International Journal of Pharmaceutical Science and Research
ISSN: 2455-4685, Impact Factor: RJIF 5.28
www.pharmacyjournal.net
Volume 1; Issue 5; July 2016; Page No. 21-29

Formulation and evaluation of pulsatile drug delivery system

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Abstract
The present work deals with design and evaluation of oral site-specific, pulsatile drug delivery chonopharmaceutical 'Tablet in Capsule' system containing Salbutamol Sulphate (SBS), as model drug. It can be targeted to colon in a pH and time dependent manner, to modulate the drug level in synchony with the circadian rhythm of nocturnal asthma. The core tablets of SBS were formulated using wet granulation method with a superdisintegrant. Eudragit S100 and Eudragit L100 were used as pH dependent polymers for coating the core tablet which was filled in to the capsule. The ratio of Eudragit S100 and Eudragit L100 on *In-vitro* drug release and the coating level was optimized using 3^2 full factorial designs. Dissolution studies of 'Tablet-in-Capsule' device in media with different pH have been carried out. The lag time prior to drug release was highly affected by the coating level. The level of coating and the ratio of polymer has significant role on drug release behaviours. The gamma scintigraphic study pointed out the capability of the system to release the drug in lower parts of gastro intestinal tract after a programmed lag time for nocturnal asthma.

Keywords: Chronopharmaceutical, Circadian rhythm, Scintigraphic

1. Introduction
Oral controlled drug delivery systems represent the most popular form of controlled drug delivery systems for the obvious advantages of oral route of drug administration. Such systems release the drug with constant or variable release rates. These dosage forms offer many advantages, such as nearly constant drug level at the site of action, prevention of peak-valley fluctuations, reduction in dosage of drug, reduced dosage frequency, avoidance of side effects, and improved patient compliance.

However, there are certain conditions such as release pattern is not suitable [1, 3]. These conditions, demands release of drug after a lag time. In other words, it is required that the drug should not be released at all during the initial phase of dosage forms [4]. Such as release pattern is known as pulsatile release [5]. A pulsatile drug delivery system is characterized by a lag time that is an interval of no drug release followed by rapid drug release. The first pulsed delivery formulation that released the active substance at a precisely defined time point was developed in the early 1990s. In this context, the aim of the research was to achieve a so-called sigmoidal release pattern. The characteristic feature of the formulation was a defined lag time followed by a drug pulse with the enclosed active quantity being released at once. Thus, the major challenge in the development of pulsatile drug delivery system is to achieve a rapid drug release after the lag time [6, 9]. In chonopharmacotherapy (timed drug therapy) drug administration is synchonized with biological rhythms to produce maximal therapeutic effect and minimum harm for the patient. By basing drug delivery on circadian patterns of diseases, drug effect can be optimized and side effects can be reduced [10, 14]. If symptoms occur at daytime a conventional dosage form can be administered just prior the symptoms are worsening. If symptoms of a disease became worse during the night or in the early morning, the timing of drug administration and nature of the drug delivery system need careful consideration. Control release systems for 12 or 24 h drug release are not suitable for diseases, which follow circadian variation. In that condition there is requirement for pulsatile drug delivery system. Many body functions that follow circadian rhythm. A number of hormones like rennin, aldosterone, and cortisol show daily fluctuations in their blood levels [15, 18]. Circadian effects are also observed in case of pH and acid secretion in stomach, gastric emptying, and gastro-intestinal blood transfusion. Diseases like bronchial asthma, myocardial infarction, angina pectoris, rheumatic disease, ulcer, and hypertension display time dependence.

2. Preparation of core tablets
Required amount (70 g batch size) of SBS, lactose and starch were passed though sieve No. 40 prior to wet granulation and mixed uniformly in a planetary mixer. PVPK-30 was dissolved in required quantity of water. The starch paste was prepared by dispersing power starch in boiling water and mixed thoroughly with PVPK-30 solution (PVPK-30 and starch as binders) and then granulated. The granules so obtained were dried at 60 °C for 2 h in the tray drier. Dried granules were passed though 20 number sieve and the fines were separated using 40 number sieve to obtain 20-40 mesh number granules. Sodium starch glycolate (SSG) (2mg) was added to obtain a fast disintegrating and Aerosil were passed through 40 # sieve and mixed with dried granules and lubricated with magnesium stearate. The contents were compressed into tablets. The composition of core tablets is given in Table 1.

