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Original Article

FORMULATION AND EVALUATION OF TIME-RELEASE COMPRESSION COATED TABLET CONTAINING ACEBROPHYLLINE FOR CHRONOTHERAPY OF ASTHMA

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ABSTRACT

Objective: The aim of present research was to develop compression coated tablet for pulsatile drug delivery of Acebrophylline used for chronotherapy of asthma. The drug delivery system was designed to deliver the drug at such a time when it could be most needful to patient of asthma.

Methods: The compression coated tablets containing Acebrophylline in the inner core were formulated by direct compression method with an outer coating of different amounts of HPMC K4M.

Results: The release profile of press coated tablet exhibited a lag time depending upon the amount of HPMC K4M in compression coating, followed by burst release. Optimization was done using 3^2 factorial design considering two independent factors at three levels. Data was evaluated statistically by Stat Ease Design Expert 7.0.0 software. The optimized batch F6 gave a lag time of 6 hr and drug release of 94% in which the concentration of HPMC K4M is 40% and the concentration of SSG is 2.5 %.

Conclusion: The chronodelivery of Acebrophylline was achieved by formulating the tablet by compression coating technique.

Keywords: Compression coated tablet, Lag time, Chronotherapy, Acebrophylline, Asthma.

INTRODUCTION

In the last several decades has to be seen the development of many controlled-release formulation having the constant drug release rates to maintain the concentration of drug in the human body, apart from the patient's physiological condition. However, the long-term constant concentration of drug in the human blood and tissue can be the source of problem like tolerability, resistance, and drug side [1]. People are different significantly in their physiological and biochemical condition during any 24 hr period, because of circadian rhythm, and as a result the constant drug delivery into the body seems both needless and unwanted. If the drug release profile mimics a living system's pulsatile hormone secretion, then it may improve drug's effectiveness, and reduce the toxicity of a specific drug administration schedule.

The medication and treatments provided according to the human body's circadian rhythms will result in better outcomes [2]. This can be provided by a chronopharmaceutical dosage regimen with pulsatile release which matches the circadian rhythm resulting from a disease state, so optimizing the therapeutic effect while minimizing side effects [3]. The compression coating technique is a simple and distinctive technology used to provide tablets with a programmable lag phase, followed by a rapid, or rate-controlled, drug release after administration. This technique has many advantages, and there is no special coating solvent or coating equipment is required for manufacturing this type of tablet. Pulsatile drug delivery systems (PDDS) are ahead importance because these systems deliver the drug at particular time as per the pathophysiological need of the disease, resulting in better patient therapeutic efficacy and compliance [4, 5]. Diseases in which PDDS are promising include cardiovascular diseases, asthma, arthritis, hypercholesterolemia, and peptic ulcer. The pathophysiology of arthritis and patients with osteoarthritis tend to have less pain in the morning and more at night; while those with rheumatoid arthritis, have pain that usually peaks in the morning and decreases throughout the day [6, 7].

Compression-coating presents an attractive alternative to spray-coating techniques for high molecular weight polymers. Thick coatings can be applied rapidly and it is a solvent-free coating Process [8].

Compression-coating has been used in the pharmaceutical field for different purposes:

(1) To protect hygroscopic, light-sensitive, oxygen-labile or acid-labile drugs [9].

(2) To combine and separate different therapeutic drugs [10, 11].

(3) To modify a drug release pattern (delayed, pulsatile and programmable release of different drugs in one tablet) [12, 13].

Various materials have been investigated as compression coatings to obtain time-controlled release: HPMC [14, 15, 16] hydroxypropyl cellulose [17], polyethylene oxide [18], micronized ethyl cellulose [17], Eudragit RS [18], behenic acid [19]. Bimodal drug release usually obtained with multilayered matrix tablets [20] can also be obtained with compression-coated tablets [21, 22]. The purpose of this study was to develop time-release compression coated tablet containing acebrophylline for chronotherapy of asthma. The oral press coated tablet was developed to achieve the time-controlled disintegrating or rupturing function with a distinct predetermined lag time. The HPMC-compression-coating resulted in release profiles with a distinct lag time depending on the amount of HPMC in compression coating. Burst release was obtained by incorporating a super disintegrant (SSG) within the core tablet.

