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Formulation and Optimization of Compress Coated Pulsatile Tablet of Cilnidipine for Treatment of Chronotherapy of Hypertension

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ABSTRACT

Cilnidipine, a novel calcium antagonist accompanied with L-type and N-type calcium channel blocking function, is mainly used in treatment of hypertension. Due to its N-type calcium-channel blocking properties, it has more advantages compared to conventional calcium-channel blockers.The present investigation is aimed to formulate a pulsatile drug delivery system with a lag time of about 6 hr. Core tablet was prepared by direct compression method and Croscarmellose sodium used as superdisintegrant. The core tablet was compression coated with different ratio of HPMC K4M and HPMC E50LV. 3^2 Full factorial design was used for optimization of barrier layer. Total amount of polymer (X_1) and % of HPMC K4M (X_2) were selected as independent variables. The lag time (t_{10}) and time require for release 90% of drug were selected as dependent variables. Tablets were evaluated for hardness, friability, weight variation, drug content and *in vitro* drug release. Formulation F7 containing 2% Croscarmellose sodium coated with 25% of HPMC K4M with 330 mg coat weight was considered optimum because it showed desired lag time of 6 hour.

INTRODUCTION

Over recent years, controlled drug delivery systems have acquired very important role in pharmaceutical Research and Development (R&D) business, because these dosage forms offer many advantages. Nowadays, the emphasis of pharmaceutical galenic research is turned towards the development of more efficacious drug delivery systems with already existing molecules rather than going for new drug discovery because of the inherent hurdles posed in drug discovery and development process (1). Traditionally, drug delivery has meant a simple chemical absorbed predictably from the gut or from the site of injection. A second-generation drug delivery goal has been the perfection of continuous, constant rate or "zero order" delivery of the bioactive agents. However, living organisms are not essentially ''zero-order'' in their requirement or response to drugs. They are predictable resonating dynamic systems, which require different amounts of a drug at predictably different times within the circadian cycle which will maximize desired and minimize undesired drug effects (2-3).

Through a number of clinical trials and epidemiological studies, it is well documented that the levels of disease activity of number of clinical disorders have a pattern associated with the circadian rhythm of the body. Circadian rhythm regulates many functions in human body like metabolism, physiology, behaviour, sleep pattern, hormone production. There are number of disease conditions which show circadian pattern and advantage of these conditions could be taken by timing and adjusting the administration of drugs according to the circadian rhythm of the disease. Diseases such as cardiovascular, asthma, peptic ulcer, arthritis etc. follow the body's circadian rhythm (4).

All these acted as push for the development of pulsatile drug delivery which release the drug after a predetermined lag time means during certain period of time there is no release of drug after that rapid and complete release of drug that ideally match the circadian pathophysiology of particular disease (5).

Morning hypertension is a condition in which blood pressure is specifically higher in the morning than at other times of day. As the criterion of hypertension based on home blood pressure is 135/85 mm Hg, an average blood pressure early in the morning of ≥135/85 mm Hg is defined as morning hypertension in a broad sense. Cardiovascular events

frequently occur early in the morning, and blood pressure increases from the night-time to early in the morning due to diurnal changes. As early morning blood pressure is significantly associated with the risk of brain, heart and kidney damage and all cardiovascular risks, morning hypertension, in which the blood pressure is increased in the time of the highest cardiovascular risk, is important (6).

Thus present study attempts to design & evaluate a chronomodulated drug delivery system of Cilnidipine used for treatment of early morning hypertension. It was aimed to have a lag time of 6 hour means if the system is taken at the bed time around 11 am then it expected to release the drug after a period of 6 hour at the 5 am when early morning hypertension more exacerbates. Such time controlled pulsatile system can be formulated mainly with drug containing cores coated with various erodible polymers. Because coating of polymer to the core, it protects the core from the environment e.g. water, acidic pH and enzymes until the drug is released after a predetermined lag phase. The coatings can erode/dissolve rupture or alter their permeability at the required time (7).

Cilnidipine is the novel calcium antagonist accompanied with L-type and N-type calcium channel blocking function. Compared with other calcium antagonists, Cilnidipine can act on the N-type calcium-channel that existing sympathetic nerve end besides acting on L-type calcium-channel that similar to most of the calcium antagonists. Due to its N-type calcium-channel blocking properties, it has more advantages compared to conventional calcium-channel blockers.

