ORIGINAL ARTICLE

Formulation and evaluation of press coated tablets of salbutamol sulphate for time controlled release

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The objective of the present study was to formulate and evaluate a press coated pulsatile drug delivery system of salbutamol sulphate in order to attain a time controlled release for treatment of nocturnal asthma. The core was prepared by direct compression, while press coating technique was used in coating the outer layer there by preparing a press coated tablet. The immediate release core formulations comprised of salbutamol sulphate and disintegrants like crospovidone, croscarmellose sodium and sodium starch glycolate in different ratios with the drug. The outer coat formulations were prepared using a hydrophilic (HPMC) and hydrophobic (EC) polymer of similar viscosity. The polymers were reviewed individually for their influence on lag time further obtaining the lag time using polymer combinations were assessed by employing central composite design. All the preliminary trials were evaluated for various post compression parameters along with the dissolution study that was performed using USP paddle method at 50 rpm in 0.1 N HCl and phosphate buffer pH 6.8. The formulation containing 300 mg of EC N50 and 75-100 mg of HPMC E50 may be regarded as the minimum quantity required in outer press coat so as to attain a predetermined lag time of 6 h.

Key words: *Central composite design, ethylcellulose, hydroxypropyl methylcellulose, press coat, salbutamol sulphate, time controlled release*

INTRODUCTION

In the field of modified release, there has been a growing interest in time specific oral pulsatile delivery, which generally refers to the preprogramed release of drugs following the administration to achieve improved therapeutic efficacy.[1] This time specific (delayed/ pulsatile) release pattern can help in treatment of a disease influenced by biological rhythms as it takes into consideration of such rhythmic variation. A controlled release drug delivery developed, majorly aims at maintaining constant drug concentration in the biological system with the assumption that this will result in optimal therapeutic effects.[2] These plasma drug levels may be unwanted and undesirable when there is a diurnal variation and also need of highest drug levels at the point of peak symptoms appearance. For instance, incidence of asthmatic attacks increases during the early morning hours with a maximum at 4 a.m. Therefore a therapeutic scheme taking into account of diurnal variation should be more effective. This could be realized by a pulsatile dosage form, taken at bedtime with a programed drug release in the early morning hours.[3]

The pulsatile drug delivery system (PDDS) is intended to deliver a rapid, or transient, and quantified medication release after a predetermined off-release period (lag time).[4,5] Lately, drug delivery systems based on press-coated functional layers have been proposed for delayed, pulsatile, and programable release of different drugs in a single tablet. Recently, the application of this technology was investigated in the development of timed release dosage forms, time clock systems, and delayed-release tablets.[6-8] The press coating technique

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Access this article online

Quick Response Code:

Website: www.asiapharmaceutics.info

DOI: 10.4103/0973-8398.139179

offers advantage of modification of the drug release profile. In general, a press-coated tablet consists of an inner core tablet and an outer coating shell. The selection of outer layer materials has a significant impact on the performance of the tablet.[9]

In nocturnal asthma the symptoms are aggravated in early morning hours. Among the antiasthmatic drugs utilized, the dominant β_2 stimulants utilized in nocturnal asthma are salbutamol, terbutaline and fenoterol. Best studied are salbutamol and terbutaline. They have a fairly selective β_2 stimulating effect; tachycardia is the dose-limiting side effect in only a few per cent of the patients.[10] Salbutamol sulphate has site-specific absorption in stomach and upper part of the small intestine.[3] The objective of the present study is to formulate and evaluate the press coated tablets of salbutamol sulphate for time controlled release of the drug. The study is carried out using a hydrophilic and a hydrophobic polymer and furthermore to assess their influence over lag time. Therefore, efforts are made to develop a chronomodulated drug delivery system for the treatment of nocturnal asthma.

MATERIALS AND METHODS

Materials

Salbutamol sulphate, colloidal silicon dioxide (Aerosil), croscarmellose sodium, crospovidone, magnesium stearate, microcrystalline cellulose (pH 101), sodium starch glycolate obtained from Bright Scientifics, Hyderabad were used to formulate the core tablet. The outer time controlled release coat was prepared using Ethylcellulose (EC N 50, Bright Scientifics Hyderabad), Hydroxypropyl methylcellulose (HPMC E50, Yarrow Chem Products, Mumbai), Lactose (Bright Scientifics Hyderabad), magnesium stearate and talc.

Methods

Drug excipient compatibility study

The drug and excipient compatibility was observed using Fourier Transform - Infra Red spectroscopy (FT-IR). The FT-IR spectra obtained from Bruker FT-IR Germany (Alpha T) was utilized in determining any possible interaction between the pure drug and the excipients in the solid state. The potassium bromide pellets were prepared on KBr press by grounding the solid powder sample with 100 times the quantity of KBr in a mortar. The finely grounded powder was then introduced into a stainless steel die and was compressed between polished steel anvils at a pressure of about 8 t/in^2. The spectra were recorded over the wave number of 8000 to 400 cm^{-1}.

Differential scanning calorimetry

Salbutamol sulphate and excipients were passed through sieve#60 and mixed properly. Accurately weighed 5 mg of salbutamol sulphate alone and mixture of salbutamol sulphate and excipients were transferred into the pierced DSC aluminum pan and scanned at the temperature range of 25-300°C at heating rate of 20°C/min. The differential thermograms obtained were compared for any changes in melting point between salbutamol sulphate and with that of the drug and excipient mixture.