MATERIALS AND METHODS

Materials

Acebrophylline was obtained as a gift sample from Kores India Ltd. (Mumbai, India.) Sodium Starch Glycolate (SSG), magnesium stearate microcrystalline cellulose (MCC) and Ludipress (directly compressible lactose) were obtained as gift samples from Wockhardt Ltd. (Aurangabad, India.) HPMC K4M was obtained from Colorcon Asia Pvt. Ltd. (Goa) as a gift sample.

Methods

Fourier Transform Infrared (FTIR) spectroscopy

The FTIR spectrum was recorded using Prestige-21 (SHIMADZU) with IR resolution software. The procedure consisted of, placing a drug sample in FTIR cuvette. The drug sample was placed in the light path and scanned over the range of 4000-400 cm^{-1} on Shimadzu

FTIR Prestige-21. The obtained spectrum was recorded and analyzed.

Drug-excipients compatibility study

The Drug-excipients compatibility study was carried by DSC with their physical mixture in ratio 1:1. The mixtures were prepared by triturating the drug with excipients and the mixtures were stored for 24 hours at room temperature. The mixtures were then filled in aluminum pan specially made for DSC sampling and the DSC thermogram was recorded.

Drug solubility study

The drug solubility study was carried in water and different buffer solutions with pH 1.2, 6.8 and 7.4. The excess amount of drug was added in the buffer solution to make saturated solution.

Then saturated drug solutions were sonicated thrice, each time for 10 min. The solutions of Acebrophylline were kept overnight for attainment of equilibrium with solvent. Prepared solutions were filtered using Whatman filter paper no 42. The filtrate was analyzed spectrophotometrically.

Characterization of blend of API and excipients

The drug (Acebrophylline), microcrystalline cellulose (MCC) and superdisintegrant (Sodium Starch Glycolate) were thoroughly blended for 20 min. Later on magnesium stearate was added and again blended for 2 min. The blend was evaluated for Angle of repose, Hausner's ratio, Bulk density, Tapped density, Carr's index, and similar evaluation was done for the blend of outer coating material.

Formulation of RRCTSs

RRCTS were prepared by direct compression method as per the formula given in Table 9. The ingredients (Acebrophylline, MCC and SSG) were accurately weighed and mixed in geometric proportion. The mixture was blended for 20 min in a sealable polythene bag. Then magnesium stearate was weighed and added to the mixture and again blended for 2 min. The resulting uniform blend was compressed to form the tablets using the 8 mm, circular, flat faced punch on 12 station Labpress compression machine. The total weight of tablets was kept constant at 200 mg. The tablet press setting was kept constant across all formulations.

Table 1: Formulation composition for factorial batches

Tablet ingredient(mg)	Factorial batches								
	F1	F2	F3	F4	F5	F6	F7	F8	F9
Core tablet									
Acebrophylline	100	100	100	100	100	100	100	100	100
SSG	3	4	5	3	4	5	3	4	5
MCC	95	94	93	95	94	93	95	94	93
Magnesium stearate	2	2	2	2	2	2	2	2	2
Total weight	200	200	200	200	200	200	200	200	200
Coat									
HPMC K4M	70	70	70	80	80	80	90	90	90
Ludipress	128	128	128	118	118	118	108	108	108
Magnesium stearate	2	2	2	2	2	2	2	2	2
Total weight	200	200	200	200	200	200	200	200	200
Total weight of PCT	400	400	400	400	400	400	400	400	400

Evaluation of RRCTSs

Physical characterization

The prepared RRCTSs were evaluated for the physical characteristics such as thickness; diameter, hardness and weight variation test according to the Indian Pharmacopoeia (IP) 2007.

Drug content

Twenty tablets were taken and powdered. Tablet powder equivalent to 25 mg of acebrophylline was weighed, sufficient volume of phosphate buffer was added and volume was made upto 100 ml with phosphate buffer pH 7.4.

