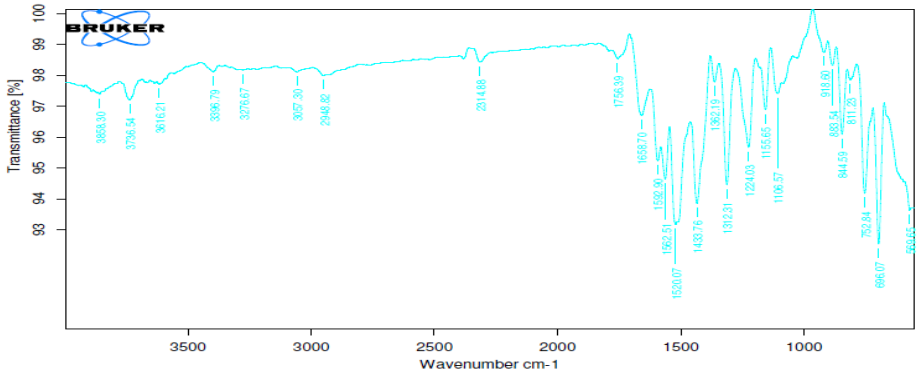


Fig. 5a: FT-IR spectrum of a pure drug (pitavastatin)

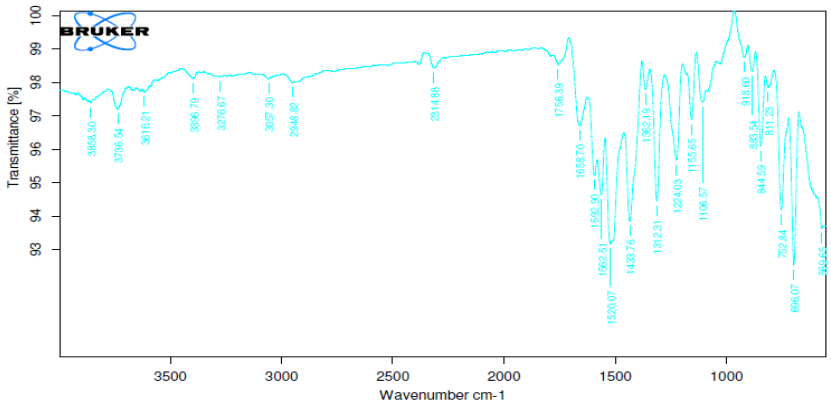


Fig. 5b: FT-IR Spectrum of pitavastatin formulation

FTIR spectrum of Pitavastatin (fig. 5a) shown characteristic peaks at 1433.7 cm^{-1} due to C=C bending, peak at 1658.70 cm^{-1} indicated C=O stretching, peak at 2948.82 cm^{-1} indicated the presence of C-H stretching, peak at 3396.79 cm^{-1} indicated O-H stretching and peak at 3858.3 cm^{-1} represented N-H stretching. Based on fig. 5b, no changes were found in the main bands of a drug due to the presence of excipients in optimized formulation; hence it revealed the physical and chemical compatibility between drug and excipients.