Table 1: Composition of first (T1) and second (T2) pulse tablets of SBS

Ingredients	Quantity (mg/tablet) (T1)	Quantity (mg/tablet) (T2)
Salbutamol sulphate	2.4	4.8
Lactose	35.4	33
Starch (intragranular)	25.2	25.2
Starch (binder solution)	3.5	3.5
PVP-k30 (binder solution)	0.5	0.5
Magnesium stearate	1	1
Aerosil	1	1
sodium starch glycolate	1	2
Total weight	70	70

3. Preparation of coating solution

Coating solution was made using different ratios of Eudragit L100 and Eudragit S100. Required quantity of polymers were dissolved in mixture of solvents and stirred on magnetic stirrer to get homogeneous coating solution. Diethyl phthalate was added to above solution as plasticizer (1% w/v), and homogeneous solution coating have been carried out on tablets (Table 2). Three formulations for each batch were formulated by varying the weight gain on tablet upon coating with Eudragit S100 alone and in combination of Eudragit S100 and Eudragit L100 (Figure 1).

Table 2: Composition of coating solution

Ingredients (gm)	Eudragit S100			Eudragit S100 + Eudragit L100		
	F1	F2	F3	F4	F5	F6
Eudragit L100	-	-	-	15	15	15
Eudragit S100	25	25	25	15	15	15
Diethyl Pthalate	3	3	3	3	3	3
Acetone	250	250	250	250	250	250
Isopropyl Alcohol	250	250	250	250	250	250
% coating	8	10	12	8	10	12

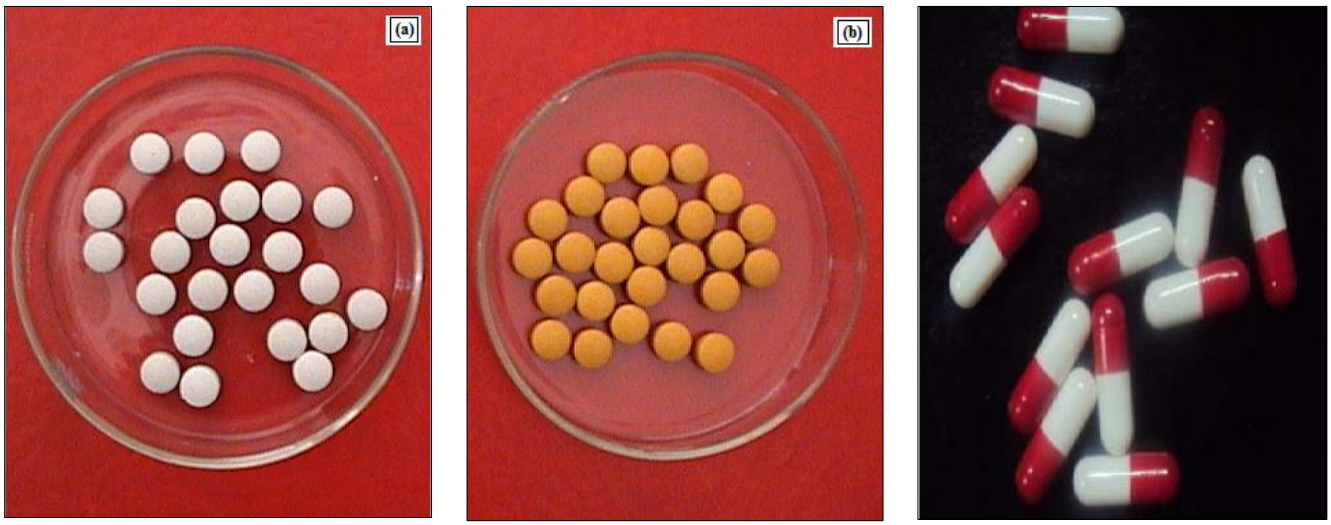

Fig 1: Core tablets of (a) non coated, (b) Coated formulation and (c) granules filled in capsule

4. Characterization

(a) Determination of micromeritic properties of prepared tablets

Both first (T1) and second (T2) pulse tablets were evaluated for shape, thickness, hardness, friability, weight variation, tablet dosage form assay and *in vitro* disintegration time and the measured values were given Table 3. The test results were well within the Indian Pharmacopoeia standard.

Table 3: Physical properties of tablet formulations

Properties	T1	T2
Uniformity of thickness (mm)	2.8 ± 0.1	2.8 ± 0.1
Weight variation (mg)	70.15 ± 0.64	70.60 ± 0.64
Hardness	3.0 ± 0.28	3.5 ± 0.5
Friability (%)	0.56	0.42
% Drug content	98.17 ± 0.33	98.56±0.30
Disintegration time (min)	2.5 ± 0.25	4.5 ± 0.25