Preparation of press coated tablet of salbutamol sulphate

The development of press coated tablet was carried out in two steps. Firstly, the immediate release core tablet is formulated using various disintegrants by employing direct compression process. Core tablet formulations will then be compared and optimized based on their dissolution profile. The optimized core tablet will then be set for press coating and further optimized.

Formulation of core tablet of salbutamol sulphate

The immediate release core tablets of salbutamol sulphate were formulated by incorporating disintegrants like croscarmellose sodium, crospovidone and sodium starch glycolate in appropriate ratios with the drug. Furthermore, microcrystalline cellulose was utilized as diluent whereas aerosil and magnesium stearate functioned as glidant and lubricant respectively. The ingredient were weighed accurately and transferred to a clean mortar and pestle except magnesium stearate and aerosil. The powder blend was mixed for 10 min after which magnesium stearate and aerosil were added to the blend and the mixing was continued for another 5 minutes. After obtaining a uniform blend, it was passed through sieve#60 and was prepared for direct compression. The compression of the powder blend was carried out using multi station punching machine (KARNAVATI-RIMEK minipress II D) by employing concave punches of 6 mm diameter and adjusting thickness and hardness accordingly. The content of each tablet is listed in Table 1.

Formulation of press coated tablet using optimized core tablets of salbutamol sulphate

Hydroxypropyl methylcellulose E50 (HPMC E50) and Ethylcellulose N50 (EC N50) were used as time controlled release polymers in outer coating material of the press coated tablet. These polymers were individually tested for their influence over the lag time. After their individual assessment, combination of these polymers was optimized using the central composite design by employing Design expert (Version 7.0). A uniform blend of outer coating material containing the polymer and other excipients shown in Table 2 was prepared using mortar and pestle. After passing through sieve#60 the blend was used for press coating. The core tablets were subjected to press coating with 12 mm flat punches in manner as shown in Figure 1.

The process of press coating proceeds in following order as shown in Figure 1.

I. Prefilling half amounts of outer coating materials into the die
II. Core tablet is placed on the powder bed of outer coating material

Table 1: Formulation chart for core tablet

Core	C1	C2	C3	C4	C5	C6	C7	C8	C9
Drug	4.8	4.8	4.8	4.8	4.8	4.8	4.8	4.8	4.8
Crospovidone	4.8	9.6	14.4	-	-	-	-	-	-
Croscarmellose sodium	-	-	-	4.8	9.6	14.4	-	-	-
Sodium starch glycolate	-	-	-	-	-	-	4.8	9.6	14.4
Magnesium stearate	2	2	2	2	2	2	2	2	2
Aerosil	2	2	2	2	2	2	2	2	2
Microcrystalline cellulose	46.4	41.6	36.8	46.4	41.6	36.8	46.4	41.6	36.8
Total weight (mg)	60	60	60	60	60	60	60	60	60

Table 2: Formulation chart for outer coating material

Formulations	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10	F11
HPMC E50	150	200	250	-	-	-	-	150	100	200	75
EC N50	-	-	-	150	200	250	300	150	200	100	225
Magnesium stearate	5	5	5	5	5	5	5	5	5	5	5
Talc	5	5	5	5	5	5	5	5	5	5	5
Lactose	140	90	40	140	90	40	130	130	130	130	130
Core	60	60	60	60	60	60	60	60	60	60	60
Total weight (mg)	360	360	360	360	360	360	500	500	500	500	500

HPMC: Hydroxypropyl methylcellulose, EC: Ethylcellulose

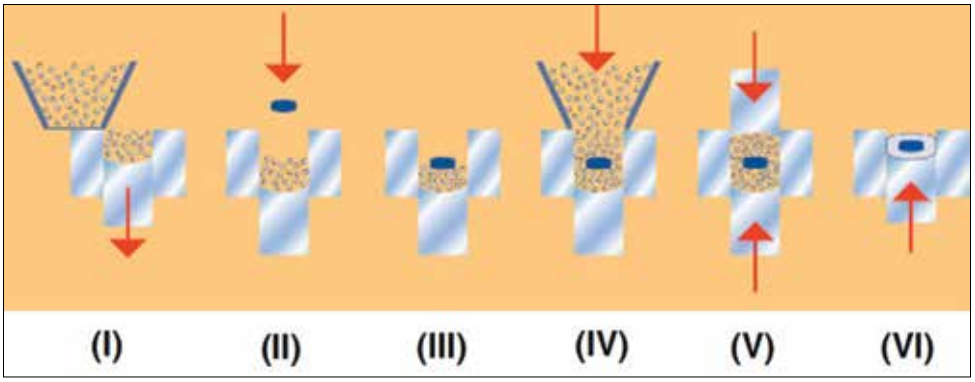

Figure 1: Process of press coating

III. Centering
IV. Filling the residual half amounts of outer coating material
V. Compression
VI. Ejection of press coated tablet from the die.

The core and final press coated tablets formulated were evaluated for various post compression parameters. After assessing the individual effect of both polymers on lag time an optimum range for both polymers was selected. A set of runs was produced using the central composite design (CCD) in order to optimize the press coated tablet and to obtain solutions corresponding to the desired lag time. Lactose was used as the only excipient which served the purpose of filler while formulating the runs. Therefore, two variables were evaluated at three levels by employing a face centered CCD which followed a response surface methodology. The details of the design executed can be obtained from [Figure 2].