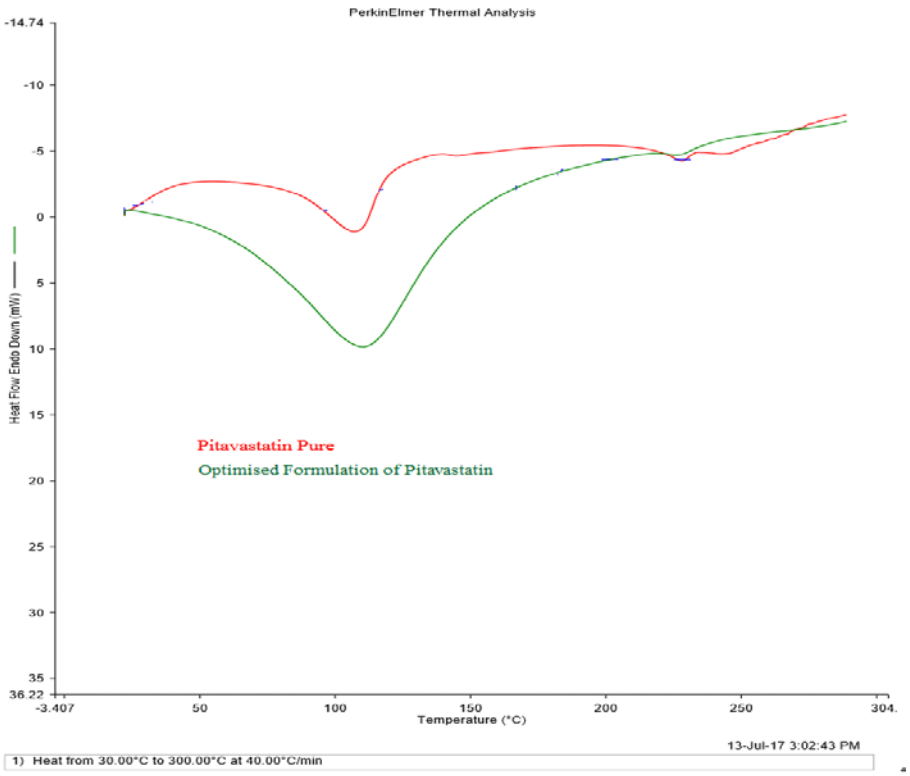


Fig. 6: DSC thermograms of pitavastatin pure and its optimized formulation

Table 7: Results of all parameters on stability studies of optimized formulation

S. No	Test parameter	0 d	30 d	90 d
1	[a]Thickness (mm)	3.5±0.1	3.50.1	3.50.1
2	[a]Hardness(kg/cm^2)	2.2±0.3	2.2±0.3	2.2±0.2
3	[a]Weight (mg)	149.5±0.5	149.5±0.6	149.3±0.5
4	[b]% loss in friability	0.65±0.3	0.65±0.5	0.64±0.6
5	[a]Wetting time(sec)	15±1.0	16±0.5	16±1.0
6	[a]Water absorption ratio	125±0.3	128±0.5	123±0.3
7	[a]Drug content (%)	101.5±0.3	101.1±0.2	101±0.6
8	[c]Disintegration time(sec)	18±1.0	20±1.2	21±1.0
9	[a]*In vitro* drug release (%)	96.6±0.2	92±0.6	93±0.5

[a]n=3,[b]n=10,[c]n=6, All values represent mean±SD

DSC thermograms of pure Pitavastatin and optimized formulation are shown in fig 6. A sharp endothermic peak was observed at 139 °C in the case of pure pitavastatin reflecting the purity in crystalline form. The intensity of peak was less sharp and suppressed in case of optimized formulation might be due to decreased crystallinity of drugs upon compression into a tablet using a sublimating agent.

The results of short term stability studies indicated that the post-compression parameters were satisfactory within the limits after storage for 90 d. *In vitro* drug release profile also not changed on storage. Hence, stability studies confirmed the stability of prepared optimized formulation (table 7).

CONCLUSION

Fast dissolving tablets of Pitavastatin were prepared and optimized using 3^2 full factorial design. The concentration of indion414 and camphor were selected as two independent variables which significantly ($p<0.05$) affected the dependent parameters, water absorption ratio, disintegration time and drug release. Design expert trial version11 was used to optimize and to draw respective polynomial equations, response surface plots. A stable optimized formulation was prepared as per composition generated by numerical and graphical optimization in the form of desirability and overlay plots. The optimized formulation exhibited a water absorption ratio of 113, disintegration time of 21 sec. and drug release of 93% within 12 min which were closed to predicted values confirmed the validity of the design. The compatibility and stability of optimized formulation were proved.

FUNDING

Nil

AUTHORS CONTRIBUTIONS

All the authors have contributed equally.

CONFLICT OF INTERESTS

Declared none

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