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Formulation and *in-vitro* Evaluation of Press Coated Tablets of Valsartan: Effect of Concentration of Polymers on Lag Time and Drug Release

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Abstract

The main objective of the present study was to explore the feasibility of time dependent pulsatile drug delivery system (PDDS) of Valsartan (VLSN) for the treatment of hypertension. The core tablet formulations were prepared by direct compression method and optimized core tablet formulation was coated by press coating technique. The immediate release core tablets consist of VLSN and some other disintegrants in different ratios with the drug concentration. Coating layer consists of Hydroxy Propyl Methyl Cellulose (HPMC), Ethyl Cellulose (EC), Guar gum (GG) and Xanthan gum (XG) as release retarding polymers in varying ratios. The obtained results of pre and post compression parameters were complied with the official limits. The core tablet formulation F5 was optimized based on the results obtained from disintegration and dissolution studies. Polymer ratio of 1:1 (HPMC: EC) showed a desired lag time of 7 h. The desired lag time of 7 h was satisfied by the formulation CF4 and showed the maximum drug release of 98%. The increase in HPMC concentration showed decrease in lag time and vice versa in the case of EC.

Key words: Chronodrug delivery, Direct compression, Hypertension, Lag time, Valsartan.

1. Introduction

For achieving the chronomodulated therapeutic drug delivery, Pulsatile Drug Delivery System (PDDS) is one of the promising time specific systems that releases the drugs after a predetermined time i.e. lag time [1]. The lag time of developed tablets depend on the nature of therapeutic application, type of the polymers

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used and core to coat ratio of the tablets. PDDS is required especially for the treatment of some chronomodulated diseases such as angina pectoris, hypertension and rheumatoid arthritis with early morning or night symptoms [2]. There are so many methods existing for preparation of tablets but the direct compression is most preferable method of manufacture because of its ease of process, time saving and better stability characteristics [3]. Compression coating method i.e. press coating technique is a preferred method of coating than the film coating because of its safety, inexpensiveness that doesn't require special coating equipment and mainly it is free of solvents. It could be expected that the coating though compression offers greater stability than the film coating techniques [1].

Hypertension is commonly exhibiting its symptoms during the early morning times and it is difficult to take a drug in early morning times by the patients. Hence, the developed pulsatile tablet must release the drug during the early morning times for effective treatment. To achieve this, the drug must be released from its dosage form after the predetermined time i.e. lag time. VLSN is also called as an antihypertensive agent who lowers the blood pressure through Renin-Angiotensin-Aldosterone System. VLSN selectively inhibits the binding of angiotensin-II to AT_1 and also inhibits the AT_1 mediated vasoconstrictive effects thereby it decreases the blood pressure [4]. VLSN has biological half life of 6 h, hence it could be considered for development of time controlled release dosage forms. Previously pulsatile core-in-cup VLSN tablets were developed [5]. Hence, an attempt has been taken to develop pulsatile VLSN tablets by direct compression method and coated by press coating technique. In the present study, the role of polymer type and its concentration on lag time and drug release was studied.

2. Experimental

2.1. Materials

VLSN was obtained from Bridge Pharmaceuticals Pvt. Ltd, India and Micro Crystalline Cellulose (MCC) from Degussa India Pvt. Ltd., Mumbai, India and Crospovidone (CP), Sodium Starch Glycolate (SSG), Croscarmellose Sodium (CCS), Magnesium Stearate were obtained from S.D. Fine Chem. Ltd, Mumbai, India and Talc from ESSEL Fine Chem. Mumbai, India. The outer controlled release coating layer was prepared by using HPMC (Sisco Research Lab Pvt. Ltd., Mumbai, India), EC (Sisco Research Lab Pvt. Ltd., Mumbai, India), GG (MYL CHEM, Mumbai, India) and XG (MYL CHEM, Mumbai, India).

2.2. Methods

2.2.1. Fourier Transform Infra-Red (FTIR) studies

It was performed to check the chemical interactions between the drug and excipients used in the formulations by the KBr disc method using the FTIR spectrophotometer (Perkin Elmer, USA). One to two milligram of solid fine powder of VLSN and 200-300 mg of dry powder of KBr (IR grade) were taken in a mortar and mixed well with the help of spatula followed by disc was prepared. Similar procedure was followed to prepare the disc of optimized formulation. Both the discs were scanned in the wavelength region of 4000-400 cm^{-1} by FTIR spectrophotometer. The obtained IR spectrum of pure drug was compared with the spectrum of physical mixture to check the possible drug-excipients interactions [6].