Then the solution was sonicated for 30 min. and filtered. The filtrate (4 ml) was further diluted with phosphate buffer pH 7.4 upto 100 ml to get required concentration. The absorbance of resulting solution was measured UV spectrophotometer at 273.2 nm.

***In-vitro* disintegrating time**

In vitro disintegration time of six tablets from was determined by using disintegration test apparatus. To test for disintegration time 1 tablet was dropped in each glass tube, and the basket rack assembly was set in a 1L beaker of water at 37±2°C.

***In-vitro* dissolution studies**

The *in-vitro* dissolution studies were carried out in 0.1N HCl (900 ml) at 37 ± 0.5°C using USP dissolution apparatus type II. The speed of rotation was maintained at 100 rpm. 5 ml samples were withdrawn at predetermined time interval and content of Acebrophylline was determined by using UV spectrophotometer at 273.2 nm.

Formulation of PCTs

PCTs were prepared by compression coating of prepared 8 mm diameter RRCTSs into 11 mm diameter tablets. The composition of batches containing varying amount of HPMC K4M and SSG were as shown in Table 1.

Compression or press coating of the tablets was done by placing half amount of the compression coat blend into the die cavity, then manually placing the RRCTS on the powder bed centrally.

Further remaining half quantity of the compression coating material was added in the die cavity from above. Then finally the tablet was compressed by the tablet compression machine.

Evaluation of PCTs

Hardness of PCTs was measured by Monsanto hardness tester and thickness by using vernier caliper. The friability of the tablets was determined by using Roche friabilator. The % friability was calculated by the following formula:

$$\% F = \left(\frac{W_0 - W}{W}\right) \times 100$$

Where, F is friability, W_0 is the weight of tablets before test, W is weight of tablets after test.

***In-vitro* dissolution study**

The *in vitro* dissolution study of press coated tablets was performed by using 0.1 N HCl pH 1.2 (acid stage) as dissolution medium for first two hours and then remaining time in phosphate buffer pH 7.4 (buffer stage) in a USP Type II Paddle Apparatus containing 900 ml of dissolution medium maintained at 37±2°C with a speed of 100 rpm.

Lag time

Lag time is the time before the drug release has started or the time in which less than 10% of the drug has released. The lag time (t10) and release time (t80–10) were defined as the times in hr of 10% and 80–10% drug released, respectively. The lag time (hr) for different formulations was obtained from the *in vitro* dissolution study of PCTs.

Water uptake study (% Swelling)

In this study tablet of each batch was separately placed in the basket of dissolution apparatus by using water as immersion medium at 37±2°C. Tablets were withdrawn at a time interval of 3 hr and blotted with tissue paper to remove the excess water.

The weight of tablet after swelling was measured on an analytical balance. The initial and final weights of the tablet were used to calculate % swelling or water uptake of the tablet as follows

$$\% \text{ Water uptake} = \left(\frac{W_t - W_0}{W_0}\right) \times 100$$

Where, W_t and W_0 are the final weight after swelling and initial dry weight of the tablet respectively.

Transverse and longitudinal section view of press coated tablets

To demonstrate the central positioning of the core tablet within the press coated tablet, the core tablet blend was mixed uniformly with Erythrosine, a red dye. This was then compressed to produce red coloured tablet cores.

Transverse and longitudinal sections of press coated tablets were made using surgical blade in order to verify the position of position of core tablet. Figure No. shows the photographs of these sections. From this, it is clear that core tablet is placed in center of coated tablet

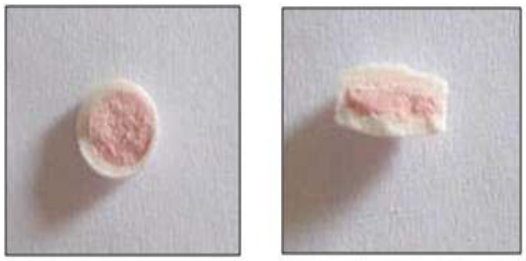

Fig. 1: A) Transverse and B) Longitudinal section view of press coated tablets

Optimization by 3^2 factorial design

A 3^2 full factorial design was used in the present study. In this design 2 factors were evaluated each at 3 levels, and experimental trials were performed at all 9 possible combinations. The amount of release retarding polymer HPMC K4M (X1) and amount of superdisintegrant, SSG (X2) were selected as independent variables and each factor being studied at -1, 0, +1 level. The % DR (drug release) and lag time were considered as the dependant variables.