*Standard deviation n = 3

(b) *In-vitro* drug release studies of coated tablets and factorial formulations

The *In-vitro d*rug release studies of coated tablets were carried out using a USP XXIII dissolution test apparatus initially for 2 h in 0.1 M HCl, as the average gastric emptying time is about 2 h. Then the dissolution medium was replaced with pH-5.5 phosphate buffer for 1h and then at pH 6.8 phosphate buffer for 2 h as the average small intestinal transit time is about 3 h. After 5 h, the dissolution medium was replaced with pH 7.4 phosphate buffer and tested for drug release up to complete drug release. At the end of the time period 10 ml of the samples were taken and analyzed for SBS content using UV spectrophotometer at 276 nm. Cumulative % drug release after 7 h was found to be 79.14%, 75.29% and 79.16% for formulation F1, F2 and F3 respectively. The release before completion of lag time was found to be 36.49%, 30.16% and 25.74% for formulations F1, F2 and F3 respectively. The results clearly indicates that, tablet coated with Eudragit S100 alone failed to achieve a lag time, required burst effect after completion of lag time and therefore release profile was not desirable, inorder to overcome this so further study was designed with a combination of Eudragit S100 and Eudragit L100 in different concentration. The cumulative percentage release of salbutamol sulphate as a function of time for all the formulations are shown in Table 3. The *In-vitro* release cumulative % drug release after 7 h was found to be 91.52%, 84.17% and 82.16% for formulation F4, F5 and F6 respectively (Table 4). The release before completion of lag time was found to be 36.49%, 37.19% and 33.33% for formulations F4, F5 and F6 respectively. The coating of tablets with Eudragit L100: Eudragit S100 showed the lag time of nearly 5 h before burst effect. From the result, the combination of Eudragit L100 and Eudragit S100 can be successfully utilized to create desire release profile similar to the targeted release profile in futher study. On the basis of the preliminary trials in the present investigation a 3^2 full factorial design was applied to study the effect of independent variables, i.e., ratio of Eudragit L100: Eudragit S100 (X1) and % coating of tablets (X2) on dependent variables like, % drug release at Q5 and Q6 (Table 5).

Table 4: *In-vitro* drug release of tablets coated with Eudragit S100 and Eudragit L100: Eudragit S100 formulations

Dissolution Medium	% Cumulative Drug Release						
	Eudragit S100			Eudragit S100 + Eudragit L100			
	Time (h)	F1	F2	F3	F4	F5	F6
0.1 N HCl	1	5.23	0	0	3.16	0	0
	2	12.43	8.19	5.26	14.16	9.46	8.75
pH 5.5 buffer	3	19.43	14.84	11.84	22.74	17.64	16.62
pH 6.8 buffer	4	27.36	22.16	19.63	28.75	28.16	25.84
	5	36.49	30.16	25.74	36.49	37.19	33.33
pH 7.4 buffer	6	68.23	62.16	60.36	82.16	82.16	84.15
	7	79.14	75.29	79.16	91.52	84.17	82.16

(c) Effect of Independent variables on dependent variables by 3^2 full factorial design of Salbutamol sulphate for Pulsatile Release

The factorial batches were prepared by using independent variables like ratio of Eudragit S100: Eudragit L100 and % coating and to check its effect on dependent variables like Q5 and Q6 which are tabulated in Table 5. Factorial batches of SBS for pulsatile release designed were evaluated for the *In-vitro* drug release and by its regression analysis. The cumulative percentage of SBS released for F7 to F15 formulations are given in Table 6. The effects of the individual polymer and combination of the polymers have been studied. The result of regression analysis showed that all the co-efficient bear a different sign, which indicates that both the independent variables shows significant effect on dependent variables. Drug release at 5^{th} h (Q5) gives correlation co-efficient 0.97736071. The P value for variable X1 and X2 were 0.002 and 0.0380 respectively ($P<0.05$), it indicates that both variables shows significant effect on drug release and combination cefficient was negative but the P value was not less than 0.05, which indicates that combination of independent variable does not show significant effect at 5^{th} h. Drug release at 6^{th} h (Q6) has less linearity compared to Q5 with correlation co-efficient 0.76426095. The P value for variable X_1 and X_2 were 0.56 and 0.18 ($P<0.05$), it indicate that both variables does not show significant effect on the drug release at 6 h.

Also the combination co-efficient was negative but the P value was not less than 0.05 so, we say that the combination of independent variable does not give the significant effect at 6h release. The co-efficient of X_1 and X_2 were negative indicating that when concentration of both the variable increases the drug release decreases. The Q_5 and Q_6 for F7 to F15 batches varied from 12.79 % to 33.33 % and 71 % to 87.77 % with correlation coefficient as 0.9773 and 0.7643 respectively. Formulation F15 showed the least drug release at Q_5 with only 12% but it failed to completely release the drug at second pulse of only 71%. Formulation F11 showed 17.23 % drug release at Q_5 but it showed maximum release at Q_6 with 87.77 %. The response surface plot was plotted against X variable, Y variable and Z variable. X variable taken as ratio of Eudragit S100:L100, Y variable taken as % coating and Z variable considered as drug release at 5^{th} and 6^{th} h as shown in Figures 2 and 3.