2.2.3. Preparation of core and press coated tablets of VLSN

The core tablets of immediate release were prepared by direct compression method using the super

disintegrants such as CCS, CP and SSG in appropriate ratio with the drug. The drug concentration was kept constant at 40 mg for all the formulations. All the ingredients (Table 1) were weighed accurately and transferred into mortar except Magnesium stearate and Talc. This powder blend was mixed for about 15 min with the help of pestle. Then the Magnesium stearate and Talc were added to the above mixture and then again, it was mixed for about 5-7 min. After obtaining the uniform powder mixture, it was passed through the sieve no. 60 and obtained powder blend was subjected to the direct compression using 9 mm flat punches (RIMEK rotary tablet punching machine, India) [7]. The optimized formulation was coated by press coating technique using the polymers such as HPMC, EC, GG and XG in different concentrations (Table 1). Different compositions of the polymers were weighed, dry blended for about 10 min and then passed through sieve no. 60. Then the 50% of this polymer blend was placed in 12 mm die and core tablet was placed on it. Further, remaining 50% of the polymer blend was placed on core tablets followed by compressed using the RIMEK rotary tablet punching machine [8].

Table 1. Composition of core and coated tablets.

Core Tablets									
Ingredients (mg)	**F1**	**F2**	**F 3**	**F 4**	**F5**	**F6**	**F7**	**F8**	**F9**
VLSN	40	40	40	40	40	40	40	40	40
CCS	7.5	11.2	15	---	---	---	---	---	---
CP	---	---	---	7.5	11.2	15	---	---	---
SSG	---	---	---	---	---	---	7.5	11.2	15
MCC	96.5	92.75	89	96.5	92.75	89	96.5	92.75	89
Magnesium stearate	3	3	3	3	3	3	3	3	3
Talc	3	3	3	3	3	3	3	3	3
Total Weight (mg)	150	150	150	150	150	150	150	150	150
Press Coated Tablets									
Ingredients (mg)	**CF1**	**CF2**	**CF3**	**CF4**	**CF5**	**CF6**	**CF7**	**CF8**	
Weight of core tablet	150	150	150	150	150	150	150	150	
HPMC	100	300	200	150	100	---	---	---	
EC	100	---	100	150	200	300	150	150	
GG	---	---	---	---	---	---	150	---	
XG	---	---	---	---	---	---	---	150	
Total Weight (mg)	350	450	450	450	450	450	450	450	

VLSN: Valsartan; MCC: Micro Crystalline Cellulose; CCS: Croscarmellose Sodium; CP: Crospovidone; SSG: Sodium Starch Glycolate; HPMC: Hydroxy Propyl Methyl Cellulose; EC: Ethyl Cellulose; GG: Guar gum; XG: Xanthan gum.

2.3. Evaluation studies

2.3.1. Micromeritic studies

These studies were performed to know the flowability characteristics of the powder blend. A quantity of 5 mg powder blend from each formulation was taken and filled into a 25 ml of measuring cylinder separately. Initial bulk volume was measured and no-Hausner's ratio (HR) were calculated using the BD ted. Then the cylinder was allowed to tap from the height of 2.5 cm with the frequency of 25±2 rpm/min followed by tapped volume was measured. The bulk density (BD) and tapped density (TD) were calculated using the bulk volume and tapped volume respectively [9-10]. The Carr's index (CI) and and TD values according the formula described

previously [11-12]. Angle of repose was determined by fixed funnel method [13-14].

2.3.2. Physical characterization of core and coated tablets

2.3.2.1. Thickness

The thickness of the both core and coated tablets was measured using Vernier calipers by taking 10 tablets from each formulation and performed in triplicate (n=3). Similarly the thickness of the coating layer was determined by deducting the thickness of the core tablets from the thickness of the coated tablets [15].