Thus, this study focus on the development of press coated pulsatile tablet of Cilnidipine for providing the relief from hypertension. For optimization of the formulation 3^2 full factorial design were employed to investigate the effect of two factors which is total amount of coating and % of HPMC K4M because they affect the lag time and cumulative release of pulsatile drug delivery system.

MATERIALS AND METHODS

Materials

Cilnidipine was gifted by J. B. Chemicals & Pharmaceuticals Ltd. Mumbai. Lactose Monohydrate and Microcrystalline cellulose were gifted by DFE Pharma, Germany and JRS

Pharma, Germany respectively. HPMC K4M and HPMC E50LV were obtained from Coral Chemical, New Delhi, India. Croscarmellose sodium was procured from FMC Biopolymer.

Methods

Identification of drug

Identification of Cilnidipine was carried out by Infra-Red absorption spectroscopy (FT-IR).

Preformulation studies

Bulk density, tapped density, Hausner's ratio, Carr's index and angle of repose were performed for core powder blend (8).

Drug – excipients compatibility studies

Compatibility must be established between the active ingredient and other excipients to produce a stable, efficacious, attractive and safe product.

Fourier Transform Infra-red Spectroscopy (FTIR):

FT-IR spectra (400-4000 cm^{-1}) of Cilnidipine, used in formulations and physical mixture were obtained on a Thermo scientific FT-IR spectrophotometer. Samples were prepared by KBr pellet technique by mixing weighed amount of drug (3 mg) with 100 mg of potassium bromide (dried at 40-50^{o}C). The mixture was taken and subjected to compress under 10 ton pressure in a hydraulic press to form a transparent pellet (9).

Formulation of press coated tablet

Formulation of core tablet by direct compression method

Core tablet of Cilnidipine was prepared by direct compression method using the composition as shown in below Table:

Table 1: Composition of core tablet

Ingredients(mg)	Batch code		
	C1	C2	C3
Cilnidipine	10.00	10.00	10.00
Lactose monohydrate (Super tab SD 11)	141.44	141.44	141.44
Microcrystalline cellulose (Vivapur-112)	64.16	61.96	59.76
Croscarmellose sodium (Ac-di-sol)	2.2	4.4	6.6
Magnesium stearate	2.2	2.2	2.2
Total	220	220.0	220

All ingredients used in formulation including Cilnidipine, Lactose monohydrate, microcrystalline cellulose and Croscarmellose sodium were passed through 40 # sieve and dry blended for 10 minutes. Lubricated this blend with pre-sifted Magnesium stearate through 60 # sieve and mixed for 3 minutes.

Final lubricated blend was directly compressed using 8.0 mm round, concave punch by using rotary tablet compression machine (Hardik Eng. Pvt. Ltd, Ahmadabad, India) (10,11).

Development of Press-coated tablets

The core tablet was compression coated with different quantities of coating material containing different ratio of HPMC K4M and HPMC E50LV. Powder blend for press-coated tablet was prepared by dry blending together different compositions of the HPMC.

Half the quantity of the coating polymer was placed in the die cavity; the core tablet was carefully placed in the centre of the die cavity and filled with the other half quantity of the coating polymer. The coating material was compressed by using rotary tablet compression machine (Hardik Eng. Pvt. Ltd, Ahmadabad, India) (9, 12, 13).

Formulation optimization

In this study, a 3^2 full factorial design was used for the optimization by using STATISTICA®7 (StatSoft® Inc.) software. In this design 2 factors were evaluated, each at 3 levels, and experimental trials were performed at all 9 possible combinations (14). Two independent

variables i.e. X_1: Total amount of polymer and X_2: % of HPMC K4M were selected against two dependent variable Y_1: Lag time (t_{10}) and Y_2: Times require for 90% drug release for optimization.