Table 5: Regression analysis values for pulsatile release of SBS tablets

Coefficients	b_0	b_1	b_2	b_{12}	b_{11}	b_{22}	R^2
Q5	22.28	-0..816	-0.0285	-0.0076	0.0491	0.0069	0.0977
Q6	77.99	0.0107	-0.0282	-0.0073	-0.0604	-0.0372	0.7642

*Standard deviation n = 3

Table 6: Formulation of Factorial batches

Ingredients (g)	F7	F8	F9	F10	F11	F12	F13	F14	F15
Eudragit L100	15	15	15	15	15	15	15	15	15
Eudragit S100	15	15	15	30	30	30	45	45	45
Diethyl phthalate	3	3	3	3	3	3	3	3	3
Acetone	250	250	250	250	250	250	250	250	250
Isopropyl alcohol	250	250	250	250	250	250	250	250	250
% Coating	12	15	18	12	15	18	12	15	18

Table 7: *In-vitro* drug release study of factorial batches (F7-F15)

Dissolution Medium (pH buffer)	Time (h)	% Cumulative Drug Release								
		F7	F8	F9	F10	F11	F12	F13	F14	F15
	0	0	0	0	0	0	0	0	0	0
0.1 N HCl	1	0	0	0	0	0	0	0	0	0
	2	8.75	7.98	5.16	2.35	0	0	0	0	0
pH 5.5	3	16.62	14.13	11.47	10.15	8.74	7.62	6.67	4.54	3.13
pH 6.8	4	25.84	24.10	21.03	18.46	12.86	11.98	11.01	8.58	5.89
	5	33.33	32.16	30.74	24.34	17.23	15.46	18.41	16.08	12.79
pH 7.4	6	85.55	82.4	75.65	79.12	87.77	79.16	71.42	68.23	66.49
	7	92.41	91.63	93.75	97.43	95.09	97.43	94.13	91.45	88.14

4.1 Optimization by using 3^2 full factorial designs

A 3^2 full factorial design method was employed to study the effect of independent variables, i.e., ratio of Eudragit L100: Eudragit S100 (X_1) and % coating (X_2) on dependent variables, % drug release at Q5 and Q6. A statistical model (see equation) incorporating interactive and polynomial terms were utilized to evaluate the responses (Tables 8 and 9)**.**

$$Y=b_0+b_1X_1+b_2X_2+b_{12}X_1X_2+b_{11}X_1^2+b_{22}X_2^2 \quad (1)$$

Where, Y is the dependent variables, b0 is the arithmetic mean response of the nine runs, and b_1 is the estimated coefficient for the factor X_1. The main effects (X_1 and X_2) represent the average result of changing one factor at a time from its low to high value. The interaction terms (X_1 and X_2) shows how the response changes when two factors are simultaneously changed. The polynomial terms (X_{12} and X_{22}) are included to investigate non-linearity. The results indicate that all the dependent variables are strongly dependent on the selected independent variables as they show a wide variation among the nine batches (F7 to F15). The fitted equations (full model) relating the responses for % drug release. The polynomial equation can be used to draw conclusions after considering the magnitude of coefficient and the mathematical sign it carries, i.e., positive or negative. The high values of correlation coefficient for the dependent variables indicate a good fit. The equation may be used to obtain estimate of the response because small error of variance was noticed in the replicates.

Table 8: 3^2 full factorial design layout

Batch	Independent variables	
	X1	X_2
F7	-1	-1
F8	-1	0
F9	-1	1
F10	0	-1
F11	0	0
F12	0	1
F13	1	-1
F14	1	0
F15	1	1
Concentration of independent variable		
Level	Ratio of Eudragit L100: S100	% Coating
-1	1:1	12
0	1:2	15
1	1:3	18

Table 9: Effect of independent variable on dependent variable by 3^2 full factorial design of SBS for pulsatile release

Batch	Independent variables		Dependent variable (%)	
	X1	X1	Q5	Q6
F6	-1	-1	33.33	85.55
F8	-1	0	32.16	82.40
F9	-1	+1	31.00	75.65
F10	0	-1	24.34	79.12
F11	0	0	17.23	87.77
F12	0	+1	15.46	79.16
F13	+1	-1	18.41	71.42
F14	+1	0	16.08	68.23
F15	+1	+1	12.79	66.49
Independent Variables	Real Value			
	Low (1)	Medium (0)	High (+1)	