2.3.2.2. Hardness

The hardness of the both core and coated tablets was determined by using the Monsanto hardness tester. Average of three determinations was calculated (n=3) [16].

2.3.2.3. Friability

Friability generally refers to the loss in weight of the tablets in the containers due to the removal of fines from the tablet surface. Twenty tablets were weighed and the initial weight of these tablets was recorded. Then the tablets were placed in Roche friabilator, set at the speed of 25 rpm and operated for 4 min i.e. 100 revolutions. Tablets were removed from the friabilator, dusted off the fines followed by reweighed the tablets and % friability was calculated by the formula described in earlier studies [17].

2.3.2.4. Weight variation

The weight of the tablet being made was routinely determined to ensure that a tablet contains the proper amount of the drug. The USP weight variation test was performed by weighing the 20 tablets individually, calculating the average weight and comparing the individual weights to the average. The tablets met the USP specification that not more than 2 tablets are outside the percentage limits and no tablet differs by more than 2 times the percentage limit [18].

2.3.2.5. Content uniformity

The tablets were finely powdered and a quantity of the powder equivalent to the 10 mg of VLSN was accurately weighed followed by transferred into the volumetric flask containing 100 ml of pH 6.8 phosphate buffer. It was thoroughly mixed by using the rotary shaker and this solution was filtered through 0.45 µm filter paper. The obtained filtrate was diluted suitably and estimated for VLSN content at 251 nm by UV-Visible spectrophotometer (Lab India 1700 UV-Visible spectrophotometer, India) [19].

2.4. *In-vitro* dissolution study of core tablets

In-vitro dissolution test for the core tablets was performed by Electro lab TDT-06N USP dissolution test apparatus type-II (Paddle method) using 900 ml of Phosphate buffer solution (pH 6.8) for 1 h. The rotation of paddle was set at 50 rpm and temperature of the medium was maintained at 37±0.5°C. At the specified intervals (0, 5, 10, 15, 30, 45 and 60 min), 5 ml of sample was withdrawn and the same amount was replaced with the fresh buffer solution. The withdrawn samples were diluted suitably and analyzed by UV-Visible spectrophotometer at 251 nm for the presence of drug using the buffer solution as blank [20-21].

2.5. *In-vitro* dissolution study of coated tablets

In-vitro dissolution testing is an important tool in the development of solid dosage forms. Dissolution testing of PDDS with the conventional paddle method at 50 rpm and 37±0.5°C has usually been conducted in different buffers for different periods of time to simulate the GI tract pH and transit time that the PDDS might encounter *in-vivo*. At the physiological environment of the stomach, the coats

are remain intact, it will be known by conducting the drug release studies in 900 ml of pH 1.2 HCl buffer (pH 1.2) for first 2 h and in small intestine, it will be known by conducting the drug release studies in phosphate buffer (pH 6.8) for remaining 6 h (intestinal transit time) using USP dissolution test apparatus. The samples were withdrawn at regular intervals (0.5, 1, 2, 3, 4, 5, 6, 7 and 8h), diluted suitably and analyzed by the UV-Visible Spectrophotometer for the presence of the drug [22].

2.6. Swelling index determination

The individual tablet weight was determined and it was designated as W_1. Then the tablets were placed separately in glass beakers containing 100 ml pH 1.2 HCl buffer for the first two hours followed by transferred into the beaker containing 100 ml of phosphate buffer (pH 6.8). The temperature of the both buffers was maintained at 37°C±0.5°C. At regular one hour time intervals upto 8th h, the tablets were removed from the beakers and the tablet contains excess amount of liquid was carefully removed by using the filter paper. After removal of liquid from swollen tablets, those tablets were reweighed and it was designated as W_2. Finally, the swelling index was calculated by using the following formula [23].

$$\text{Swelling Index} = \frac{W_2 - W_1}{W_1} \times 100$$

2.7. Lag time

The procedure for determination of lag time was same as like the dissolution test but here the lag time was recorded as the time point when outer coat of pulsatile tablet was ruptured and removed [5].