Evaluation of core and press coated tablet

All the pre and post compression parameters were evaluated for both core and press coated tablet according to the official methods. The evaluated pre compression parameters were angle of repose, bulk and tapped density, compressibility index (Carr's index) and Hausner's ratio. The common post compression parameters evaluated for both core and press coated tablets were thickness, hardness and uniformity of weight. The core tablets were specifically evaluated for disintegration time and drug content (assay) whereas the press coated tablets was assessed for percentage friability. All the above methods were performed according to the pharmacopeial procedures and the post compression results are expressed as mean ± standard deviation.[11,12]

Dissolution study performed for core tablets

Drug dissolution rate was studied by using USP XXIII dissolution test (USP type-II Apparatus, Lab India DS 8000).

Study Type	Response Surface	**Runs**	9
Initial Design	Central Composite	**Blocks**	No Blocks
Design Model	Quadratic		

Factor	Name	Units	Type	Low Actual	High Actual	Low Coded	High Coded	Mean	Std. Dev.
A	HPMC E50	mg	Numeric	50.00	100.00	-1.000	1.000	75.000	20.412
B	EC N50	mg	Numeric	250.00	300.00	-1.000	1.000	275.000	20.412

Response	Name	Units	Obs	Analysis	Min	Max	Mean	Std. Dev.	Ratio	Trans	Model
Y1	LagTime	hrs	9	Polynomial	3	6	4.667	0.943	2	None	RLinear

Figure 2: Design summary

Samples of 5 ml were withdrawn from dissolution medium at predetermined intervals and replaced with same volume of fresh dissolution media. The samples were assayed for drug content by measuring the absorbance at 276 nm using UV-Visible spectrophotometer (Lab India UV 3000$^+$).

Details of parameters set
Paddle rpm : 50 rpm
Stirrer depth : 25 mm
Dissolution media : Phosphate buffer pH 6.8
Media volume : 900 ml
Media temperature : 37 ± 0.5°C
Sampling intervals : 1, 3, 5, 10, 15, 20, 30 and 45 min

Dissolution study performed for press coated tablets

The apparatus and procedure employed was similar to that of core tablets. The study was carried for 8 h with the parameters set up as below.

Details of parameters set
Paddle rpm : 50 rpm
Stirrer depth : 25 mm
Dissolution media : 0.1N HCl pH 1.2 for first 2 h, later on Phosphate buffer pH 6.8
Media volume : 900 ml.
Media temperature : 37 ± 0.5°C
Sampling intervals : 0.5, 1, 2, 3, 4, 5, 6 and 8 h

RESULTS AND DISCUSSION

Drug excipient compatibility

Drug and excipient compatibility was confirmed by comparing spectra of FTIR analysis of pure drug with that of various excipients used in the formulation. It was found that there was no chemical interaction between salbutamol sulphate and excipients used because there were no changes in the characteristic peaks of salbutamol sulphate in the IR spectra of mixture of the drug and excipients as compared to IR spectra of pure drug. This can be observed in Figure 3.

Differential scanning calorimetry

There were no major changes in glass transition temperature of salbutamol sulphate when DSC was performed along with the other excipients.

Evaluation of flow property

Core tablet blend

The flow properties of different core formulation blend are shown in the Table 4. The results obtained for angle of repose (θ) vary from 19.2^0-26.5^0 which fall within the official range for good flow i.e. <30^0. Therefore the blends have good flow property.

The bulk and tapped density of core tablet blend were from 0.55-0.60 gm/cc and 0.60-0.68 gm/cc respectively. Carr's index calculated showed to vary from 7.2-14.7% indicating that the blend has a good flow property. Whereas Hausner's ratio analyzed is in 1.07-1.17 range representing a good flow.

Press coating material blend

The flow properties of different outer coating material formulation are shown in the Table 5. The results for angle of repose (θ) obtained was found to vary from 23.2^0-31.3^0 which indicates the coating material has fairly good flow property and can be used for press coating. The bulk and tapped density of outer coating material blend were from 0.43-0.50 gm/cc and 0.48-0.58 gm/cc respectively. Carr's index calculated showed to vary from 9-14.5% indicating that the blend has an excellent flow property. Whereas Hausner's ratio analyzed is in 1.10-1.17 range representing a good flow.

Evaluation of core tablets

All the evaluated parameters performed for core tablets are shown in the Table 6. The hardness of core tablets in each formulation batch ranges from 1.5-2 kg/cm^2, therefore ensuring appropriate strength. The thickness observed was 2.5 mm and is even for all batches. All the (60 mg) tablets selected from various batches passed uniformity of weight test prescribed in IP. The individual weight of different batch tablets was within the official limits (±10%) of % deviation

IR spectra	Peak1	Peak2	Peak3	Peak4	Peak5	Peak6	Peak7	Peak8	Peak9
Pure drug	2981.63	1615.88	1507.40	1439.12	1244.38	1113.44	1030.45	838.88	618.60
Core	2978.85	1614.23	1506.98	1439.97	1245.05	1110.95	1029.72	838.46	618.45
Press coated tablet	2978.36	1617.98	1502.65	1439.63	1244.77	1114.53	1031.33	838.95	618.67