Analysis of data by design expert software

A 3^2 full factorial design was selected and the 2 factors were evaluated at 3 levels, respectively. The statistical treatment and interpretation of data was done by Stat Ease Design Expert 7.0.0 software.

The analysis of variance (ANOVA) is represented in table (Table 9, 10). The data were also subjected to 3-D response surface methodology to study the interaction of independent variables (Figure 4, 5).

RESULTS AND DISCUSSION

Fourier Transform Infrared (FTIR) spectroscopy

FTIR spectrum of acebrophylline was recorded and characteristic peaks were observed.

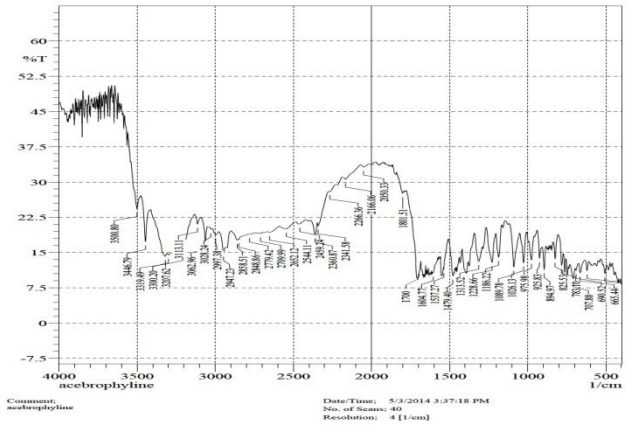

Fig. 2: FTIR spectrum of Acebrophylline

The descriptions of the observed peak are given in the following table.

Table 2: FT-IR characteristic peaks of Acebrophylline

S. No.	Assignment	wave number cm^{-1} (Recorded)
1	-N-H group	3500.80
2	-N-H2 group	3446.79
3	-OH group	3319.49
4	-C=O Stretch	1700
5	-COOH group	1700

Drug-excipient compatibility study

The possible interaction between the drug and the polymers was studied by differential scanning calorimeter (DSC). There was no considerable change in DSC endothermic values, comparing pure Acebrophylline and with the excipients (HPMC K4M, SSG, MCC and Ludipress) which indicated the absence of any interaction between drug and excipients used in the preparation. Peak value was obtained at 215°C which is very much nearer to pure drug i. e 217 ºC. DSC thermogram is shown in Figure 3.

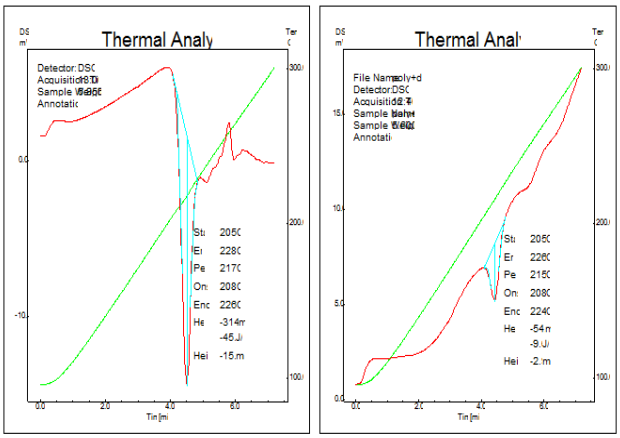

Fig. 3: DSC thermogram of: A) Acebrophylline B) Acebrophylline + excipients

Drug solubility study

Solubility profile of acebrophylline indicated that the drug is slightly soluble in water and methanol and soluble in ethanol.

Characterization of blend of api and excipients

The blend of API and excipients was evaluated for parameters like Angle of repose, Bulk density, Tapped density, Compressibility index and Hausner's ratio. The results obtained were as shown in Table 3.

Evaluation of RRCTSs

The immediate release core tablets were evaluated for weight variation test, hardness, thickness, % friability, in vitro disintegration time and drug content.