3. Results and Discussion

The time controlled release tablets of VLSN were prepared by direct compression method and optimized formulation was coated by press coating technique. The final tablets consist of two parts i.e. center core tablet and outer coating layer. The process of press coating technique was depicted in the (Figure 1). Preformulation studies were primarily performed to investigate the physico-chemical properties of the drug and its compatibility with the excipients. Drug-excipients compatibility studies were performed using FTIR to determine the possible interactions of VLSN with the excipients used in the formulations. The FTIR spectrum of the pure drug was compared with the FTIR spectrum of the optimized formulation. The characteristic absorption peaks of pure drug were observed at the wave numbers of 3444, 1411, 655 and 2870 cm^{-1} corresponding to the O-H stretching (carboxylic acid), C-H bending (alkane), C-H bending (disubstituted aromatic) and C-H stretching (alkane) respectively. It was observed, that there were no shifts in characteristic peaks of pure drug in the spectrum of optimized formulation (Figure 2). Hence, it was confirmed that both the drug and excipients were compatible with each other.

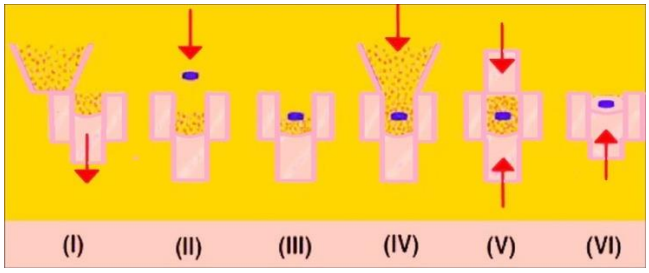

Figure 1. Process of press coating technique. I. Die was filled with half amount of coating material; II. Placing of core tablet on coating material; III. Tablet was centered in the die on the coating material; IV. Filling of remaining coating material on the tablet; V. Punching was done; VI. Ejection of press coated tablet.