Figure 3: Peaks observed in pure drug and optimized formulations

Table 3: Interpretation of characteristic peaks of salbutamol sulphate IR spectra

Peak observed (cm^{-1})	Wavenumber range (cm^{-1})	Characteristic IR bands assignment
2981.63	3000-2800 (2960)	Methyl symmetric C-H stretching of (alkane) aliphatic hydrocarbon
1615.88	1680-1600	C=C stretching of (alkene) aliphatic hydrocarbon
	1660-1610	N-H bending of primary amines
1507.40	1510-1450	C=C-C[a] for aromatic ring stretch
1439.12	1600-1430	C=C stretching of aromatic compounds
1244.38	1275-1000	In-plane C-H bending of aromatic compounds
1113.44	1130-1080	Sulphate ion (SO_4^{2-})
1030.45	1060-1020	S=O stretching of sulphur compounds
	1090-1020	Primary amine C-N stretching
	1055-1000	Cyclohexane ring vibrations
838.88	860-800	1, 4-Disubstitution (para) of aromatic ring
618.60	680-610	Sulphate ion (SO_4^{2-})

IR: Infra red

Table 4: Flow properties of core tablet blend

Core formulation	Angle of repose (θ)	Bulk density (gm/cc)	Tapped density (gm/cc)	Carr's index (%)	Hausner's ratio
C1	21.8	0.57	0.66	13.6	1.15
C2	22.7	0.55	0.62	12	1.13
C3	26.5	0.58	0.62	7.2	1.07
C4	19.2	0.60	0.68	11.7	1.13
C5	24.2	0.58	0.64	9.4	1.10
C6	25.6	0.55	0.60	8.3	1.09
C7	20.3	0.58	0.68	14.7	1.17
C8	22.7	0.57	0.64	10.9	1.12
C9	25.1	0.57	0.62	8.8	1.09

Table 5: Flow property of press coating material blend

Formulations	Angle of repose (θ)	Bulk density (gm/cc)	Tapped density (gm/cc)	Carr's index (%)	Hausner's ratio
F1	31.3	0.47	0.52	9.6	1.10
F2	29.2	0.45	0.52	13.4	1.15
F3	26.5	0.47	0.55	14.5	1.17
F4	25.6	0.50	0.58	13.7	1.16
F5	30.9	0.47	0.55	14.5	1.17
F6	30.1	0.45	0.50	10	1.11
F7	23.2	0.50	0.55	9	1.10
F8	26.1	0.45	0.52	13.4	1.15
F9	27	0.43	0.50	14	1.16
F10	24.7	0.43	0.48	10.4	1.11
F11	27.9	0.45	0.51	11.7	1.13

Table 6: Parameters evaluated for core tablets

Core	Hardness (Kg/cm²)	Thickness (mm)	Uniformity of wt (%)	Disintegration (sec)	Drug content (%)
C1	1.6±0.22	2.5	59.8±1.3	119.6±0.9	100.2±1.6
C2	1.9±0.22	2.5	60.2±1.1	99.6±1.14	98.5±2.5
C3	2±0.00	2.5	60.1±1.2	80.2±0.83	99.5±3.1
C4	1.9±0.22	2.5	60.1±0.8	109.6±0.5	96.4±3.5
C5	1.5±0.00	2.5	60.1±1.5	119.6±1.1	95.3±3.8
C6	1.9±0.22	2.5	59.7±1.1	99.6±1.14	96.5±3.4
C7	2±0.00	2.5	60.3±1.4	100.4±0.5	96.7±2.9
C8	2±0.00	2.5	60.8±1.8	90.4±1.14	99.6±2.9
C9	2±0.00	2.5	60±1.1	90.8±0.83	98.9±2.3

from average weight. The disintegration time of core tablet with different disintegrants was in range of 80.2 ± 0.83 to 119.6 ± 1.1 sec. The least disintegration time was provided by core tablet formulation C3. The % drug content of all the core tablet formulation ranged from 95.3 ± 3.8% to 100.2 ± 1.6% all within the acceptable limits.

Dissolution study of core tablets

Based on the results obtained from the dissolution study of core tablets in phosphate buffer (pH 6.8) shown in Table 7, the core tablet formulation C3 formulated with crospovidone in ratio of 3:1 with drug or 24% (w/w) of total tablet weight provided a burst release of 33% within 1st min and therefore was selected to continue with press coating.

Evaluation of press coated tablets

All the evaluated parameters result obtained from different formulations of press coated tablet is shown in Table 8. Hardness of various press coated tablet were in range of 5 ± 0.0-5.9 ± 0.22 kg/cm². The thickness observed was 3 mm and 4 mm for F1-F6 and F7-F11 batches respectively. The press coated tablets selected from different formulation passed the uniformity of weight test prescribed in IP. The individual tablet weights when compared with average weight were within the official limit (±5%) of % deviation. The friability of press coated tablet formulations were within the acceptable limits and ranged from 0.61-1%.

Dissolution study of press coated tablets

The results acquired from the 8 h dissolution study of press coated tablets are shown in Table 9. Initially tablets were subjected to dissolution in 0.1 N HCl (pH 1.2) for 2 h and after that the medium was changed to phosphate buffer (pH 6.8). The time interval when 10% or more amount of salbutamol sulphate was detected in dissolution media was considered as end of lag time. Formulations F1, F2 and F3 were formulated with only Hydroxypropyl methylcellulose E50 (HPMC E50) so as to assess its influence over lag time. All the above three formulations did not show any significant lag time or hindrance to drug release, therefore HPMC E50 alone cannot provide the desired lag time. Formulations F4, F5, F6 and F7 were formulated using Ethylcellulose N50 (EC N50) as the only polymer in order to evaluate its effect on lag time. Among the formulations, F4 and F5 did not show any lag time whereas F6 and F7 provided a lag time of 1 hr and 2 hr respectively.