The weight of all the tablets was found to be within the range, hardness was constant and % friability of the tablets was also within the acceptable limits. The results obtained were as shown in Table 4.

Table 3: Evaluation of precompression parameters

Batch code	Evaluation of parameters					
	Angle of repose(°)	Bulk density	Tapped density	Compressibility index (%)	Hausner's ratio	Flowability
F1	28.32	0.281	0.319	15.4	1.12	Good
F2	29.42	0.285	0.331	13.8	1.11	Good
F2	27.20	0.350	0.249	15.3	1.17	Good
F4	29.31	0.260	0.240	12.51	1.15	Good
F5	28.22	0.264	0.317	14.80	1.14	Good
F6	27.20	0.319	0.271	13.17	1.16	Good
F7	28.22	0.218	0.299	15.39	1.21	Good
F8	29.42	0.270	0.313	15.21	1.19	Good
F9	29.8	0.281	0.320	14.10	1.11	Good

Table 4: Evaluation of tablets of RRCTSs

Batch code	Evaluation parameters					
	Weight variation (Mg)	Hardness (kg/cm2)	Thickness (mm)	Drug content (%)	In vitro DT (Sec)	Friability (%)
F1	200.61	3-3.5	2.76	99.71	34.5	0.396
F2	200.30	3-3.5	2.75	99.82	33.7	0.383
F3	200.66	3-3.5	2.76	100.45	33.1	0.410
F4	200.70	3-3.5	2.75	100.58	31.9	0.371
F5	200.60	3-3.5	2.77	99.99	30.9	0.381
F6	200.59	3-3.5	2.78	100.53	30.8	0.355
F7	200.81	3-3.5	2.76	99.83	29.8	0.452
F8	200.41	3-3.5	2.75	100.41	28.8	0.310
F9	200.72	3-3.5	2.72	100.60	28.5	0.351

The press coated tablets were evaluated for weight variation test, hardness, thickness, % friability and drug content. The results obtained were as shown in Table 5.

Table 5: Evaluation of tablets of factorial batches (PCTs)

Batch code	Evaluation parameters				
	Weight variation (mg±S. D)	Hardness (kg/cm2)	Thickness (mm±S. D)	Drug content (%)	Friability (%)
F1	400.66±1.18	5.5-6	5.43±0.31	99.72±0.18	0.468±0.23
F2	400.22±1.26	5.5-6	5.44±0.48	99.81±0.21	0.448±0.15
F3	401.77±0.94	5.5-6	5.46±0.052	100.45±0.10	0.472±0.36
F4	399.83±0.78	5.5-6	5.45±0.114	100.58±0.19	0.455±0.18
F5	400.55±1.14	5.5-6	5.42±0.047	99.97±0.23	0.446±0.22
F6	400.55±1.24	5.5-6	5.47±0.068	100.53±0.19	0.452±0.27
F7	400.93±1.27	5.5-6	5.48±0.070	99.93±0.24	0.351±0.37
F8	400.33±1.29	5.5-6	5.40±0.085	100.41±0.11	0.237±0.28
F9	400.8±1.08	5.5-6	5.42±0.091	100.60±0.35	0.404±0.41

Values are mean ± SD, n=3.

Lag Time

The lag time of the PCTs was measured by determining the time for which there is no release or less than 10% release of the drug from the dosage form. It was done by in vitro dissolution testing of the dosage form.

From the dissolution profile of PCTs (Table 7 and Figure 4), it is evident that the PCTs exhibited a specific lag time which depended on the polymer concentration in that batch. The lag time increases as the polymer concentration was increased, it was 4 hr for 35% 6 hr for 40% and 8hr for 45% HPMC K4M concentration.

The lag time showed a direct relationship with the amount of HPMC K4M in the outer coating.

Water uptake study (% Swelling)

A direct correlation between Swelling Index and Lag Time was observed from the obtained results. The lag time was found to be increased with increasing swelling index. Higher Swelling Indices were observed in formulation batches containing higher amount of HPMC K4M.

This may be due to uptake of water and swelling of the polymer which is hydrophilic and forms a gel upon hydration.