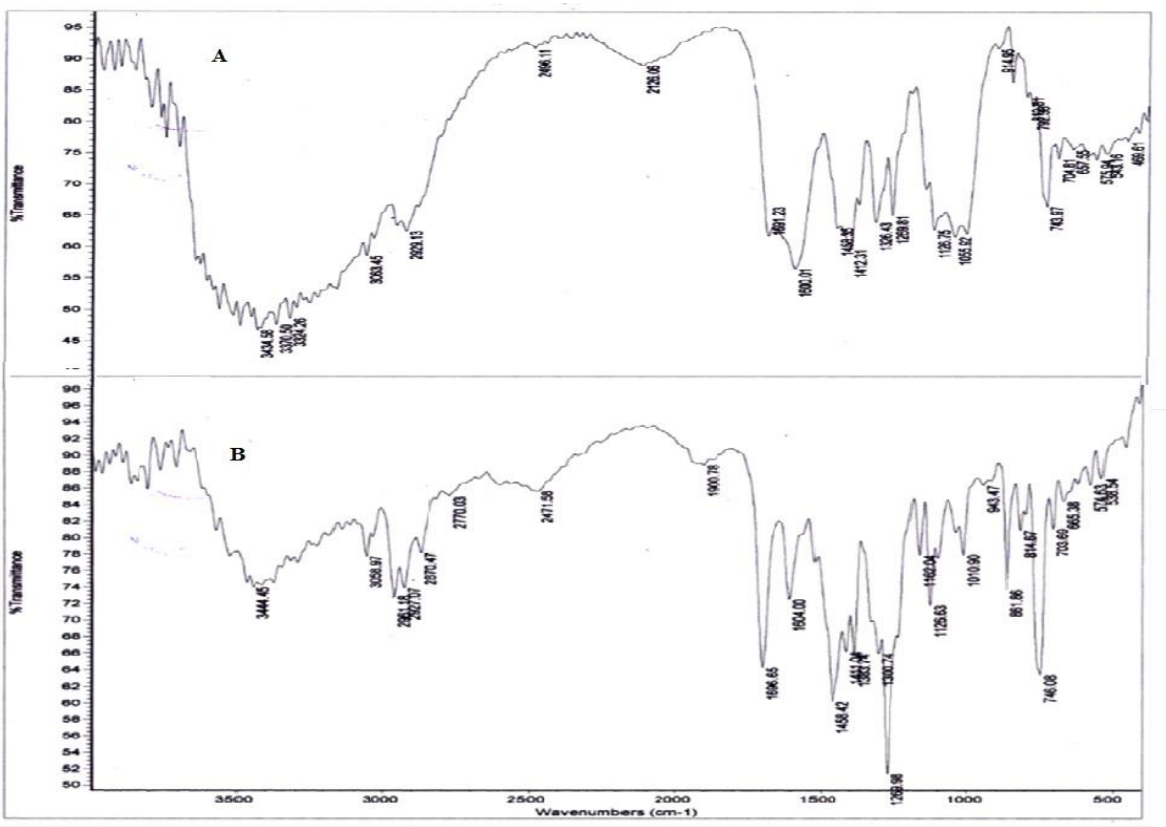

Figure 2. FTIR studies. A. IR spectra of optimized formulation, B. IR spectra pure drug.

3.1. Evaluation of precompression parameters of core tablets

The flow properties of the powder blends were showed in (Table 2). The BD and TD of core tablet blends were ranged from 0.41 ± 0.045 to 0.47 ± 0.044 gm/cc and 0.47 ± 0.07 to 0.54±0.01 gm/cc respectively. The obtained results for the AR (θ) vary from 23.58 ± 0.15 to 29.52 ± 0.19, which fall in the official range of <30º indicates the good flowability. CI was vary from 11.36 ± 0.8 to 13.50 ± 0.01 which fall in the official range of 11-15 % indicates the good flowability, whereas the HR analyzed was in the range of 1.11 ± 0.04 to 1.15 ± 0.09 which fall in the official limits of 1.10-1.18 indicates the good flow characteristic of the powder blend [24].

Table 2. Evaluation of flow properties of powder blends.

Formulation	BD (gm/cc)	TD (gm/cc)	CI (%)	HR	AR (º)
F1	0.42 ± 0.045	0.47 ± 0.07	11.90 ± 0.6	1.11 ± 0.04	23.58 ± 0.15
F2	0.44 ± 0.044	0.49 ± 0.09	11.36 ± 0.8	1.13 ± 0.08	25.44 ± 0.11
F3	0.43 ± 0.01	0.47 ± 0.02	13.50 ± 0.01	1.14 ± 0.01	24.46 ± 0.12
F4	0.45 ± 0.045	0.51 ± 0.04	13.33 ± 0.1	1.15 ± 0.06	26.36 ± 0.13
F5	0.47 ± 0.044	0.54 ± 0.01	14.89 ± 0.6	1.18 ± 0.08	29.52 ± 0.19
F6	0.42 ± 0.02	0.48 ± 0.01	11.87 ± 0.02	1.13 ± 0.02	22.92 ± 0.11
F7	0.41 ± 0.045	0.46 ± 0.04	12.19 ± 0.8	1.13 ± 0.09	27.32 ± 0.19
F8	0.43 ± 0.045	0.48 ± 0.04	13.59 ± 0.8	1.15 ± 0.09	25.69 ± 0.19
F9	0.44 ± 0.044	0.49 ± 0.09	11.36 ± 0.8	1.13 ± 0.08	25.44 ± 0.11

Results expressed in mean (n=3) ± SD (Standard Deviation).

3.2. Evaluation of post compression parameters of core tablets

Hardness of the core tablets was ranged from 3.5±0.78 to 4.2±0.35 kg/cm^2, therefore it ensuring the appropriate strength of the tablets. The thickness observed was 2.26±0.38 to 2.27±0.68 mm and is mostly even for all the batches. All the tablets selected from developed formulations were passed content uniformity test. The individual weight of different batch tablets was within the official limits (±5%) of percent deviation from average weight [25]. The disintegration time of core tablet was in the range of 70±0.96 to 175±0.50 sec. The least disintegration time was exhibited by the core tablet formulation F5 than other formulations (Table 3).

Table 3. Physical evaluation parameters of core tablets.