Eudragit S100:Eudragit L100 (X1)	1:1	1:2	1:3
% Coating (X2)	12	15	18

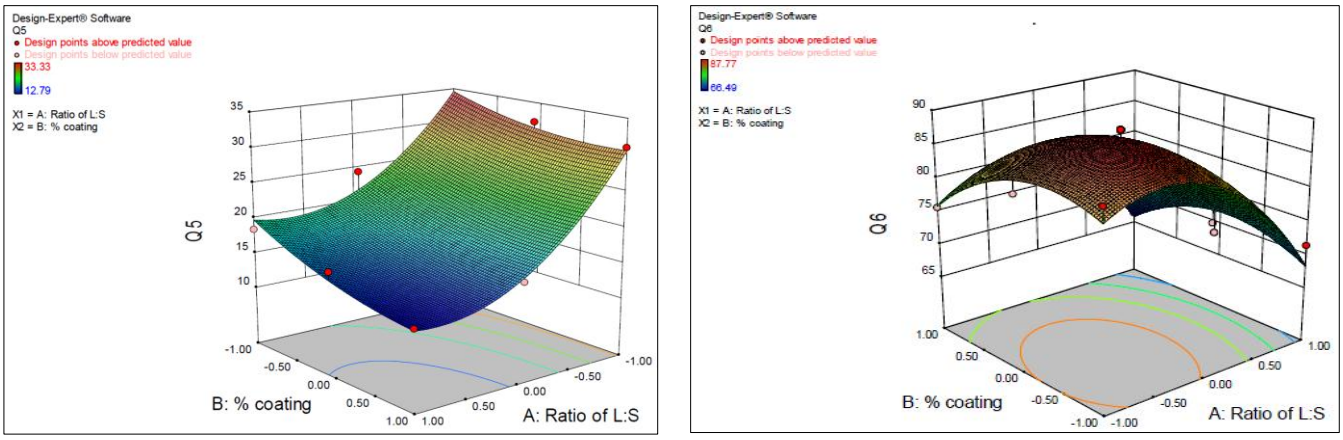

Fig 2 & 3: Surface response curve at 5th h of formulation and 6th h of formulation (F12)

(d) In-vitro drug release studies of "Tablet-in –Capsule" device

The best promising formulation F12 was selected for the study of *in vitro* drug release profile. The 100% drug released from the first pulse tablet within 15 min and 87.77% drug released after completion of lag time. Drug released before lag completion of lag time was found to be 17.23%. The cumulative percentage of salbutamol sulpahte released from "Tablet-in –Capsule" device as a function of time for all the formulations. The drug release profile showed sigmoidal release pattern which is considered to be an ideal for the pulsatile drug delivery system.

4.2 Effect of paddle speed on the lag time and release characteristics

Drug release from the device, need to be independent of agitational intensity of the release media. In order to verify effect of agitational intensity, the dissolution studies were conducted at thee different agitation speed (75, 100, and 150 rpm). Formulation F12 was considered for this study. Dissolution studies were carried out using USP- Type II dissolution apparatus and results are given in Table 10. The cumulative percentages of drug release from the device were found to be 92.74, 94.15 and 95.74% correspondingly for 50, 75, and 100 rpm. No significant difference in drug release pattern was observed for different rotational speed. This shows an advantage for the system, as it predicts no change in the performance of the system as increased gastric motility.

Table 10: *In-vitro* drug release study of 'Tablet in Capsule' (F12) with different rotational speed

Dissolution medium (pH buffer)	Time (h)	Initial	% Cumulative drug release different paddle speed (rpm)		
			50	75	100
	0	0	0	0	0
0.1 N HCl	1	33.0	33.0	33.0	33.0
	2	33.0	33.0	33.0	33.0
pH 5.5	3	41.7	40.5	41.3	41.7
pH 6.8	4	45.8	43.1	43.9	45.8
	5	50.2	49.3	51.4	50.2
pH 7.4	6	87.7	85.7	86.6	87.7
	7	95.7	92.7	94.1	95.7

(e) Fourier Transformed Infrared (FT IR) Spectroscopic studies

SBS and PVK-K30, optimized (F12 formulation, Eudragit L-100 and Eudragit S-100 were subjected for FT-IR spectroscopic analysis, to ascertain whether there is any interaction between the drug and polymers used. The FTIR spectra obtained are presented in Figures 4,5,6 and 7. From the study it was observed that similar characteristic peaks of SBS and optimized formulation F12) appears with minor differences at frequencies 2720 cm^{-1} (C=0 stretching), 2575 cm^{-1}(C=C stretching), 1986 cm^{-1} (C=N stretching) and 1689 cm^{-1} (C-N, C=O vibration). Hence, it can be concluded that the characteristics bands of pure drugs were not affected after successful loading without any change in their position, indicating no chemical interaction between drug and used carriers.