Table 6: Swelling Index of PCTs

Batch code	F1	F2	F3	F4	F5	F6	F7	F8	F9
Swelling Index (%)	41.45	42.2	42.88	58.04	57.00	55.85	70.14	72.12	71.09

Table 7: Dissolution profile of RRCTSs

Time (min)	% DR								
	F1	F2	F3	F4	F5	F6	F7	F8	F9
2	30.8	32.13	33.92	46.89	44.96	45.2	54.01	50.9	51.2
5	53.98	57.21	58.98	64.2	68.8	67.1	73.1	73.9	79
10	84.01	89.11	90.09	86.11	90.5	86.9	86.4	92.6	96.1
15	90.12	91.3	95.8	92.2	94.01	97.7	92.4	96.3	98.4

Drug release studies of RRCTSs and PCTs

The in vitro dissolution of RRCTSs showed more than 80% drug release within 10 min. (Table 7 and Figure 4). The maximum drug release was obtained from batches having highest amount of Superdisintegrant (SSG). The amount of drug released exhibited a direct relationship with the amount of SSG in core tablet.

The graphical representation of the dissolution profile of RRCTSs is shown in Figure 4. It was evident that core tablets of all the batches showed an immediate release before it was compression coated with an outer layer consisting of HPMC K4M and Ludipress. The mechanism of action of SSG involves rapid and extensive swelling which causes burst release of the drug. The PCTs of different batches showed a variable lag time depending on the concentration of HPMC K4M in the outer coating layer. The PCTs showed a lag time before the drug release because the RRCTSs were completely surrounded by the polymer layer which prevented the release of drug from the RRCTSs. Burst release after a specific lag time occurred due swelling and erosion of the outer hydrophilic polymer layer.

When the polymer layer swelled adequately, it allowed sufficient dissolution medium to enter into it and reach the core tablet. The superdisintegrant in the core swelled extensively which exerts a pressure on the outer layer resulting in burst release of the drug.

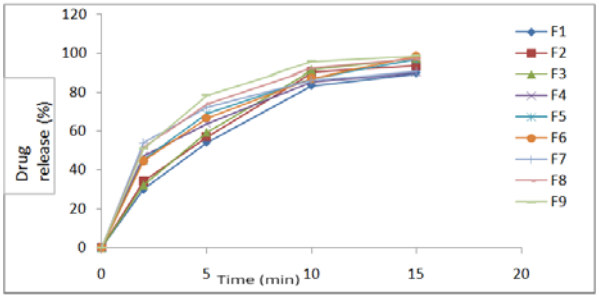

Fig. 4: % Drug release from RRCTSs

Table 8: Dissolution profile of factorial batches (PCTs)

Time (hr)	% DR								
	F1	F2	F3	F4	F5	F6	F7	F8	F9
1	0.002	0.006	0.003	0.004	0.005	0.004	0.0031	0.003	0
2	0.006	0.008	0.006	0.006	0.006	2.66	0.007	0.006	0.002
3	1.213	3.026	2.198	1.94	1.957	1.95	1.999	1.782	0.005
4	6.69	8.4	7.17	4.9	4.21	2.8	2.712	3.011	1.821
5	76	93	86	7.6	7.991	6.4	3.001	3.691	2.712
6	72.51	90.6	89	8.3	9.38	9.5	4.123	5.91	3.45
7	78.6	92	86	86.8	89	94	7.421	7.771	4.98
8				96	96	87.3	9.01	9.81	7.8
9				92.3	92.5	85.9	79	94.6	88.5
10				94.2	94	84.8	88.32	95-01	91
11							87.4	96.48	93
12							86.21	94.83	95.4

The graphical representation of the dissolution profile of PCTs is shown in Figure 5. The batches F1-F3, F4-F6 and F7-F9 showed a lag time of 4, 6 and 8 hr respectively.