Table 7: Dissolution profile of core tablets

T (min)	C1	C2	C3	C4	C5	C6	C7	C8	C9
0	0	0	0	0	0	0	0	0	0
1	5	9	33	13	0	5	7	3.4	20
3	41	86	86	39	33	69	45	47	88
5	92	86	94	47	60	77	64	69	96
10	98	94	100	67	67	90	81	79	98
15	100	94	102	77	73	94	83	84	100
20	101	96	103	77	75	81	77	84	102
30	103	98	103	79	81	98	77	96	105
45	103	102	104	81	79	96	77	105	103

Table 8: Parameters evaluated for press coated tablets

Formulation	Hardness (Kg/cm²)	Thickness (mm)	Uniformity of weight (%)	Friability (%)
F1	5±0.00	3	360±2.9	0.80
F2	5.1±0.22	3	360.6±2.2	0.83
F3	5.5±0.22	3	360.3±2.3	0.97
F4	5±0.00	3	360.9±2.6	0.61
F5	5±0.22	3	360.2±1.7	0.86
F6	5±0.00	3	361±3.0	0.91
F7	5.9±0.22	4	500.4±1.8	0.82
F8	5.6±0.22	4	500.2±2.2	0.86
F9	5±0.00	4	499.8±2.4	1
F10	5±0.00	4	500.7±2.4	0.90
F11	5±0.00	4	499.9±1.7	0.98

Table 9: Dissolution profile of press coated tablets

T (hrs)	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10	F11
0	0	0	0	0	0	0	0	0	0	0	0
0.5	101	18.6	11	64	81	1.5	3.4	5	0	82	3.4
1	103	103	104	105	104	0	0	77	75	103	16
2	96	104	105	104	107	99	3.4	99	101	104	82
3	81	104	103	102	100	103	100	99	106	100	98
4	78	105	100	101	104	100	102	105	106	102	101
5	79	104	99	99	104	100	98	102	105	103	100
6	80	102	96	105	103	101	101	104	102	101	98
8	88	100	91	104	106	101	96	104	106	91	96

Combination of HPMC E50 and EC N50 in the ratio of 1:1, 1:2, 2:1 and 1:3 [in 68.2% ($^{w}/_{w}$) of the total weight of press coating material i.e. 440 mg] was utilized to formulate F8, F9, F10 and F11 respectively. Among these formulations F10 did not show any defined lag time since it had more amount of HPMC E50 when compared to EC N50 (2:1). Therefore the press coat could not offer enough mechanical strength for the growing swelling energy produced by crospovidone in the tablet core. This cause may also be responsible for failure of formulations F1, F2 and F3 in creating a characteristic lag time. While F8, F9, and F11 managed to give a pulsatile pattern, with a lag time of 0.5 h which is not sufficient.

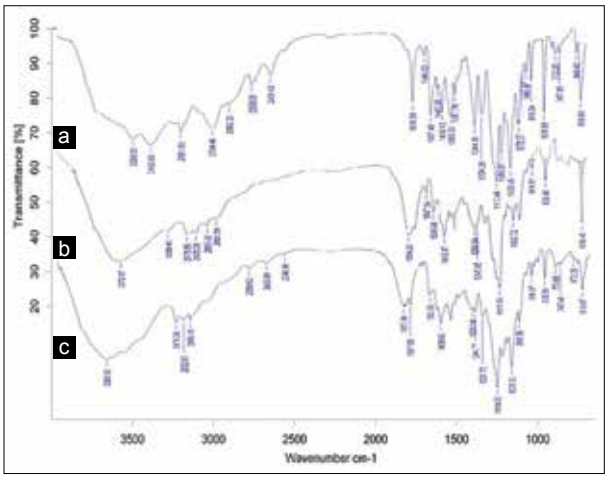

Figure 4: FT-IR spectra of (a) pure drug, (b) optimized core and (c) press coated tablet formulation