Table 2: Formulation Design layout for 3^2 full factorial design

Batch code	Coded value		Actual value	
	X_1	X_2	Total amount of polymer (mg) X_1	% of HPMC K4M X_2
F1	-1	-1	110	25
F2	-1	0	110	50
F3	-1	+1	110	75
F4	0	-1	220	25
F5	0	0	220	50
F6	0	+1	220	75
F7	+1	-1	330	25
F8	+1	0	330	50
F9	+1	+1	330	75

Table 3: Compression coat formula for different tablet batches

Ingredient(mg)	Batch code								
	F1	F2	F3	F4	F5	F6	F7	F8	F9
Core tablet	220	220	220	220	220	220	220	220	220
HPMC K4 M	27.5	55	82.5	55	110	165	82.5	165	247.5
HPMC E 50LV	82.5	55	27.5	165	110	55	247.5	165	82.5
Total wt	330	330	330	440	440	440	550	550	550

Evaluation of compress coated tablets

Core and compress-coated tablets were evaluated for post compression parameters such as weight variation, thickness, hardness, friability test, content uniformity test and *in vitro* drug release study (15, 16).

Weight variation

Weight variation test was carried out by weighing 20 tablets individually, calculating the average weight, comparing the individual tablet weight to average weight. The tablet meet USP-XXIX test if no tablet differs by more than two times of percentage deviation.

Hardness and Thickness

For each formulation, the hardness of 10 tablets was determined using Monsanto hardness tester and Thickness of 5 tablets was determined using Vernier caliper.

Friability

Twenty tablets were weighed and placed in the Roche friabilator and apparatus was rotated at 25 rpm for 4 minutes. After revolutions the tablets were dedusted and weighed again. The percentage friability was measured using the formula,

$$\% \text{ Friability} = \frac{\text{Initial weight} - \text{Final weight}}{\text{Initial weight}} \text{X } 100$$

Drug content

10 tablets of Cilnidipine were taken and crushed. Amount of the powder equivalent to 10 mg of Cilnidipine was dissolved in 100 ml of distilled water, filtered, diluted suitably and analysed for drug content at 291 nm using UV-spectrophotometer (17).

***In Vitro* dissolution study**

In-vitro dissolution study was performed using USP Type I dissolution apparatus (Basket type) at speed of 100 rpm.0.1 N HCl of pH 1.2 was first used for 2 hr, which was then replaced with phosphate buffer pH 6.8 and kept up to 12 hr. Aliquot of dissolution medium (5 ml) were

withdrawn at specific time intervals of 1 hr and filtered each with Whatman filter paper. Equal amount of fresh dissolution medium was replaced immediately after each withdrawal. The amount of drug present in each sample was determined by UV-spectrophotometer at 291 nm.

RESULTS AND DISCUSSION

An absorption maximum was determined by scanning different concentration of solution of Cilnidipine. It was found to be 291 nm and method obeys Beer's law in concentration range 5 to 40 µg/ml, R^2 was found to be 0.998.

Pre-compression evaluation like angle of repose, bulk density, tapped density, % compressibility and Hausner's ratio of core powder blend are shown in below Table:

Table 4: Pre-compression parameters of core powder blend

Parameters	Observation (n = 3)
Angle of repose (radian)	28±1.057
Bulk density (gm/ml)	0.51±0.002
Tapped density (gm/ml)	0.65±0.007
Carr's index	21.53±0.03
Hausner's ratio	1.27±0.13

The values of pre-compression parameters of core powder blend were within prescribed limit as per USP XXVII and indicate good flow properties.

FT-IR spectra of Cilnidipine and physical mixture are shown in below Figure 1.