Physical parameters	F1	F2	F3	F4	F5	F6	F7	F8	F9
Weight variation (mg)	150±0.01	149±0.02	151±0.05	150±0.30	150±0.40	149±0.61	151±0.76	150±0.40	152±0.98
Hardness (kg/cm^2)	3.5±0.78	3.9±0.87	3.9±0.51	4.1±0.61	4.1±1.01	3.6±0.86	4.0±0.97	3.7±1.40	4.2±0.35
Thickness (mm)	2.26±1.30	2.26±0.98	2.26±0.85	2.27±0.68	2.26±1.34	2.26±0.73	2.26±0.89	2.26±1.15	2.26±0.38
Friability (%)	0.6±0.35	0.55±0.15	0.41±0.85	0.45±0.74	0.45±0.25	0.38±1.29	0.62±1.68	0.57±0.94	0.59±0.86
Disintegration Time (sec)	175±0.50	133±0.65	140±0.40	90±0.64	70±0.96	85±0.81	160±0.73	140±0.34	155±0.38

Results expressed in mean (n=3) ± SD (Standard Deviation).

3.3. Evaluation of post compression parameters of press coated tablets

The post compression parameters namely weight variation, hardness, thickness and friability were performed for the coated tablets and the results were reported in (Table 4). The weight variation of the coated tablets was complied with the pharmacopoeial limits of ±5%. The hardness of all the formulations was ranged between 6.9 kg/cm^2 to 8.2 kg/cm^2, ensures good handling characteristics of all the batches. The % friability was vary from 0.36 to 0.44 i.e. <1%, ensuring that all the tablets were mechanically stable. Thickness of the coated formulations was measured with digital Vernier calipers and it was ranged from 3.48 to 3.59 mm, which ensures a uniform coating to all the batches. The percent of drug content for CF1 to CF8 in pH 1.2 HCl buffer was found to be between 97.55 ± 1.66% and 100.33 ± 2.42 % and in phosphate buffer (pH 6.8), it was ranged from 97.35 ± 1.98 % to 100.24 ± 2.33 %, which complies with the official specifications (Table 5).

Table 4. Evaluation of post compression parameters of coated tablets.

Physical parameters	CF1	CF2	CF3	CF4	CF5	CF6	CF7	CF8
Weight (mg)	349±1.08	450±0.94	449±0.56	451±1.20	450±2.04	450±0.88	449±0.68	451±1.85
Hardness (Kg/cm^2)	6.1±0.56	6.9±0.18	7.0±0.24	7.5±0.75	8.2±0.96	8.0±0.84	7.0±0.78	8.2±0.34
Thickness (mm)	3.10±1.08	3.59±0.92	3.55±1.44	3.50±1.36	3.48±098	3.49±0.84	3.55±0.68	3.48±1.45
Friability (%)	0.38±0.14	0.39±0.08	0.41±0.60	0.42±0.34	0.36±0.86	0.41±0.24	0.39±0.52	0.37±0.96

Results expressed in mean (n=3) ± SD (Standard Deviation).

Table 5. Drug content uniformity.

Formulation	0.1N HCl buffer (pH 1.2)	Phosphate buffer (pH 6.8)
CF1	98.77 ± 2.93	98.79 ± 1.72
CF2	98.14 ± 2.10	98.04 ± 2.76
CF3	100.07 ± 2.85	99.82 ± 3.10
CF4	100.33 ± 2.42	100.22 ± 2.17
CF5	98.37 ± 2.50	98.10 ± 3.11
CF6	99.37 ± 1.15	99.07 ± 1.31
CF7	97.55 ± 1.66	97.35 ± 1.98
CF8	98.64 ± 2.10	100.24 ± 2.33

Results expressed in mean (n=3) ± SD (Standard Deviation).

3.4. Swelling index

The Swelling index was performed for coated tablets and the results were reported in (Table 6). From the results, the tablets consist of EC exhibited the highest swelling index compared to the other polymers due to its hydrophobic nature and viscosity properties. Tablets with HPMC have faster absorption of water followed by the rapid erosion of the outer gel layer due to its hydrophilic characteristic. It could be expected that the tablets with more amount of EC exhibits stronger outer gel layer than the tablets with more amount of HPMC. Hence, it can propose that the EC concentration was directly proportional to the swelling index of the tablets. The tablets consist of equal amounts of EC and GG have showed comparatively more swelling index than the tablets consist of equal amounts of EC and XG. It was observed from the Swelling index studies that the swelling index less than 100% showed the drug release within 8 h but more than 100% showed drug release after 8 h. GG showed less swelling index than XG because of its low viscosity and disintegrating property than the XG [26].