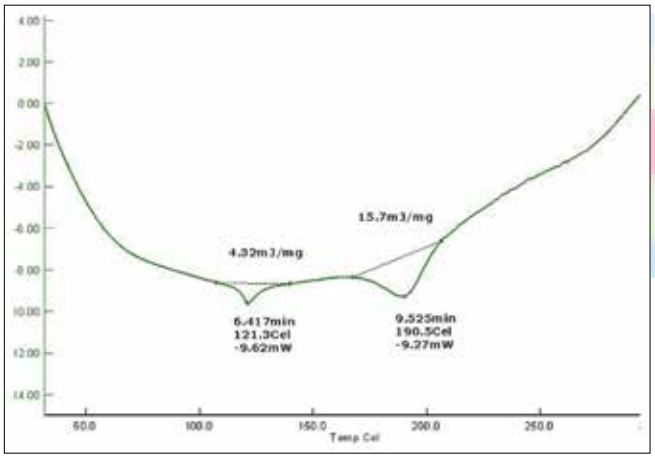

Figure 5: DSC plot of pure salbutamol sulphate

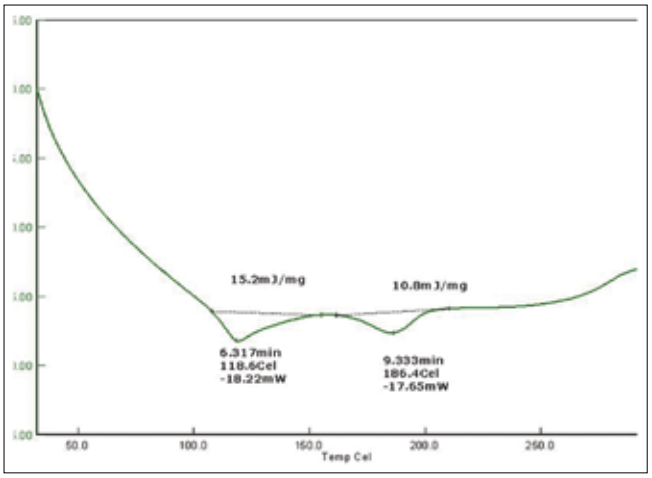

Figure 6: DSC plot of salbutamol sulphate and excipient mixture

Among the formulation F1-F11, F7 alone offered a lag time of 2 h which was formulated with 300 mg of EC N50 in press coating material. The press coating material constitutes 88% of the tablet weight (500 mg). The dissolution study of these formulations was performed in order to obtain an optimum range of both erodible (HPMC E50) and rupturable (EC N50) polymer. This range was utilized in execution of central composite design to attain an optimized formulation.

Central composite design

HPMC E50 and EC N50 are the two independent variables whose effect was assessed on the dependent variable or response i.e. Lag time. The actual value of these independent variables can be studied in the design summary shown in the Figure 2. A face centered central composite design was carried out in response surface methodology which provided 9 runs as showed in the Figure 9. The dissolution study was performed for all the runs and the results are presented in Table 10.

All the runs from R1-R9 provided lag times in the range of 3-6 h that could be useful for chronotherapy purpose. The minimum lag time of 3 h was observed in case of R7 which was formulated with 75 mg of HPMC E50 and 250 mg of EC N50 in press coating layer. The lag time of 6hrs was noticed in case of R4 and R9 formulations which is the desired lag time in the present study. EC N50 weighing 300 mg was utilized in formulating both R4 and R9 along with 75 mg and 100 mg of HPMC E50 respectively in press coating layer.

ANOVA

Analysis of variance (ANOVA) showed that values of "Prob > F" less than 0.0500 indicate model terms are significant. In this case EC N50 has a $P = 0.0025$ indicating

Table 10: Dissolution profile of 9 runs

Time (hrs)	Run 1	Run 2	Run 3	Run 4	Run 5	Run 6	Run 7	Run 8	Run 9
0	0	0	0	0	0	0	0	0	0
0.5	0	3	0	1.5	0	0	0	1.5	0
1	1.5	0	5	0	5	0	0	0	0
2	1.5	0	3	3	0	0	0	3	0
3	0	0	0	0	0	0	51	0	0
4	0	0	63	0	92	79	90	0	0
5	85	70	92	0	92	92	94	96	0
6	103	92	100	102	96	100	103	106	97
8	105	102	103	104	101	105	100	104	102