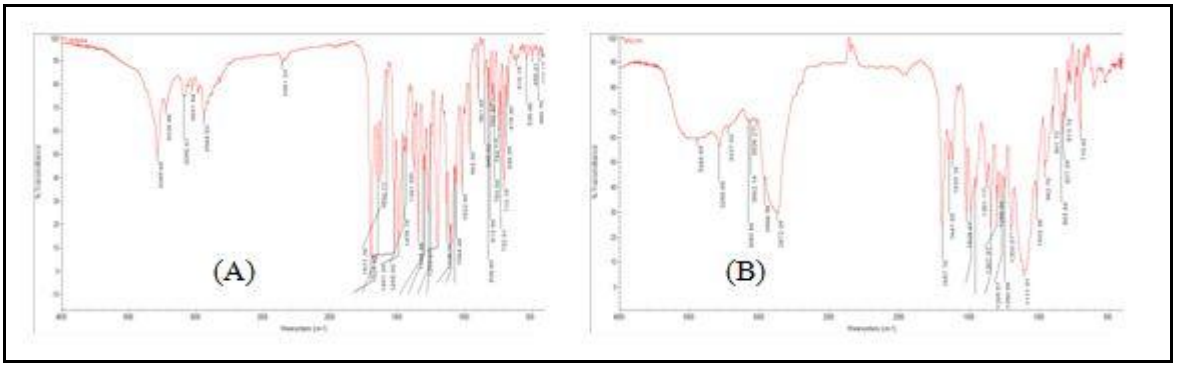

Figure 1: FT-IR spectra of (A) Cilnidipine and (B) final formulation

In the FT-IR spectrum of Cilnidipine the characteristic peaks corresponding to an amide C=O stretching, N-H stretching, N=O stretching were identified, which were also found in final formulation. Thus there was not any interaction between drug and excipients.

Core tablet (C1-C3) was characterized for post-compression parameters like weight variation, thickness, hardness, friability, drug content and disintegration time.

Table 5: Post-compression parameters of core tablet

Batch code	Weight variation (mg)	Thickness (mm)	Hardness (Kg/cm^2)	Friability	Disintegration time (sec)
C1	222 ± 2.37	3.85 ±0.21	3.5±0.81	0.45±0.07	54±3.54
C2	221 ± 2.57	3.86± 0.19	3.4±0.58	0.47±0.05	35±3.47
C3	223 ± 2.24	3.86±0.20	3.5±0.13	0.49±0.04	35±2.99

From the result of post compression parameters of core tablet, deviation in weight is less than 10% indicated that there was no significant weight variation in the core tablets. Hence, all the tablet formulations passed the USP-XXIX weight variation test. The hardness test indicates good mechanical strength. Friability of all formulation was less than 1%, which indicates the tablets had good mechanical resistance. Drug content was found to be uniform in all formulations. From the result of disintegration time of core tablet it was found that minimum disintegration time was observed with formulation C2 and C3 containing 2% and 4% croscarmellose sodium. So the formulation C2 containing 2% croscarmellose sodium is selected as optimized core tablet for further preparation of compress coated tablet.

Compress coated tablet (F1- F9) was characterized for weight variation, thickness, hardness and friability. Results are shown in below Table:

Table 6: Post-compression parameters of press coated tablet

Formulation	Weight variation(mg)	Thickness (mm)	Hardness (Kg/cm^2)	Friability
F1	331.5±2.78	4.40±0.21	6.9±0.78	0.39±0.04
F2	331.9±2.25	4.37±0.13	6.8±0.68	0.37±0.03
F3	330.7±3.05	4.43±0.16	7.0±0.81	0.40±0.04
F4	442.2±2.98	5.10±0.17	6.9±0.91	0.39±0.03
F5	439.8±3.10	5.08±0.13	7.2±0.82	0.37±0.05
F6	440.8±3.24	5.02±0.19	7.4±0.79	0.45±0.04
F7	553.1±2.78	5.61±0.12	6.8±0.81	0.42±0.09
F8	552.4±3.68	5.70±0.15	7.1±0.91	0.37±0.04
F9	550.9±2.25	5.69±0.11	7.5±0.49	0.36±0.03

From the result of post-compression parameters of core tablet, deviation in weight is less than 5% indicated that there was no significant weight variation in the core tablets. Hence, all the tablet formulations passed the USP-XXIX weight variation test. The percentage friability was less than 1% in all the formulations, indicating that the friability is within the prescribed limits. The hardness test indicates good mechanical strength. The tablet thickness was found to be 4.37 mm to 5.70 mm.

In-vitro drug release profile of all nine formulations was found typical sigmoidal curves with a distinct lag time. It showed that lag time increased with increasing concentration of HPMC K4M. This might be due to the greater degree of hydration with simultaneous swelling. This would result in corresponding lengthening of the drug diffusion pathway.