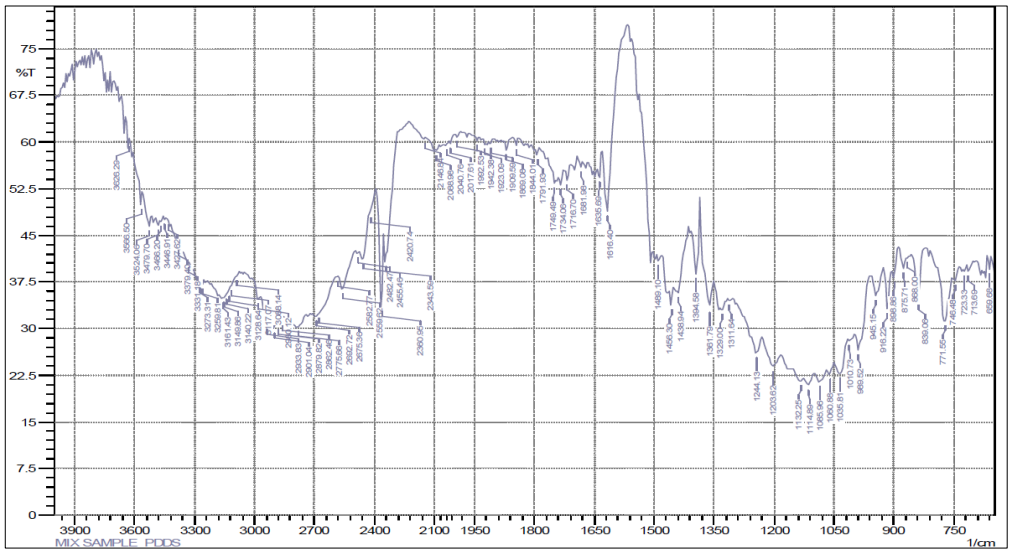

Fig 4: FT-IR spectrum of optimized formulation (F12)