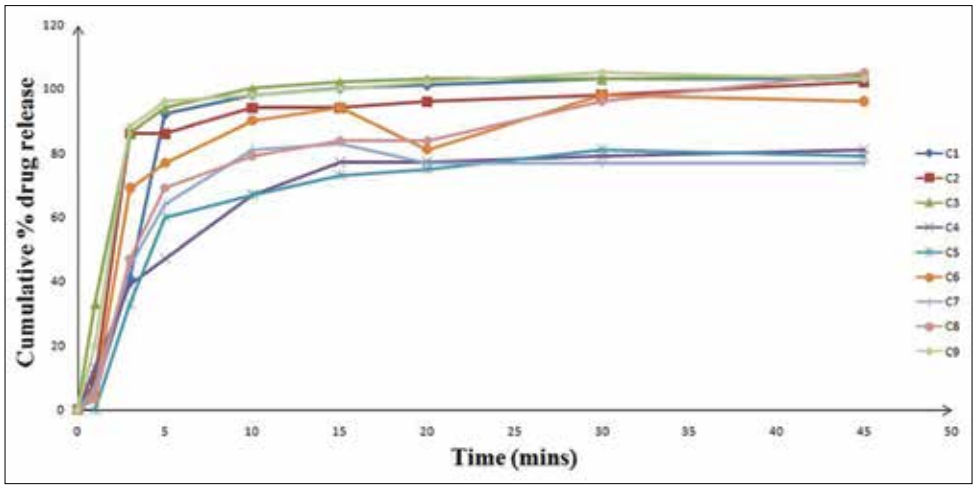

Figure 7: Dissolution profile of core tablets with different disintegrant

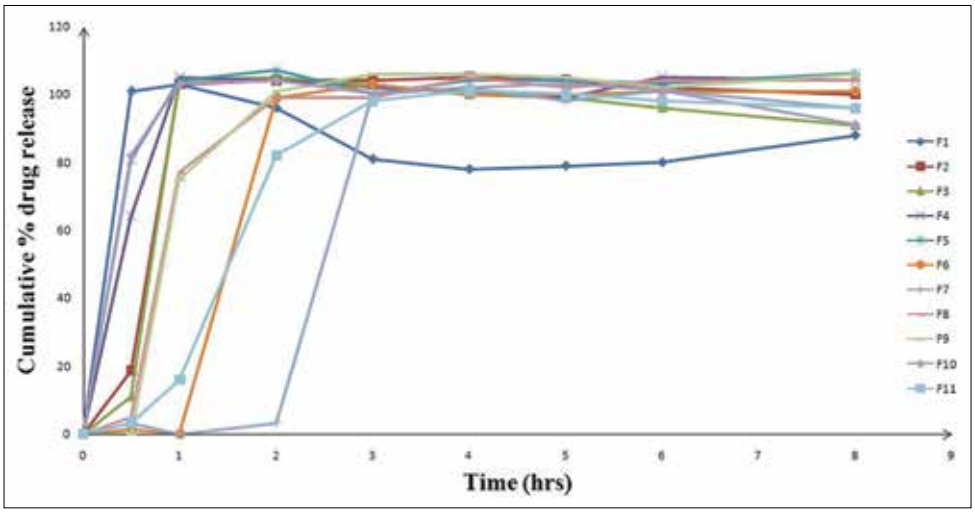

Figure 8: Dissolution profile of F1-F11 press coated tablet formulations

Run	Block	Factor 1 A:HPMC E50 mg	Factor 2 B:EC N50 mg	Response 1 LagTime hrs
1	Block 1	50.00	300.00	5
2	Block 1	100.00	275.00	5
3	Block 1	50.00	250.00	4
4	Block 1	75.00	300.00	6
5	Block 1	100.00	250.00	4
6	Block 1	50.00	275.00	4
7	Block 1	75.00	250.00	3
8	Block 1	75.00	275.00	5
9	Block 1	100.00	300.00	6

Figure 9: Runs created from central composite design

a significant model term. The value of R-squared which should be close to one is measure of the amount of variation around the mean. The Predicted R-squared is in reasonable agreement with the Adjusted R-squared. Adequate precision measuring signal to noise ratio is below 4. All these values are shown in Figure 11.

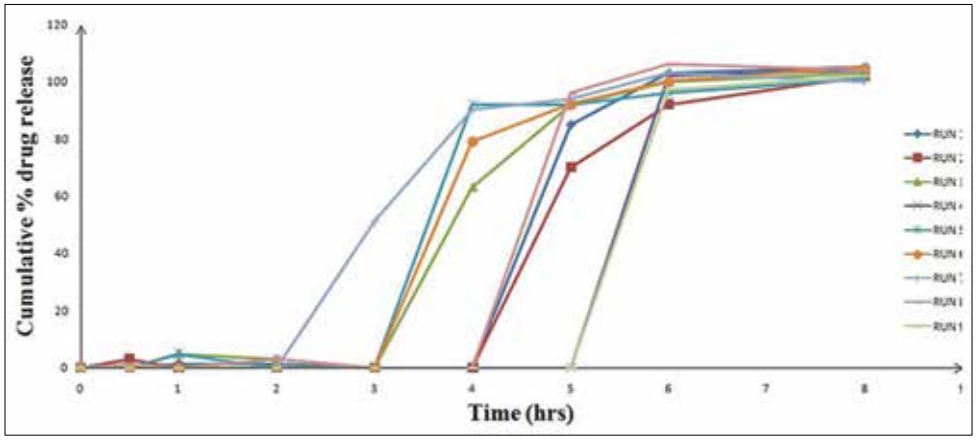

Figure 10: Dissolution profile of RUN 1- RUN 9 press coated tablet formulations

Final Equation in Terms of Actual Factors:

$$\text{Lag Time} = -6.33333 + 0.04000 * \text{EC N50}$$

Diagnostics

The diagnostic plot predicted versus actual, provide a good correlation between the experimental and predicted values. The plot indicates that the observed responses were very close to the predicted values.

Model graph

The two-dimensional contour plots and 3-D response surface plots shown in Figures 13 and 14 respectively are very useful to study the interaction effects of the factors on the response. These types of plots help in studying effects of two factors on the response at one time. The plots exhibit a linear relationship of response with independent variable EC N50. The lag time was found to increases proportionally with increasing amount of EC N50. Whereas increase in amount of HPMC E50 did not have any optimization effect over lag time instead it had a constant outcome throughout the experiment. But, HPMC E50 was essential in the formulation along with EC N50 in order to attain the desired response as it decreased water permeability of press coat.

Studies conducted previously to develop time controlled release dosage form using salbutamol sulphate, emphasized that increasing concentration of a hydrophilic swelling polymer like HPMC cause decrease in lag time, as it facilitated the entry of dissolution medium into the core.[13] Therefore, concentration of HPMC E50 necessary to delay the burst release and avoiding the drug diffusion to the dissolution medium was used. Simultaneously as per studies performed, the use of hydrophobic polymer like EC would help in retaining the makeup of the press coat.[14] Hence the amalgamation of Hydroxypropyl methylcellulose with Ethylcellulose N50 is necessary in maintaining the required integrity and pulsatile pattern of the developed time controlled pulsatile dosage form.