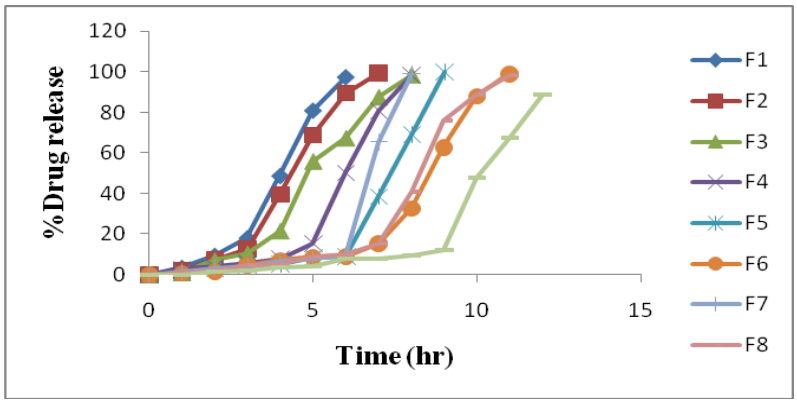

Figure 2: Dissolution profiles of final batches (F1-F9)

From release profile of all nine batches it was observed that drug release from tablet was inversely proportional to concentration of HPMC K4M. From all the batches, formulation F1 to F4 shows >10% of drug released before the lag time of 6 hours while significant retardation was observed from the batches F6, F8 and F9 containing higher amount of HPMC K4M in the outer shell.

Formulation F5 and F7 show less lag time of 6 hours (<10% drug release) and nearer 99% of drug release at the end of 8 to 9 hours.

Rupture sequence of pulsatile release tablet showed that at 0 hr coating of HPMC layer was intact, after 2 hrs there was slightly swelling of HPMC coating was observed. After 6 hrs there was start of rupture of HPMC occurred. When rupturing of HPMC layer was occurred, fluid penetrates into inner core of tablet. Because of penetration of fluid swelling of croscarmellose sodium causes burst release of drugs and complete release of drug observed within 9 hrs.

Result of dependent variable of 3^2 full factorial design (Table 7) showed that batch F5 and F7 have lag time of 6 hours and time requires for release 90% of drug are 7-8 hours. But batch F7 showed much more drug release as compared to batch F5 after lag time. So, based on the all dependant variables batch F7 was selected as optimized batch.

Table 7: Results of dependent variables

Batch code	Coded value		Response	
	X_1	X_2	Y_1	Y_2
F1	-1	-1	2.06	5.55
F2	-1	0	2.45	6.06
F3	-1	1	2.82	7.22
F4	0	-1	4.26	7.52
F5	0	0	6.02	8.68
F6	0	1	7.06	10.17
F7	1	-1	6.00	7.74
F8	1	0	5.84	10.15
F9	1	1	8.15	11.93

A three factor and two level (3^2) full factorial design was applied in this study to optimize the formulations. Total amount of coating and % of HPMC K4M were chosen as the independent variables while lag time (t_{10}) and time require for release 90% of drug were taken as dependent variable.

The polynomial equation for 3^2 full factorial design is described as follows:

$$Y = b_0 + b_1X_1 + b_2X_2 + b_{11}X_1X_1 + b_{22}X_2X_2 + b_{12}X_1X_2$$

Where, Y is the dependent variables, β_0 is the arithmetic mean response of the nine runs, and β_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_1X_2) show how the response changes when two factors are simultaneously changed. The polynomial terms (X_{11} and X_{22}) are included to investigate non-linearity.

The polynomial equations (equations 1-3) relating the response lag time (Y_1) and time require for release 90% of drug (Y_2) with the independent variables are given below.

$$Y_1 = 5.58+2.11X_1+0.95X_2+0.34X_1X_2-1.22X_1X_1+0.28X_2X_2 (r^2= 0.958) \quad \_ \_ \_ \_ (1)$$

$$Y_2= 8.75+1.83X_1+1.41X_2+0.63X_1X_2-0.68X_1X_1+0.05X_2X_2 \quad (r^2 = 0.995) \quad \_ \_ \_ \_ (2)$$

When amount of total polymer was increased (X_1), lag time (Y_1) and time require for 90% drug release (Y_2) was increased and when % of HPMC K4M was increased (X_2), lag time (Y_1) and time require for 90% drug release (Y_2) was increased.

The relationship between the dependent and independent variables was further elucidated using surface plot and contour plot as shown in Figure 4.