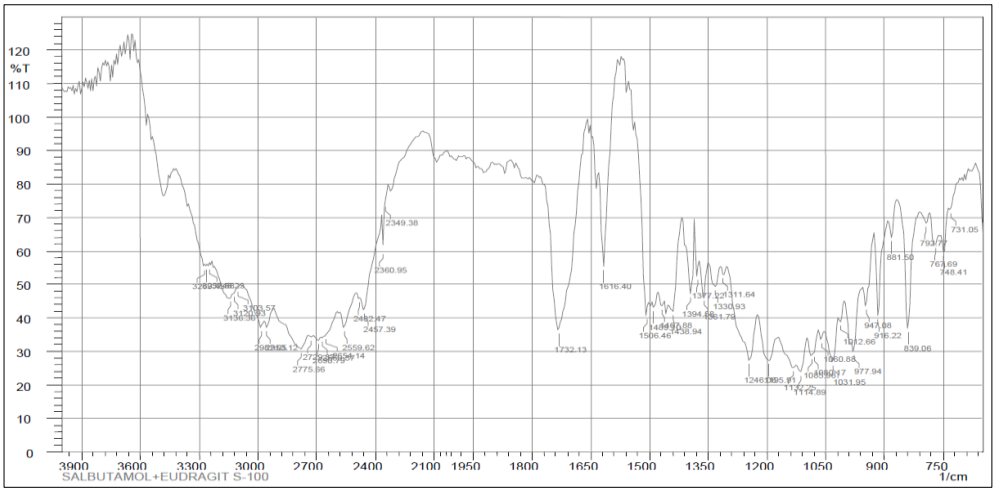

Fig 5: FT-IR spectrum of pure SBS / Eudragit S-100

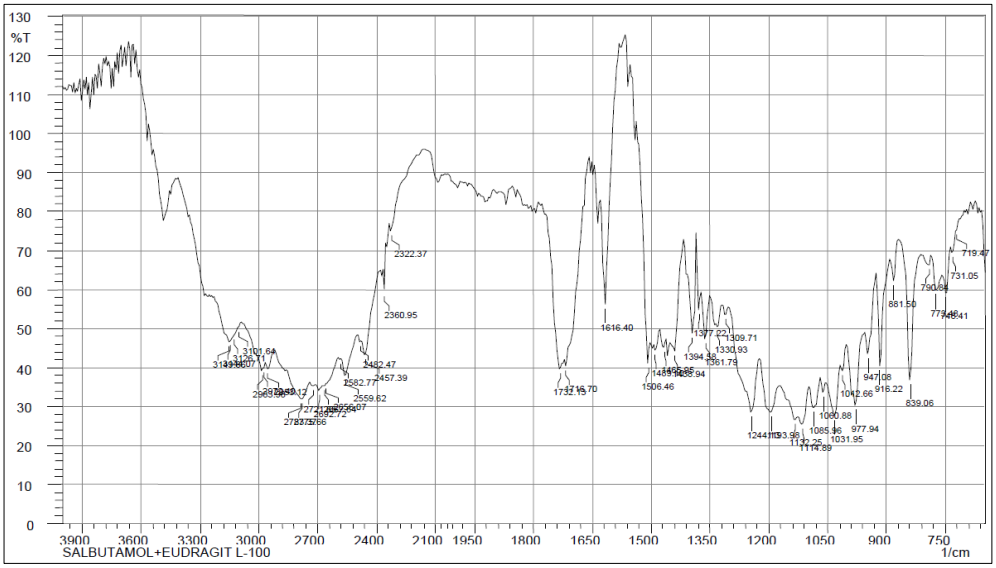

Fig 6: FT-IR spectrum of pure SBS/ Eudragit L-100

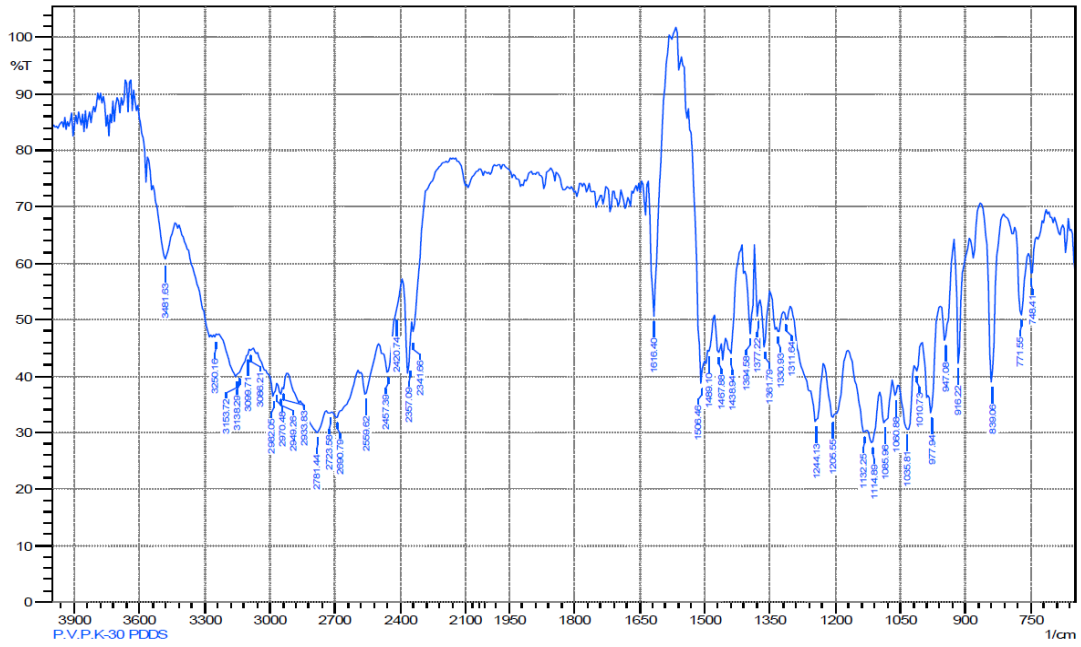

Fig 7: FT-IR spectrum of pure SBS/ PVP K-30

(f) *In-vivo* Gamma-Scintigraphic Studies

Gamma scintigraphy, a noninvasive technique, is a reliable tool for evaluating the *In-vivo* performance of dosage form in the different regions of GIT. An adult male rabbit was used to carryout scintigraphy study (Figure 8). The radio labeled capsule was administered and then rabbit was immobilized and seated comfortably in the rabbit cage. The rabbit had small sealed source of 0.06MBq firmly taped to the skin at the position of its shoulder joint and hip joint on the same side, which was depicted as an anatomical reference marker. The source was also used for repositioning when the images were taken. Scintiscans were taken after 30 min, 2, 4 and 5.5 h.

In- vivo test in rabbit, by gamma scintigraphic studies indicated that the second pulse tablet remained intact in the stomach and intestine and released upon reaching the colon.