3.5. Lag time

It was studied for the coated tablets to know the time at which the burst release of drug happened and the results were presented in (Table 6). The actual fixed lag time was 7 h, hence the tablet must be ruptured at or after 7th hour and completely the drug must be released within 8 h. It was satisfied by the formulation CF4. Remaining formulations were failed to show the desired lag time i.e. less than the lag time (CF1, CF2, CF3, CF7 and CF8) or more than the lag time i.e. >8h (CF5, CF6). Hence, these formulations were not considered for further studies.

Table 6. Swelling index and lag time of press coated tablets.

Formulation	Swelling Index (%)*	Lag Time (h)
CF1	49±1.05	3.20
CF2	78±1.31	3.30
CF3	80±1.45	4.30
CF4	100±1.61	7.00
CF5	140±1.46	8.30
CF6	180±1.10	9.45
CF7	95±1.63	6.30
CF8	100±1.87	6.20

*Results expressed in mean (n=3) ± SD (Standard Deviation).

3.6. Dissolution studies of core tablets

All the 9 core tablet formulations of VLSN were subjected to *in-vitro* drug release studies by taking pH 1.2 HCl buffer as a medium and performed for 1 h. The results for dissolution test were tabulated in (Table 7) and it was found that the 65.34% as lowest drug release and maximum of 90.36% in 1h study. According to the concept of PDDS, the core tablet must show the burst release of drug after the lag time. The formulation F5 satisfied the criteria of PDDS and it showed the maximum drug release of 85.67±0.90 % within 15 min of study which is also supported by the results of disintegration time. The properties of disintegrants showed their effect on drug release from its dosage form. Among the disintegrants, CCS and SSG showed concentration dependent effect on drug release i.e. drug release was directly proportional to the concentration upto the optimum level, beyond that inversely proportional to the concentration but the CP showed that the drug release was directly proportional to the concentration. Some of the works reported that the SSG has a capability of rapid absorption of water followed by swelling occurs. Due to the swelling property, there are lots of chances to form a gel layer around the core tablets thereby it delays the drug release. But it is in case of CP, it has low tendency to form a gel layer around the core tablet and also possessing the solubility enhancing property thereby it shows the rapid drug release [26].

Table 7. Dissolution data of core tablet formulations (F1-F9).

Time (min)	F1	F2	F3	F4	F5	F6	F7	F8	F9
0	0	0	0	0	0	0	0	0	0
5	15.18±0.35	26.77±1.34	22.12±0.64	37.51±1.30	40.11±0.82	26.33±1.46	18.07±0.88	21.68±1.36	21.22±0.81
10	23.02±0.65	39.18±0.28	36.41±0.38	63.08±1.08	71.95±0.60	42.38±1.35	24.18±0.68	35.25±1.56	30.41±0.67
15	35.78±0.86	47.59±0.64	46.32±0.80	75.24±1.68	85.67±0.90	70.41±1.22	36.58±1.64	40.06±0.92	39.81±0.39
30	51.37±0.97	58.45±1.46	58.84±1.02	83.45±1.40	--	90.36±0.92	42.32±1.96	59.27±0.86	56.41±0.89
45	64.25±0.51	66.71±1.20	64.33±1.64	--	--	--	59.79±0.45	65.36±1.38	62.38±0.61
60	65.34±0.46	79.86±0.66	76.42±0.32	--	--	--	71.34±0.78	74.56±1.08	72.48±0.73

Results expressed in mean (n=3) ± SD (Standard Deviation).

3.7. Dissolution studies of coated tablets

It was performed for 8h time period and the obtained results were presented in (Table 8). In this study, the lag time (the time during which drug release will be minimal or nothing to b happens) was fixed for 7 h followed by burst release of drug will be expected to anticipate the circadian rhythms of the disease [27-28]. The formulations consist of HPMC in high concentration were failed to show desired lag time of 7 h and released the drug during the lag time itself. HPMC has a hydrophilic nature, hence it absorbs the water rapidly thereby it forms like a jelly like structure around the dosage form but it couldn't resist the drug for long time. EC has hydrophobic nature; hence it will take much time to absorb the water. When it is in mutual contact with the water for longer time, it forms a gel layer around the tablet. But EC forms a stronger gel layer than that of HPMC due to its hydrophobic and viscosity enhancing capacity [26].