Table 9: Analysis of Variance for R1 (lag time)

Source	Sum of Squares	Degrees of Freedom (df)	Mean Square	F Value	p- value Prob > F	Model
Model	24.00	5	12.00	6.366E+007	< 0.0001	significant
A	24.00	1	24.00	6.366E+007	< 0.0001	
B	0.000	1	0.000	6.366E+007	< 0.0001	
Residual	0.000	6	0.000	-	-	
Core Total	24.00	8	-	-	-	

The Model F-value of 63660000.00 implies the model is significant.

There is only a 0.01% chance that a "Model F-Value" this large could occur due to noise. Values of "Prob > F" less than 0.0500 indicate model terms are significant. In this case A, B are significant model terms. Values greater than 0.1000 indicate the model terms are not significant.

Table 10: Analysis of Variance for R2 (% DR)

Source	Sum of Squares	Degrees of Freedom (df)	Mean Square	F Value	p- value Prob > F	Model
Model	407.84	5	81.57	958.58	0.0001	significant
A	8.17	1	8.17	95.97	0.0023	
B	395.28	1	395.28	4645.31	0.0001	
Residual	0.26	3	0.085	-	-	
Core Total	408.1	8	-	-	-	

Optimization and Analysis of Data by Design Expert Software

The 3^2 full factorial design was selected to study the effect of independent variables, amount of HPMC K4M (A) and amount of SSG (B) on dependent variables lag time and %DR. A statistical model incorporating interactive and polynomial terms was utilized to evaluate the responses. The optimized batch was suggested by this software depending on the required lag time and maximum % drug release. ANOVA for the dependent variables, lag time and % DR, was shown in Table 9 and 10 respectively. The coefficients of X_1 and X_2 were found to be significant at $p<0.05$, hence confirmed the significant effect of both the variables on the selected responses. ANOVA and Multiple regression analysis were done using Stat-Ease Design Expert 7.0.0 software.

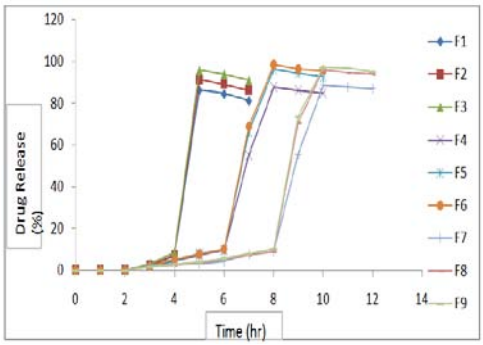

Fig. 5: % Drug released from PCTs

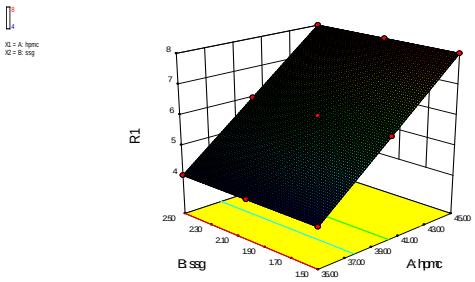

Fig. 6: 3D response surface graph for lag time

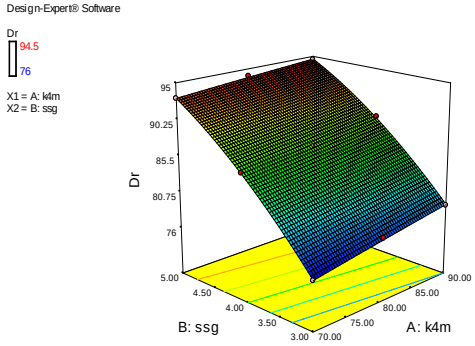

Fig. 7: 3D response surface graph for % DR

CONCLUSION

A chronotherapeutic dosage form was formulated by press coating technique. The lag time and time-controlled release behavior of Acebrophylline from press-coated tablets could be modulated by varying the concentration of polymer in outer coating layer and thickness of the compression coating. Formulations F4-F6 compression coated tablets achieve a burst release after 6 hr lag time. The dosages should be timed to ensure that the highest blood levels of the drug coincide with peak pain. For asthma the optimal time for an bronchodilators to be taken is after the evening meal. Considering this the preferable lag time would be of 6 hr. All the batches formulated showed a pulsatile release pattern of Acebrophylline which is suitable for chronotherapy of asthma.

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