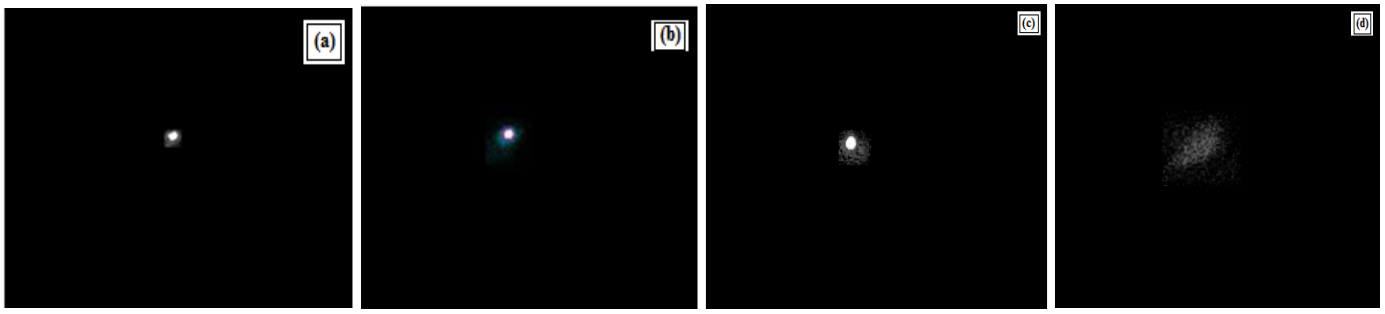

Fig 8: Scintiscan images of tablet in capsule after (a) 30 min, (b) 2 h, (c) 4 h and (d) 5.5 h

(g) Stability study of "Tablet in Capsule" device

The stability study was carried out at 40°C /75% RH for formulation F12 up to 30 days. At every 10 days time interval, evaluated for *In vitro* drug release and drug content study in 0.1N HCl, pH 5.5, pH 6.8 and pH 7.4 phosphate buffer solutions. The results of accelerated stability study are tabulated in Table 11. The result of accelerated stability study reveals that there was no change in the formulation after one month. *In-vitro* drug release study showed that after 10, 20 and 30 days; values obtained were 95.62%, 94.84% and 93.62% respectively. The 100% drug released from the first pulse tablet within 15 min and 87.77% drug released after a completion of lag time. Drug released before lag completion of lag time was found to be 17.23%. The drug release thoughout 7 h and it is within range of targeted release profile. After 1 month accelerated stability study the assay result was stable and the drug release profile was of sigmoidal release pattern, which is considered to be an ideal for the pulsatile drug delivery system.

Table 11: *In-vitro* drug release study of 'Tablet in Capsule' device for stability testing

Dissolution medium (pH buffer)	Time (h)	Initial	% Cumulative drug release (days)		
			10	20	30
	0	0	0	0	0
0.1 N HCl	1	33.0	33.0	33.0	33.0
	2	33.0	33.0	33.0	33.0
pH 5.5	3	41.74	41.41	40.36	40.1
pH 6.8	4	45.86	45.12	44.92	44.12
	5	50.23	50.23	49.56	48.22
pH 7.4	6	87.77	87.77	86.12	85.75
	7	95.74	95.62	94.84	93.62

5. Conclusions

The polymers used (Eudragit S100 and Eudragit L100) in this investigation were suitable for colon target. FT-IR studies, reveals that similar characteristic peaks appear with minor differences for the drug and its formulation hence, it appears that there was no chemical interaction between the drug and polymers for the pellets prepared. F12 was found to be optimum formulation and design 'Tablet-in-Capsule' with first pulse tablet.Drug content study results inferred that there was a proper and uniform distribution of drug within the optimized formulation (F12). Second pulse tablets were coated with Eudragit S100 and Eudragit L100 and optimization was done using 3^2 full factorial designs. From the optimization study it was found that formulation F12 (1:2 ratio of Eudragit L100: Eudragit S100 with 15% coating) was the best for Pulsatile drug delivery system.The release of drug from coated tablet was found to be proportional to the concentration of the polymer; with increase in % coating, increases the lag time.From the *in-vitro* release studies of device, it was observed that for all formulations, there was absolutely no drug release in simulated gastric fluid (acidic pH 1.2) for 2 h. Small amount of drug release was observed in simulated intenstinal fluid (pH 6.8 phosphate buffer). Burst effect was found in colonic medium (pH 7.4 phosphate buffer).*In- vivo* gamma scintigraphic studies revealed that the second pulse tablet remained intact in the stomach and small intestine and released upon reaching the colon.From the accelerated stability studies, it was observed that there was no significant change in the drug content and % release of drug during the study period, therefore the formulations were stable.A pulsatile 'Tablet in Capsule' dosage form, taken at bed time with a programmed start of drug release early in morning hours, can prevent a sharp increase in the incidence of asthmatic attacks, during the early morning hours (nocturnal asthma), a time when the risk of asthmatic attack is high.

6. References

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