The natural polymers GG and XG were also failed to show the desired lag time. When they are in contact with the water, they form a gel layer around the dosage form but this layer cannot resist the drug release for longer times. GG has disintegrant property along with the viscosity enhancing capacity thereby it shows more drug release than XG and has less retardant capacity to drug release. Among all the coated tablet formulations, CF4 showed desired lag time i.e. 7 h and showed burst release within 8 h.

Table 8. Dissolution data of press coated tablet formulations (CF1-CF8).

Time (h)	CF1	CF2	CF3	CF4	CF5	CF6	CF7	CF8
0.5	3.2±1.64	2.4±1.05	4.8±0.91	0.2±0.60	1.0±0.20	0.0	2.1±1.33	1.9±0.68
1	4.8 ±1.56	4.8±0.98	6.9±0.73	0.9±0.74	2.2±0.61	0.59±0.77	4.4±1.41	3.8±0.47
2	11.2±0.97	9.2±0.29	9.8±0.67	1.3±0.98	3.1±0.31	1.8±1.01	6.2±1.04	5.4±0.69
3	13.8±0.81	12.2±0.65	12.3±1.04	1.5±0.67	5.2±0.64	4.1±0.79	10.8±0.61	6.2±0.99
4	99.1±0.17	14.8±0.87	14.2±0.85	1.7±0.93	7.6±0.98	6.0±0.69	12.9±1.30	9.8±0.64
5	99.3±1.04	68.3±0.96	78.9±0.64	2.0±1.22	8.3±1.03	7.5±1.49	16.3±0.99	10.2±0.46
6	--	96.9±1.07	88.9±1.09	3.1±1.55	10.8±0.51	8.9± 1.82	18.4±0.68	12.2±1.32
7	--	--	99.8±0.78	3.9±1.86	11.3±0.53	9.6± 1.39	99.2±0.88	96.2±1.44
8	--	--	--	98±1.56	12.7±0.49	10.8±1.90	--	--

Results expressed in mean (n=3) ± SD (Standard Deviation).

Previous work reported that the pulsatile core-in-cup VLSN tablets were developed and concluded as the plug layer thickness decides the lag time of developed formulations [5]. Another work reported that the effect of single outer layer on lag time and explained the effect of pH on drug release [8]. They had concluded as the developed system was pH independent. In above both works, they failed to explain the nature and concentration of polymers on lag time and drug release but explained the thickness of plug layer and single layer on lag time and drug release. Both the works didn't fix for specific lag time and reported different lag times for different formulations. Some works reported on film coating of VLSN tablets [29-32] and film coating is an expensive method because it needs specialized equipment for film coating than the press coating technique. Present investigation confirms the role of different types of polymers and their concentration on lag time and drug release. It has achieved that the desired lag time of 7 h but previous works hadn't specified the fixed lag time [5, 8]. Hence, it could be revealed that the present developed press coated tablets of VLSN were explained the left over or unexplained areas of existing works and also it attracts the patient compliance because it has specific lag time thereby it releases the maximum drug at a time i.e. after the lag time. Upto our knowledge, it will be expected that the efficacy of developed tablets is more than that of the existing developed tablets because it has specificity in its drug release.

4. Conclusion

The objective of the present study was achieved and the criteria were satisfied by the formulation CF4. From the results, it could be concluded that, HPMC and EC has predominant effect on the lag time as well as on the drug release. Additionally GG and XG also showed significant effect on lag time. The polymer ratio of 1:1 (EC:HPMC) showed a desired lag time but EC:GG and EC:XG were failed to show desired lag time. The overall lag time was decided by the amount of HPMC used, as more amount of HPMC used, the lag time was shortened. Hence, the composition and proportion of the polymers is an important criterion to develop a PDDS. The formulation CF4 showed a desired lag time of 7 h and the maximum amount of drug was released within 8 h. Hence, there is lot of scope for future i*n-vivo* studies.

5. Conflict of Interest

The author(s) report no conflict(s) of interest(s). The author along are responsible for content and writing of the paper.

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NA

7. References

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