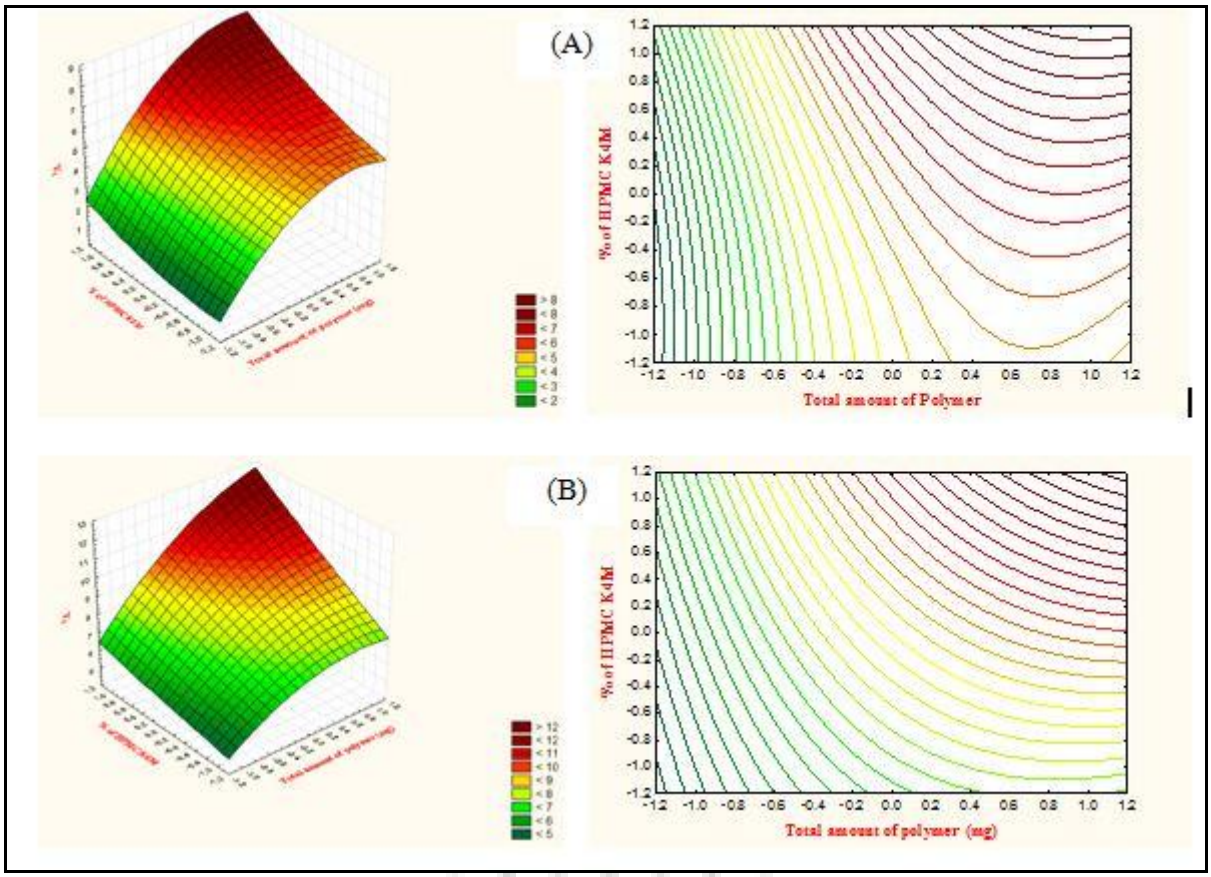

Figure 3: Surface and Contour plot of (A) lag time (Y_1), (B) time require for 90% of drug release (Y_2)

CONCLUSION

A compress coated pulsatile drug delivery system for Cilnidipine used to obtain flexible drug delivery systems based on time controlled release. Drug release of compression-coated tablets can be modified by adjusting the release controlling parameters to achieve programmable drug release for site specific drug delivery in GI tract. The formulation consisted of a core tablet containing a drug Cilnidipine and outer layer of combination of swellable hydrophilic polymer of HPMC K4M and HPMC E50 LV. From all the batches it was concluded that Formulation F7 was the ideal formulation with lag time of 6 hrs followed by burst release of drug and also meeting all specifications of pre-compression and post-compression parameters and stability studies. Thus the dosage forms can be taken at bedtime so that the content will be released in the morning hours i.e. at the time of symptoms.

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