R-Squared	0.7500
Adj R-Squared	0.7143
Pred R-Squared	0.5750
Adeq Precision	7.937

Figure 11: Values of predicted and adjusted R-squared

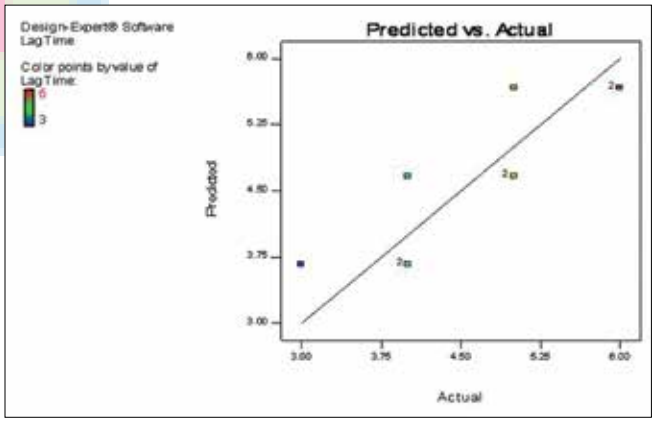

Figure 12: Predicted vs. actual plot

The properties of EC N50 such as high tensile strength, pH insensitivity, flexibility over wide range of temperatures and high softening point (156 ^{0}C) along with suitable gel temperature (56 ^{0}C) and molecular aggregation relative to viscosity of HPMC E50 causing negligible drug diffusion will probably be the reason in achieving the desired lag time. Further the union of the polymers can be exploited in producing varied and wide ranges of lag time in a pulsatile system.

The optimum formulation was selected based on the criteria of attaining the maximum value of lag time. Upon considering various responses, the formulation composition with 300 mg of

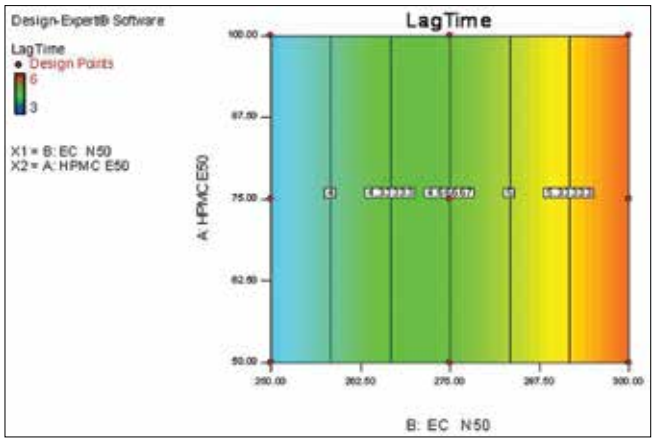

Figure 13: Contour plot

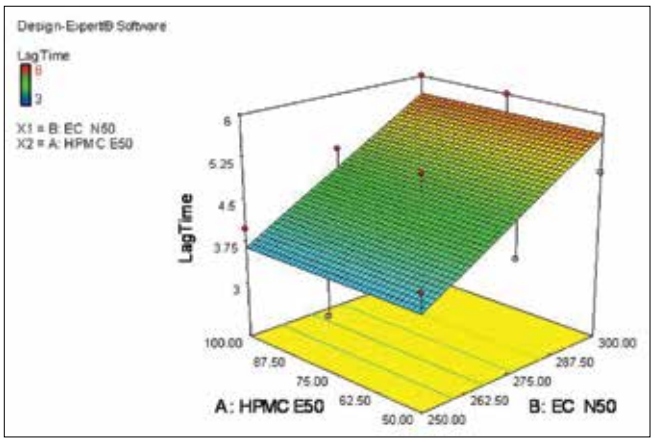

Figure 14: 3D plot

EC N50 and 75-100 mg of HPMC E50 in the press coating layer of 500 mg press coated tablet was found to satisfy the minimum basic requirement in an optimized formulation. Optimization results presented 27 solutions with respect to the lag time 5.6 h which can be selected based on feasibility evaluation.

CONCLUSION

From the present study it could be concluded that EC N50 serves as a potential candidate in the formulating a time controlled release drug delivery systems with a defined lag time. Additionally, EC N50 should be used along with HPMC E50 in order to attain reproducible result, since EC N50 individually can offer lag time of 2 h only.The amount and composition of EC N50 and HPMC E50 used should be in appropriate proportion to obtain preferred lag time. Polymers in 1:1 ratio may not yield the required result. Quantity of HPMC E50 used decides the overall lag time, as more amount of HPMC E50 might increase the permeability of the press coat, thereby shortening lag time. Furthermore, increase in proportion of EC N50 enhances lag time by providing necessary strength and support to the outer press coat layer.

ACKNOWLEDGEMENTS

The corresponding author would like to thank Mr. Mohd Moinuddin, Assistant Professor, Department of Pharmaceutical Analysis, C.M.R College of Pharmacy and Dr. Ramesh Gannu, Deputy Manager at AET (Alfred E Tiefenbacher) Laboratories Pvt. Ltd. who helped greatly in completion of the project work.

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How to cite this article: Wasimul Hasan MD, Someshwar K, Chaitanya P, Mohd AB, Pratyusha A, Rao VM. Formulation and evaluation of press coated tablets of salbutamol sulphate for time controlled release. Asian J Pharm 2014;8:161-70.

Source of Support: Nil. **Conflict of Interest:** None declared.